Zytux™

Active ingredient: Rituximab

Excipients: sodium citrate, polysorbate 80, sodium chloride, water for injection.

Dosage Forms:

100 & 500 mg, Concentrate for solution for Infusion

Each 10 mL vial contains Rituximab 100mg (10 mg/mL)

Each 50 mL vial contains Rituximab 500mg (10 mg/mL)

Mechanism of Action:

Zytux™ (Rituximab) is a chimeric monoclonal antibody (mouse/human) that binds specifically to the transmembrane antigen CD20. This antigen is a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes and expressed on >95 % of all B cell non-Hodgkin's Lymphomas (NHLs). CD20 is found on both normal and malignant B cells, but not on hematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissue.CD20 doesn't internalize, nor is it shed from the cell surface upon antibody binding. Free CD20 antigen is not found in the circulation and thus, does not compete for antibody binding.

Possible mechanisms of B cell lysis include: Complement-dependent cytotoxicity, Dependent cellular cytotoxicity and induction of apoptosis. The number of peripheral B lymphocytes after administration of the first dose of **Zytux™** become below normal levels. In patients who is treated for hematologic malignancies, B lymphocytes begin to rebuild during 6 months after treatment and its values within 9 to 12 months after completion of therapy dates back to normal.

Zytux™ make malignant B cells sensitive, which was resistant to the cytotoxic effects of chemotherapy.

Indications and Usage:

Zytux™ is indicated for the treatment of patients with:

a) Non-Hodgkin's lymphoma (NHL)

• Relapsed or chemoresistant, low-grade or follicular, CD20-positive, B-cell NHL as a single agent.

• Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to **Zytux™** in combination with chemotherapy, as single-agent maintenance therapy.

• Non-progressing, low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP chemotherapy

• Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens.

b) Chronic Lymphocytic Leukemia (CLL)

• Previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide (FC).

c) Rheumatoid Arthritis (RA)

• In patients with moderately- to severely- active rheumatoid arthritis in adults who have had an inadequate response to one or more TNF antagonist therapies. **Zytux™** can be used in combination with methotrexate.

d) Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)

• In adult patients with Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) in combination with glucocorticoids.

Dosage and Administration:

Zytux™ is administered after dilution as an IV infusion through a dedicated line. Do not administer the prepared infusion solutions as an IV push or bolus.

Zytux™ infusions should be administered in an environment where full resuscitation facilities are immediately available, and under the close supervision of an experienced physician. Patients developing respiratory symptoms or hypotension should be monitored for at least 24 hours.

Premedication consisting of an anti-pyretic and an antihistaminic, for example acetaminophen and diphenhydramine, should always be administered before each infusion of **Zytux™** (30 to 60 minutes before starting the infusion). Premedication with glucocorticoids should also be considered.

Patients should be closely monitored for the onset of cytokine release syndrome. Patients who develop evidence of severe reactions, especially severe dyspnea, bronchospasm or hypoxia should have the infusion interrupted immediately. Patients with non-Hodgkin's Lymphoma should then be evaluated for evidence of tumor lysis syndrome including by appropriate laboratory tests and, for pulmonary infiltration, with a chest x-ray.

In all patients, the infusion should not be restarted until complete resolution of all symptoms, and normalization of laboratory values and chest x-ray findings. At this time, the infusion can be initially resumed at not more than one-half the previous infusion rate. If the same severe adverse reactions occur for a second time, the decision to stop treatment should be seriously considered. Mild or moderate infusion-related reactions usually respond to a reduction in the rate of infusion. The infusion rate may be increased after improvement of symptoms.

Non- Hodgkin's Lymphoma:

Premedication with glucocorticoids should be considered if **Zytux™** is not given in combination with glucocorticoid containing chemotherapy (CHOP or CVP) for treatment of non-Hodgkin's lymphoma.

Rate of infusion:

A) First infusion: The recommended initial rate for infusion is 50 mg/hr; after the first 30 minutes, it can be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.

B) Subsequent infusions: Subsequent infusions of **Zytux™** can be infused at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30 minutes intervals, to a maximum of 400 mg/hr as tolerated.

Follicular non-Hodgkin's Lymphoma:

A) Initial treatment: the recommended dosage of **Zytux™** monotherapy in adult patients is 375 mg/m^2 body surface area, administered as an IV infusion once weekly for four weeks over a 22 days period. The recommended dosage of **Zytux™** in combination with CVP chemotherapy is 375 mg/m^2 body surface area for 8 cycles (21 days/cycle), administered on first day of each chemotherapy cycle after administration of the glucocorticoid component of CVP.

B) Maintenance treatment: In previously untreated patients with advanced high-tumor burden follicular lymphoma, after complete or partial response to induction treatment, **Zytux™** maintenance therapy should be initiated. (Eight weeks following completion of **Zytux™** chemotherapy). The recommended dosage of **Zytux™** maintenance therapy is 375 mg/m^2 body surface area as a single agent every 8 weeks for a maximum of 12 doses (two years).

C) Relapsed/refractory treatment: The recommended dose of **Zytux™** for relapsed/refractory patients after response to induction treatment is 375 mg/m^2 every 3 months until disease progression or for a maximum period of two years.

Diffuse large B cell non-Hodgkin's Lymphoma:

Zytux™ should be used in combination with CHOP chemotherapy.

The recommended dosage is 375 mg/m^2 body surface area administered on first day of each chemotherapy cycle for 8 cycles after administration of the glucocorticoid component of CHOP.

Safety and efficacy of **Zytux™** have not been established in combination with other chemotherapies.

Chronic Lymphocytic Leukemia:

The recommended dosage of **Zytux™** in combination with chemotherapy for previously untreated and previously treated patients is 375 mg/m^2 body surface area administered on first day of the first treatment cycle followed by 500mg/m^2 body surface area administered on first day of each subsequent cycle for 6 cycles in total. The chemotherapy should be given after **Zytux™** infusion.

Dosage adjustments during treatment:

No dose reductions of **Zytux™** are recommended. When **Zytux™** is given in combination with CHOP or CVP chemotherapy, standard dose reductions for the chemotherapeutic medicinal products should be applied.

Rheumatoid Arthritis:

Patients should receive 100 mg IV methylprednisolone to be completed 30 minutes prior to each **Zytux™** infusion to reduce the frequency and severity of infusion-related reactions. A course of **Zytux™** consists of two 1000 mg IV infusions with two weeks interval. There are limited clinical data on the safety and efficacy of further courses of therapy with **Zytux™**. If a repeat course of treatment is considered it should not be given at an interval less than 16 weeks.

Administration:

First infusion of each course: The recommended initial rate for infusion is 50 mg/hr; after the first 30 minutes, it can be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.

Second infusion of each course: The recommended initial rate for infusion is 100 mg/hr, and increased by 100 mg/hr increments at 30 minutes intervals, to a maximum of 400 mg/hr.

Granulomatosis with Polyangiitis (GPA, also known as Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA):

The recommended dosage of **Zytux™** for treatment of GPA/MPA is 375 mg/m^2 body surface area, administered as an IV infusion once weekly for 4 weeks. Methylprednisolone 1000 mg/day intravenously for 1 to 3 days followed by oral prednisone 1 mg/kg/day are recommended to treat severe vasculitis symptoms. This regimen should begin within 14 days prior to or with the initiation of **Zytux™** and may continue during and after the 4 week course of **Zytux™** treatment.

Instruction guidelines concerning use of Zytux™ in certain population

Geriatric usage:

No dose adjustment is required in elderly patients (aged >65 years) but use with caution in the elderly; higher risk of cardiac (supraventricular arrhythmia) and pulmonary adverse events (pneumonia, pneumonitis).

Patients with hepatic impairment

No dose adjustment is required. Of course there is not enough study and information.

Patients with renal impairment

No dose adjustment is required. Of course there is not enough study and information.

Contraindications:

Type 1 hypersensitivity or anaphylactic reaction to murine proteins, Chinese Hamster Ovary (CHO) cell proteins, or any component of the formulation; patients who have or have had progressive multifocal leukoencephalopathy (PML)

Warning and precautions:

Hepatitis B virus reactivation:

Hepatitis B virus (HBV) reactivation may occur with use and may result in fulminant hepatitis, hepatic failure, and death. Screen all patients for HBV infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) prior to therapy initiation; monitor patients for clinical and laboratory signs of hepatitis or HBV during and for several months after treatment. Discontinue **Zytux™** (and concomitant medications) if viral hepatitis develops and initiate appropriate antiviral therapy. Reactivation has occurred in patients who are HBsAg positive as well as in those who are HBsAg negative but are anti-HBc positive; HBV reactivation has also been observed in patients who had previously resolved HBV infection. HBV reactivation has been reported up to 24 months after therapy discontinuation. Use cautiously in patients who show evidence of prior HBV infection (eg, HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive); consult with appropriate clinicians regarding monitoring and consideration of antiviral therapy before and/or during **Zytux™** treatment. The safety of resuming **Zytux™** treatment following HBV reactivation is not known; discuss reinitiating of therapy in patients with resolved HBV reactivation with physicians experienced in HBV management.

Infections:

Use of **Zytux™** is not recommended if severe active infection is present; serious and potentially fatal bacterial, fungal, and either new or reactivated viral infections may occur during treatment and after completing **Zytux™**. Infections have been observed in patients with prolonged hypogammaglobulinemia, defined as hypogammaglobulinemia >11 months after **Zytux™** exposure; monitor immunoglobulin levels as necessary. Associated new or reactivated viral infections have included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C. Discontinue **Zytux™** (and concomitant chemotherapy) in patients who develop viral hepatitis and initiate antiviral therapy. Discontinue **Zytux™** in patients who develop other serious infections and initiate appropriate anti-infective treatment.

Infusion reactions:

Severe (occasionally fatal) infusion-related reactions have been reported, usually with the first infusion; fatalities have been reported within 24 hours of infusion; monitor closely during infusion; discontinue for severe reactions and provide medical intervention for grades 3 or 4 infusion reactions.

Reactions usually occur within 30-120 minutes and may include hypotension, angioedema, bronchospasm, hypoxia, urticaria, and in more severe cases pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, and/or anaphylaxis. Risk factors associated with fatal outcomes include chronic lymphocytic leukemia, female gender, mantle cell lymphoma, or pulmonary infiltrates. Closely monitor patients with a history of prior cardiopulmonary reactions or with pre-existing cardiac or pulmonary conditions and patients with high numbers of circulating malignant cells (>25,000/mm3). Prior to infusion, premedication of patients with acetaminophen and an antihistamine (and methylprednisolone for patients with RA) is recommended. Discontinue infusion for severe reactions and serious or life-threatening cardiac arrhythmias. Perform cardiac monitoring during and after the infusion in patients who develop clinically significant arrhythmias or who have a history of arrhythmia or angina. Medications for the treatment of hypersensitivity reactions (e.g. bronchodilators, epinephrine, antihistamines, and corticosteroids) should be available for immediate use; treatment is symptomatic. Mild-to-moderate infusion-related reactions (e.g. chills, fever, rigors) occur frequently and are typically managed through slowing or interrupting the infusion. Infusion may be resumed at a 50% infusion rate reduction upon resolution of symptoms. Due to the potential for hypotension, consider withholding antihypertensive drugs 12 hours prior to treatment.

Mucocutaneous reactions

Severe and sometimes fatal mucocutaneous reactions (lichenoid dermatitis, paraneoplastic pemphigus, Stevens-Johnson syndrome, toxic epidermal necrolysis and vesiculobullous dermatitis) have been reported; onset has been variable but has occurred as early as the first day of exposure. Discontinue in patients experiencing severe mucocutaneous skin reactions; the safety of re-exposure following mucocutaneous reactions has not been evaluated.

Progressive multifocal leukoencephalopathy

Progressive Mulifocal Leukoencephalopathy (PML) due to JC virus infection has been reported with **Zytux™** use; may be fatal. Cases were reported in patients with hematologic malignancies receiving **Zytux™** either with

combination chemotherapy, or with hematopoietic stem cell transplant. Cases were also reported in patients receiving **Zytux™** for autoimmune diseases who had received concurrent or prior immunosuppressant therapy. Onset may be delayed, although most cases were diagnosed within 12 months of the last **Zytux™** dose. Promptly evaluate any patient presenting with neurological changes; consider neurology consultation, brain MRI and lumbar puncture for suspected PML. Discontinue **Zytux™** in patients who develop PML; consider reduction/discontinuation of concurrent chemotherapy or Immunosuppressants.

Renal toxicity

May cause fatal renal toxicity in patients with hematologic malignancies. Patients who received combination therapy with cisplatin and **Zytux™** for NHL experienced renal toxicity during clinical trials; this combination is not an approved treatment regimen. Renal toxicity also occurred due to tumor lysis syndrome. Monitor for signs of renal failure; discontinue **Zytux™** with increasing serum creatinine or oliguria.

Tumor lysis syndrome

Tumor lysis syndrome leading to acute renal failure requiring dialysis (some fatal) may occur 12-24 hours following the first dose when **Zytux™** is used as a single agent in the treatment of NHL. Hyperkalemia, hypocalcemia, hyperuricemia, and/or hyperphosphatemia may occur. Administer prophylaxis (antihyperuricemic therapy, hydration) in patients at high risk (high numbers of circulating malignant cells ≥25,000/mm3 or high tumor burden). Correct electrolyte abnormalities; monitor renal function and hydration status.

Precautions:

Cardiovascular disease

Use with caution in patients with pre-existing cardiovascular disease or prior cardiopulmonary events. Discontinue with serious cardiac arrhythmia.

Respiratory disease

Use with caution in patients with pre-existing pulmonary disease, or prior cardiopulmonary events.

Biologic agents

Safety and efficacy of **Zytux™** in combination with other biologic agents have not been established.

Disease-modifying antirheumatic drugs:

Safety and efficacy of **Zytux™** in combination with disease-modifying antirheumatic drugs (DMARDs) other than methotrexate have not been established.

Immunizations:

Live vaccines should not be given concurrently with **Zytux™**; there is no data available concerning secondary transmission of live vaccines with or following **Zytux™** treatment. RA patients should be brought up to date with nonlive immunizations (following current guidelines) at least 4 weeks before initiating therapy; evaluate risks of therapy delay versus benefit (of nonlive vaccines) for NHL patients.

Food and drug Interaction:

- Concurrent Use of **Zytux™** with other Biological Therapeutics: The combination of **Zytux™** with other biological therapeutics used to treat the same conditions as **Zytux™** including anakinra or abatacept, is not recommended.
- Live Vaccines/Therapeutic Infectious Agents: It is recommended that live vaccines and therapeutic infectious agents not be given concurrently with **Zytux™**.
- Cytochrome P450 Substrates: The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα, IL-1, IL-6, IL-10, and IFN) during chronic inflammation. Therefore, it is expected that for a molecule that antagonizes cytokine activity, such as infliximab, the formation of CYP450 enzymes could be normalized. Upon initiation or discontinuation of **Zytux™** in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

Drug Interaction		Effect	Class
Zytux™	Abatacept	↑ risk of infection	X (Avoid combination)
Zytux™	BCG	↓ the therapeutic effect of BCG	X (Avoid combination)
Zytux™	Clozapine	↑ risk of clozapin toxicity	X (Avoid combination)
Zytux™	Tacrolimus (Topical)	↑ the toxic effect of Immunosuppressants	X (Avoid combination)
Zytux™	Natalizumab	↑ risk of infection	X (Avoid combination)
Zytux™	Vaccines (Live)	↑ risk of infection	X (Avoid combination)
Zytux™	Leflunomide	↑ the toxic effect of Leflunomide	D (Consider therapy modification)a
Zytux™	Echinacea	↓ therapeutic effect of Immunosuppressant	D (Consider therapy modification)
Zytux™	Denosumab	↑ risk of infection	C (Monitor therapy)
Zytux™	Trastuzumab	↑ the neutropenic effect of Immunosuppressant	C (Monitor therapy)
Zytux™	Vaccines (Inactivated)	↓ the therapeutic effect of Vaccines	C (Monitor therapy)

Pregnancy and lactation:

Pregnancy: There are no adequate data from the use of **Zytux™** in pregnant women. As IgG is known to pass the placental barrier, **Zytux™** may cause B cell depletion in the fetus. For these reasons **Zytux™** should not be given to a pregnant woman unless the potential benefit outweighs the potential risk. Due to the long retention time of **Zytux™** in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during treatment and for 12 months following **Zytux™** therapy. B cell levels in human neonates following maternal exposure to **Zytux™** have not been studied in clinical trials.

Lactation: Whether **Zytux™** is excreted in human milk is not known. However, because as maternal IgG is excreted in human milk, and **Zytux™** was detectable in milk from lactating monkeys, women should not breastfeed while treated with **Zytux™** and for 12 months following **Zytux™** treatment.

Effects on ability to drive and use machines:

No studies on the effects of **Zytux™** on the ability to drive and use machines have been performed, although the pharmacological activity and adverse reactions reported to date suggest that **Zytux™** would have no or negligible influence on the ability to drive and use machines.

Adverse effects

Like all medicines, **Zytux™** can cause side effects, although not everybody gets them. Most side effects are mild to moderate but some may be serious and require treatment. Rarely, some of these reactions have been fatal.

Infusion reactions

The incidence of infusion reaction is more than 50% among patients and were predominantly seen during the first two hours of the first infusion, the incidence of infusion-related symptoms decreased substantially with subsequent infusions.

Symptoms of infusion reaction mainly comprised fever, chills and rigors but other symptoms included flushing, angioedema, bronchospasm, vomiting, nausea, urticaria/rash, fatigue, headache, throat irritation, rhinitis, pruritus, pain, tachycardia, hypertension, hypotension, dyspnea, dyspepsia, asthenia and features of tumor lysis syndrome. Severe infusion-related reactions (such as bronchospasm, hypotension) occurred in up to 12% of the cases.

If any of these symptoms develop, slow down or stop the infusion. Some patients may require additional treatment such as antihistamine or acetaminophen. Normal rate of infusion can be considered when symptoms go away.

Infections

Patients may get infections more easily following **Zytux™** therapy. The symptoms of an infection are fever, cough, sore throat, Dysuria and weakness. Although most of these infections are colds but some cases of pneumonia or urinary infections and very rare case of brain infections have been reported. The symptoms of brain infections can include: dysarthria, amnesia, loss of vision and difficulty walking. It is necessary patients inform their healthcare professionals if such symptoms develop.

Other reactions

If patients are being treated for non-Hodgkin's Lymphoma or chronic lymphocytic leukemia

The most commonly reported side effects due to **Zytux™** are:

- Infections such as pneumonia and herpes or bronchitis
- Leukopenia, with or without fever, thrombocytopenia
- Allergic reactions after infusion
- Nausea
- Skin reaction (rashes, itching, Alopecia, fever, chills, physical weakness, headache
- Decreased immunity (decreased IgG levels)

Common side effect due to **Zytux™** including:

- Sepsis, pneumonia, shingles, cold, bronchi¬al tube infections, fungal infections, infections of unknown origin, sinus inflammation, hepatitis B
- Anemia, low number of all blood cells
- Hypersensitivity
- high blood sugar level, weight loss, swelling in the face and body, high levels of the enzyme LDH, hypocalcemia
- Numbness, tingling, pricking, burning, a creeping skin
- Hypoesthesia
- Akathisia, Insomnia
- Flushing
- Dizziness or anxious
- Tear secretion, tear duct obstruction, conjuncti¬vitis
- Tinnitus, Otalgia
- Cardiovascular disease – such as heart attack, tachycardia or hypotension
- Bronchospasm, inflammation, irritation in the lungs, throat or sinuses, dyspenea, rhinitis
- Vomiting, diarrhea, abdominal pain, mouth sores, Dysphagia, constipation, indigestion
- Anorexia, lack of appetite, weight loss
- Urticaria, Hyperhidrosis, night sweats
- Tight muscles, joint or muscle pain, back and neck pain
- Malaise, shaking, flu like syndrome
- Multiple-organ failure

Uncommon side effect due to **Zytux™** include:

- Coagulation disorders, decrease of blood cells production, lymphadenopathy
- Depression mood, nervousness
- Dysgeusia
- Bronchospasm, inflammation, irritation in the lungs, throat or sinuses, dyspenea, rhinitis
- Abdomen enlargement
- Infusion site pain

b) If patients are being treated for rheumatoid arthritis

The most commonly reported side effects due to **Zytux™** are:

- Pneumonia
- Urinary tract infection
- Allergic reactions after infusion
- Changes in blood pressure, nausea, rash, fever, feeling itchy, runny or nasal congestion and sneezing, tachycardia, and fatigue
- Headache

Special Considerations

Incompatibilities

There is no incompatibilities between **Zytux™** and polyvinyl chloride or polyethylene bags or infusion sets.

Interfere with diagnostic tests

Potential effects on the response to vaccination and diagnostic test that the action is based on identification of antibodies has not been investigated so far.

Specific instructions for storing

The vials should be stored at 2 to 8 °C.

keep vials in their original boxes to protect from light.

The prepared solution for infusion would be stable for 24 hours at 2 to 8 °C and for 12 h at 15 to 25 °C according to its physical and chemical properties.

For microbiological reasons solution should be used immediately after dilution unless the dilution is performed in controlled and validated aseptic conditions.

This medicinal product must not be used after the expiry date printed on the packaging.

Instructions for use and discarded medicine

Zytux™ is a clear, colorless liquid, supplied in sterile, free of preservative, single dose vials.

Take desired value with an aseptic technique and diluted in a sterile and non-pyrogenic infusion bag containing sodium chloride 0.9% or glucose 5% solution, until you reach the desired concentration.

For mixing the solution, gently turn the bag, this will prevent the foam production.

Aseptic technique should be applied, since the solution has no antimicrobial or bacteriostatic preservative.

All intravenously medicine should be visually checked for presence of particles and discoloration.

Medicines should not be disposed via wastewater or household waste. Ask your pharmacist how to dispose of medicines that are no longer required. These measures will help to protect the environment.

Discard the unused medicine according to your country law.

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