Zytux™

Active substance : rituximab

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

PHARMACEUTICAL FORM AND AMOUNT OF ACTIVE INGREDIENT PER UNIT:

Zytux 100 : Each 10 ml vial contains 100 mg rituximab(rituximab conc. 10mg/ml)

Zytux 500 : Each 50 ml vial contains 500 mg rituximab(rituximab conc. 10mg/ml)

Mechanism of action

Rituximab is a monoclonal chimeric (mouse/human) antibody which binds specifically to the transmembrane antigen CD20 located on pre-B and mature B lymphocytes, but not on hematopoetic stem cells, pro-B cells, normal plasma cells or other normal tissue. The antigen is expressed on >95% of all B cell non-Hodgkin's lymphomas. After antibody binding ,CD20 does not internalize, nor is it shed from the cell membrane.CD20 does not circulate in plasma as free antigen and thus does not compete for antibody binding. Studies to date have found no connection between the intensity of CD20 expression on the malignant cells and treatment response.

Rituximab binds to the CD20 antigen on B lymphocytes and causes B cell lysis.Possible mechanisms of of cell lysis are complement-dependent cytotoxicity (CDC) together with antibody-dependent cellular cytotoxicity (ADCC) and induction of apoptosis.

Peripheral B cell counts fell below normal after the first dose of Zytux. In patients treated for hematological malignancy,B cells began to regenerate within 6 months of completing therapy,with values reverting to normal within 9 to 12 months of completing therapy.Rituximab sensitises drug-resistant human B cell lymphoma lines to the cytotoxic effect of some chemotherapy agents.

INDICATIONS AND POTENTIAL USES

Non-Hodgkin's lymphoma

- Treatment of patients with CD20-positive follicular non-Hodgkin's lymphoma (stage III –IV) who have relapsed after , or failed to respond to, chemotherapy.

- Treatment of previously untreated patients with CD20-positive follicular non-Hodgkin's lymphoma (stage III –IV) in combination with standard CVP chemotherapy (8 cycles of cyclophosphamide ,vincristine and prednisone).

- Treatment of patients with CD20-positive diffuse large B cell non-Hodgkin's lymphoma(DLBCL) in combination with standard CHOP (8 cycles of cyclophosphamide ,doxorubicin ,vincristine and prednisone).
- Maintenance therapy of patients with relapsed or refractory CD20-positive follicular non-Hodgkin's lymphoma (stage III –IV) who have responded to induction therapy with CHOP (6 cycles of cyclophosphamide ,doxorubicin ,vincristine and prednisone) or R-CHOP(6 cycles of CHOP plus Zytux)

Chronic Lymphocytic Leukemia(CLL)

Zytux is indicated for the treatment of patients with previously untreated or previously treated B-cell chronic lymphocytic leukemia (Binet Stage B or C) in combination with fludarabine and cyclophosphamide.

The use of Zytux in CLL patients is based on an improvement in progression-free survival.

Rheumatoid arthritis

Zytux in combination with methotrexate (MTX) is indicated in the treatment of adult patients with moderate to severe active rheumatoid arthritis after failing one or more treatments with tumor necrosis factor(TNF) inhibitors.

Granulomatosis with Polyangiitis (Wegener's Granulomatosis) and Microscopic Polyangiitis

Zytux in combination with glucocorticoids is indicated for induction of remission in adult patients with severely active granulomatosis with polyangiitis and microscopic polyangiitis.

DOSAGE AND ADMINISTRATION

Zytux is administered after dilution as an intravenous infusion through a dedicated line and is suitable for ambulatory therapy.

Zytux infusions should be administered in a medical facility where effective resuscitation facilities can be immediately deployed.The infusions should be administered under the direct

supervision of an experienced oncologist/hematologist or rheumatologist.Patients developing respiratory symptoms or hypotension should be monitored at least for 24 hours.

Before every Zytux infusion (30 to 60 minutes before starting the infusion) premedication should be given with an antipyretic and antihistamine ,e.g. paracetamol and diphenhydramine.

Patients should be closely monitored for evidence of incipient cytokine release syndrome(see Warnings and precautions).In patients showing evidence of severe side effects,in particular severe dyspnea, bronchospasm or hypoxia, the infusion must be interrupted immediately. Furthermore patients with non-Hodgkin's lymphoma should be evaluated for evidence of tumor lysis syndrome, including by appropriate laboratory tests.Patients with pre-existing respiratory failure or pulmonary tumor infiltration require chest X-ray. In all patients infusion must only be restarted after all clinical symptoms have fully resolved and laboratory values are in the normal range , at which point the infusion can be reinitiated at not more than half the previous infusion rate.If the same severe side effects recur,treatment termination should be considered.

Zytux must not be injected intravenously (IV) undiluted,nor must the prepared solution for infusion be administered as a bolus infusion.

Non-Hodgkin's lymphoma

Glucocrticoid premedication should be considered if Zytux is not combined with glucocrticoid-containing chemotherapy(CHOP or CVP) for the treatment of non-Hodgkin's lymphoma.

First infusion:The recommended initial infusion rate is 50 mg/h, after the first 60 minutes it can be increased stepwise every 30 minutes by 50 mg/h to a maximum 0f 400 mg/h.

Subsequent infusions: Subsequent infusions of Zytux can be started at an infusion rate of 100 mg/h,which can then be increased at 30-minute intervals by 100 mg/h to a maximum dose of 400 mg/h.

Follicular Non-Hodgkin's lymphoma

Initial treatment:

The recommended dosage of Zytux monotherapy in adults is 375 mg/m^2 body surface area(BSA) as an IV infusion once weekly for 4 doses over a 22-day period.

The recommended dosage of Zytux in combination with CVP chemotherapy is 375 mg/m^2 BSA for 8 treatment cycles (21 days per cycle).The dose of Zytux is given on day 1 of each chemotherapy cycle after oral administration of the glucocorticoid component of the CVP chemotherapy.

Treatment of relapse:

The retreatment dose for patients responding to the initial treatment was 375 mg/m^2 BSA as an IV infusion once weekly for 4 weeks.

Maintenance therapy:

Zytux maintenance therapy can be performed in patients who have responded to induction therapy with CHOP or R-CHOP .The dosage is 375 mg/m^2 BSA every 3 months until disease progression or for a maximum duration of 2 years.

Diffuse large B cell non-Hodgkin's lymphoma

Zytux should be used in combination with CHOP chemotherapy. The recommended dosage of Zytux is 375 mg/m^2 BSA for 8 treatment cycles. The dose of Zytux is administered on day 1 of each chemotherapy cycle after IV administration of the glucocorticoid component of the CHOP chemotherapy. Administration of the other chemotherapy components should follow that of Zytux.

Dosage adjustment during treatment:

Reducing the dose of Zytux is not recommended.When Zytux is combined with standard chemotherapy, standard dose reduction should be applied for the chemotherapy agents.

Chronic Lymphocytic Leukemia(CLL)

Premedication:

Before starting infusion of Zytux an analgesic/anti-pyretic and antihistamine ,e.g. paracetamol and diphenhydramine should be given.

Premedication with Glucocrticoids : This premedication should be considered if Zytux is not combined with steroid-containing chemotherapy.

The recommended dosage of Zytux in combination with chemotherapy for previously untreated or previously treated patients is 375 mg /m2 BSA administered on day 1 of the first chemotherapy cycle. Followed by 500 mg/m^2 BSA administered on day 1 of subsequent chemotherapy cycles for 6 cycles in total. Other chemotherapy drugs should be administered after infusion of Zytux.

Prophylaxis with adequate hydration and administration of uricostatics (such as allopurinol) starting 48 hours prior to start of therapy is recommended for CLL patients to reduce the risk of tumour lysis syndrome.

For CLL patients with lymphocyte counts > 25 × 10 ^{9}/l , it is recommended to administer methylprednisolone IV shortly before infusion with Zytux to reduce the rate and severity of acute infusion-related reactions and/or cytokine release syndrome.

First Infusion:

The recommended initial rate of infusion for Zytux is 50 mg/hr. Zytux should not be mixed or diluted with other drugs. If hypersensitivity or infusion-related reactions do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If hypersensitivity or an infusion-related reaction develops, the infusion rate should be temporarily slowed or interrupted . The infusion can be continued at one-half of the previous rate upon improvement of patient symptoms.

Subsequent Infusions:

Subsequent infusions of Zytux can be administered at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr.

Rheumatoid Arthritis

One Zytux treatment cycle consists of two 1000 mg IV infusions. The recommended dosage of Zytux is 1000 mg by IV infusion,followed by a second 1000 mg IV infusion 2 weeks later. Experience with more than two cycles remain slight.

Patients with rheumatoid arthritis should receive methylprednisolone 100 mg IV 30 minutes before the administration of Zytux to reduce the frequency and severity of acute infusion reactions(see Warnings and precautions,patients with rheumatoid arthritis)

First infusion of each treatment cycle:

The recommended initial infusion rate is 50 mg/hour. After the first 30 minutes it can be increased every 30 minutes by 50 mg/hour to a maximum of 400 mg/hour.

If the patient suffers an infusion-related reaction, the infusion rate should be halved(e.g. from 100 mg/hour to 50 mg/hour). After the adverse event has resolved, the investigator should wait a further 30 minutes and meanwhile administer the infusion at the reduced rate. If well tolerated ,the infusion rate can be raised to the next highest level of the schedule for the patient concerned. In patients experiencing a moderate to severe infusion-related reaction (fever,chills or hypotension),the infusion should be interrupted immediately and aggressive symptomatic therapy initiated.

The infusion should only be restarted –and then at half the infusion rate-after all signs and symptoms have resolved. If the patient tolerates infusion at the reduced rate for 30 minutes ,the rate can be increased to the next highest level of the schedule for the patient concerned.

After infusion is completed, the IV line should be left in situ for at least 1 hour to enable drugs to be administered IV as required. If no adverse events occurr during this period the IV line can be removed.

Second infusion of each treatment cycle:

The second dose of Zytux can be started at an initial infusion rate of 100 mg/hour if no adverse event occurred in conjunction with the first infusion. The rate can be then increased at 30-minute intervals by 100 mg/hour to a maximum of 400 mg/hour.

Granulomatosis With Polyangiitis (Wegener's Granulomatosis) And Microscopic Polyangiitis

The recommended dosage of Zytux for treatment of granulomatosis with polyangiitis and microscopic polyangiitis is 375 mg/m2 BSA(body surface area), administered as an IV infusion once weekly for 4 weeks.

Glucocorticoids administration like methylprednisolone 1000 mg intravenously per day for 1 to 3days 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 treatment and may continue during and after the 4week course of Zytux treatment.

First infusion:

The recommended initial infusion rate for Zytux is 50 mg/h, subsequently, the rate can be escalated in 50 mg/h increments every 30 minutes to a maximum of 400 mg/h.

Subsequent infusions:

Subsequent infusions of Zytux can be started at a rate of 100 mg/h and increased by 100 mg/h increments every 30 minutes to a maximum of 400 mg/h.

Pneumocystis jiroveci pneumonia (PCP) prophylaxis is recommended for patients with granulomatosis with polyangiitis and microscopic polyangiitis during and following treatment wirh Zytux.

SPECIAL DOSAGE INSTRUCTIONS

Elderly patients

No dose adjustment is required in elderly patients (>65 years) . According to high risk of serious cardiac (supraventricular arrhythmias) and pulmonary(Pneumonia) adverse events in geriatric patients it should be administered by caution.

Patients with hepatic impairment

No experience of use is available in patients with hepatic impairment.

Patients with renal impairment

In patients with non-Hodgkin's lymphoma risk of renal toxicity in case of concomitant administration of Zytux and Cisplatin is increased. There is also risk of renal toxicity after tumor lysis syndrome. So it is mandatory to monitoring renal failure symptoms and infusion should be interrupted in case of serum creatinin increment or oligouria .

CONTRAINDICATIONS

-Zytux is contraindicated in patients with known Type I hypersensitivity or anaphylactic reactions to murine proteins, Chinese Hamster Ovary (CHO) cell proteins.(Hypersesitivity to the active substrate or any excipient listed under composition)

- Zytux is also contraindicated in patients who have or have had progressive multifocal leukoencephalopathy (PML).

- Treatment with Zytux should not be initiated in patients with severe active infections or severely impaired immunity(e.g. hypogammaglobulinemia,greatly reduced CD4 or CD8 cell counts).

- Treatment with Zytux should not be initiated in patients with severe heart failure(New York Heart Association [NYHA] Class IV).

-Combination of Zytux with Methotrexate during pregnancy.

WARNINGS AND PRECAUTIONS

Patients with Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia

Patients with a high circulating malignant cell count (>25,000/mm^3) or high tumor burden(lesions >10 cm),who are at increased risk of especially sever cytokine release syndrome or tumor release syndrome should be treated with extreme caution and after considering other treatment options.

Fatalities have been reported in patients suffering severe cytokine release syndrome.In isolated cases ,signs and symptoms have also been observed of tumor lysis syndrome leading to multiorgan failure with respiratory and renal insufficiency.

Prior treatment should be considered to reduce the tumor burden. These patients must be monitored particularly closely during administration of the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients.

Patients with pulmonary insufficiency or high tumor burden are at increased risk of developing severe cytokine release syndrome or tumor lysis syndrome. Clinically it may be impossible to differentiate these reactions from an allergy–induced hypersensitivity reaction. Sever cytokine release syndrome is characterised by severe dyspnea(often accompanied by bronchospasm and hypoxia),fever(febrile convulsions),chills, urticaria and angioneurotic edema. It may be associated with features of tumor lysis syndrome such as hyperuricemia , hyperkalemia, hypocalcemia, hyperphosphatemmia , elevated LDH, acute renal failure and life-threatening respiratory failure.

Acute respiratory failure may be accompanied by interstitial pulmonary infiltration or edema visible on chest X-ray. I nfusion must be discontinued immediately and aggressive symotomatic treatment initiated in patients developing severe cytokine release syndrome.

Since initial improvement in clinical symptoms may be followed by deterioration , such patients must be closely monitored until symptoms have fully resolved. Once symptom resolution is complete ,such patients have rarely suffered severe infusion-related reactions during subsequent treatment.

Patients with pre-existing respiratory failure or pulmonary tumor infiltration must be treated with extreme caution , especially if these conditions are accompanied by the severe symptoms mentioned above.

Anaphylactoid and other hypersensitivity reactions may occur in patients after IV protein administration, In contrast to cytokine release syndrome , allergic immediate-type hypersensitivity reactions occur within minutes of starting infusion .Clinical manifestation of anaphylaxis may occur resembling those of the cytokine release syndrome described above.

In the event of an allergic reaction during Zytux administration , medical products for the treatment of hypersensitivity reactions should be available for the immediate use such as epinephrine, antihistamines and glucocorticoids.

The majority of all patients treated with Zytux experience infusion-related adverse reactions. These reactions are flu-like and, in approximately 10% of all patients ,severe ,with hypotension, dyspnea or bronchospasm .They can be reversed by discontinuing the Zytux infusion and administering antipyretics and antihistamines. Oxygen ,NaCl infusion and possibly also bronchodilators and glucocorticoids may be needed.

Since a transient fall in blood pressure may occur during Zytux infusion , consideration should be given to withholding antihypertensive medication 12 hours before infusion for the duration of the infusion.

Patients with a history of heart disease (e.g. angina , arrhythmia such as atrial flutter and fibrillation, or heart failure)should be closely monitored during infusion.

Although Zytux is not myelosuppressive in monotherapy ,caution should be exercised in undertaking scheduled treatment of patients with neutrophil counts $<1.5\times10^9$/l and or platelet counts $<75\times10^9$/l, as clinical experience in these patients are limited.

Zytux is used in patients who have undergone autologous bone marrow transplantation and also in other risk groups with presumably reduced marrow function without inducing myelotoxicity.

As with other tumor therapies regular monitoring is required of the full blood count , inducing platelets.

When Zytux is combined with CHOP or CVP chemotherapy the full blood count should be regularly monitored according to standard practice.

Reactivation of hepatitis B - inducing evidence of fulminant hepatitis -has been reported in very rare cases in patients treated with rituximab; however ,most of the patients concerned also received cytostatic chemotherapy. The reported cases are confounded by the underlying disease process and the cytostatic chemotherapy. Patients with a history of hepatitis B infection should be closely monitored for evidence of active hepatitis B infection when receiving riruximab in combination with cytostatic chemotherapy.

Severe mucocutaneous reactions ,some fatal ,have been described in isolated patients receiving Zytux. These reactions occurred between 1 to 13 weeks after starting treatment . Patients concerned must receive no further infusions and undrgo immediate medical investigation. Skin biopsy is useful in differentiating between various skin reactions and determining subsequent treatment. The mucocutaneous reactions described have comprised paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobollous dermatitis and toxic epidermal necrolysis. Nothing is known about the safety of Zytux retreatment in such cases.

Patients With Rheumatoid Arthritis And Granulomatosis With Polyangiitis (Wegener's Granulomatosis) And Microscopic Polyangiitis

Infusion reactions

Zytux administration may be associated with infusion reactions related to the release of the cytokines and/or other chemical mediators. Premedication with a glucocorticoid administered IV before each infusion reduces the frequency and severity of these reactions.

Most of the reported infusion reactions are mild to moderate. The proportion of patients affected decreases with subsequent infusions. The reported reaction are generally reversible when Zytux infusion

is administered more slowly or is interrupted and an antipyretic,antihistamine and- in occasional cases as required –oxygen,IV saline or bronchodilators and glucocorticoids are administered.

After signs and symptoms have fully resolved, infusion can be resumed at half of the rate (e.g. 50 mg/h instead of 100 mg/h).

Anaphylactic and other hypersensitivity reactions have been reported at the start, during and after IV protein administration to patients. Medical products for treating hypersensitivity reactions ,e.g. adrenaline ,antihistamines and glucocoricoids, should be available for immediate use if an allergic reaction occurs during Zytux administration.

No Zytux safety data are available for patients in moderate (NYHA class III) heart failure. During Zytux administration to patients with non-Hodgkin's lymphoma, cases may be occured in which pre-existing ischemic heart disease becomes manifest and leads to symptoms such as angina, myocardial infarction and atrial fibrillation and flutter.

For this reason, before treatment with Zytux, consideration should be given to the risk of cardiovascular complications due to infusion-related reactions in patients with a history of heart disease;during Zytux administration these patients must be closely monitored. Since hypotension may occur during Zytux infusion , consideration should be given to withholding antihypertensive medication for 12 hours before Zytux infusion. Treatment discontinuation should be considered in the event of severe infusion reactions.

Infections

After treatment with Zytux there is a potentially increased risk of infection(see Contraindications).

Zytux should not be administered to patients with active infection or severely impaired immunity (e.g. hypogammaglobulinemia , severely reduced CD4 or CD8 cell counts). Caution is advised when prescribing Zytux for patients with a history of recurrent or chronic infection or underlying disease that predisposes to severe infection. Patients acquiring an infection after Zytux treatment should be rapidly investigated and treated accordingly.

There are very rare cases of hepatitis B reactivation in patients with non-Hodgkin's lymphoma receiving rituximab in combination with cytostatic chemotherapy (see Warnings and precautions, Patients with non-Hodgkin's lymphoma).

Prior TNF inhibitor treatment

Treatment with etanercept must have been discontinued for at least 4weeks, and with infliximab or adalimumab for at least 8 weeks ,before starting Zytux treatment.

The efficacy and safety of Zytux in patients with renal or hepatic insufficiency have not been determined.

No data are available in patients with significant uncontrolled pulmonary disease. For this reason Zytux should be used with caution in such patients.

There are also no data available in patients with anemia (Hb <8.5 g/dl) or neutropenia (neutrophil count <1500/µl).

IMMUNIZATION

Physicians should review the vaccination status of candidates for Zytux treatment and observe local/national guidelines for adult vaccination against infectious disease. Vaccination should be completed at least 4 weeks before Zytux is first administered. Live vaccines are not recommended for patients with low B cell count.

INTERACTIONS

Coadministration with methotrexate has no influence on the pharmacokinetics of Zytux in patients with rheumatoid arthritis.

Patients with human antimouse antibody (HAMA) or HACA titres may display allergic or hypersensitivity reactions when additionally treated with other diagnostic or therapeutic monoclonal antibodies.

Coadministration with antihypertensive drugs may induce hypotensive effect of rituximab. Also coadministaration with hypoglycemic agents can increase their effect.

The tolerability of simultaneous or sequential combination of Zytux with chemotherapies other than CHOP or CVP or with other medicinal products that can cause depletion of normal B cells has not been adequately studied.

TNF inhibitors should not be administered for at least 8 weeks after completing treatment with Zytux.

Coadministration of rituximab with cisplatin may lead to increased risk of renal failure .

Avoid the concomitant use of rituximab with live virus or live attenuated virus vaccines.

PREGNANCY AND LACTATION

Non-Hodgkin’s Lymphoma and Chronic Lymphocytic Leukemia

Pregnancy

This drug is categorised in class C during pregnancy, so is administered only to the discretion of the attending physician and the mother’s definite need. Insufficient experience is available on the use of Zytux in pregnant women. However ,since class G immunoglobulins (IgG) can cross the placental

barrier , Zytux can cause to B cell depletion in the fetus. Due to the long retention time of Zytux in B cell-depleted patients ,women of childbearing age should use effective contraceptive methods during treatment with Zytux and for up to 12 months thereafter.

Lactation

It is not known whether rituximab is excreted in human breast milk or not , however as maternal IGg is excreted in breast milk .Since that rituximab is a large protein molecule and it will be degraded in the neonate's gastrointestinal tract, its absorption is possibly weak. However, due to the unavailability of adequate studies, mothers being treated with Zytux should not breast-feed.

Rheumatoid arthritis and Polyangiitis with granulomatosis (wegener's granulomatosis) and microscopic polyangiitis

Pregnancy

Use of methotrexate is contraindicated during pregnancy and lactation. Rituximab can cross the placental barrier and impair the fatal immune system. Only limited data are available on pregnant women receiving rituximab. Women of child-bearing age should use effective contraception during treatment with Zytux and up to one year thereafter.

Lactation

It is not known whether rituximab is excreted in human breast milk or not. However ,as maternal IGg is excreted in breast milk ,mothers being treated with Zytux should not breast-feed.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies have been performed on the effects of Zytux on the ability to drive and operate machinery . The pharmacological activity and adverse events observed to date suggest that such effects are unlikely. However, the premedication (antihistamines) used to prevent infusion reactions and the treatment of these infusion reactions should be borne in mind. After infusion reactions patients should not drive or operate machines until they have been stabilised.

UNDESIRABLE EFFECTS

Non-Hodgkin's lymphoma

Monotherapy:

Possible side effects associated with the use of Zytux as monotherapy in non-Hodgkin's lymphoma are listed below .Infusion-related adverse events, including fever, chils, nausea, urticaria, bronchospasm and dyspnea occur in a majority of patients under treatment with Zytux, in particular during the first infusion.

Table 1: Possible side effects in patients under treatment with Zytux as monotherapy

Organ class	Adeverse event
Blood ,lymphatic system	Anaemia, Leukopenia, Neutropenia, Thrombo-cytopenia ,Coagulation disorders, Lymphadenopathy
Metabolism ,nutritional disorders	Facial/peripheral edema, Elevated LDH, Hypocalcaemia, Weight loss ,Angioedema, Hyperglycemia
Psychiatric disorders	Anxiety, Agitation, Insomnia, Nervousness, Depression
Nervous system	Paraesthesia Hypoaesthesia Vasodilatation Dysgeusia Dizziness
Eye/visual disorders	Lacrimation disorder, Conjunctivitis
Ears and organ of balance	Ear pain ,Tinnitus
Cardiovascular system	Hypertension ,Arrhythmia, Tachycardia, Orthostatic hypotension, Hypotension, Bradycardia,
Respiratory,thoracic and /or sternal disorders	Dyspnea ,Chest pain, Airway disease, Bronchospasm ,Throat irritation, Rhinitis, Increased cough, Asthma, Bronchiolitis obliterans, Hypoxia,
Gastrointestinal tract	Dysphagia, Diarrhea Dyspepsia Anorexia Stomatitis Constipation Vomiting Abdominal pain Nausea ,Abdominal distension
Skin and subcutaneous tissue	Night sweats ,Sweating, Pruritus,Rash, Urticaria
Skeletal muscle, connective tissue,bone	Hypertonia, Myalgia, Arthralgia, Other pain
Other reactions	Back pain, Neck pain, Tumour pain,Other

	generalized pain,Fever , Chills, Asthenia, Headache, Pain at the injection site,Facial flushing ,Malaise,Feeling of clodness

Infusion-related adverse reactions:

Infusion-related signs and symptoms consisting of fever and chills/rigors occur in the majority of patients during the first infusion of Zytux. Other frequent infusion-related reactions include nausea, urticaria, fatigue, headache, pruritus, bronchospasm, dyspnea, a feeling of tongue or throat swelling (angioedema),rhinitis,vomiting,hypotension,flushing and pain at the disease sites. These reactions generally occur 30 minutes to 2 hours after the start of infusion and resolve after the infusion is slowed or interrupted and supportive treatment is given (IV physiological NaCl solution,diphenhydramine and paracetamol). The incidence of infusion-related reactions fall gradually during next infusions.

Infections:

B cell depletion occur in most patients treated with Zytux but only in a minority of patients this is associated with decreased serum immunoglobulins.

Hematological events:

There is risk of severe thrombocytopenia and sever neutropenia following treatment with Zytux. Incidence of pancytopenia,transient aplastic anemia and hemolytic anemia after Zytux therapy is rare.

Cardiovascular events:

Hypotension and hypertension are the most frequent possible adverse events. Incidence of severe arrhythmia and angina developed into myocardial infarction is very rare.

Special populations:

The incidence of adverse events and severe adverse events after treatment with Zytux is similar in elderly and younger patients.

High tumor burden:

Patients with a high tumor burden have a higher incidence of severe adverse events than those without a high tumor burden.But the incidence of any adverse events is similar in the two groups.

Retreatment:

No increase in the incidence of adverse events (nor in serious adverse events) is observed after retreatment with Zytux.

Zytux in combination with CVP chemotherapy:

The incidence of grade 3 and 4 clinical adverse events including fatigue and neutropenia is higher in patients receiving R-CVP (Zytux plus CVP)than in patients in the CVP treatment group.

Infusion –related reactions:

The signs and symptoms of severe or life-threatening infusion-related reactions, defined as starting during or within one day of Zytux infusion in patients treated with R-CVP, are consistent with the signs and symptoms observed during monotherapy with Zytux and included rigors, fatigue, dyspnea, dyspepsia, nausea, rash and flushing.

Infections:

The incidence of infections is similar in patients receiving Zytux plus CVP and patients receiving only CVP and the most common infections are upper airway infections .

Hematological laboratory abnormalities:

The incidence of grade 3 and 4 neutropenia is higher in patients under treatment with R-CVP than in patients under treatment with CVP but the higher incidence of neutropenia in R-CVP group does not result in any increase in infection incidence. No relevant difference is between the two treatment groups in grade 3 and 4 anemia and thrombocytopenia.

Cardiac effects:

The overall incidence of cardiac disorders is low with no relevant difference between patients under treatment with R-CVP and patients under treatment with CVP.

Maintenance therapy:

The incidence of some grade 3 and 4 adverse events in patients with relapsed or treatment-resistant follicular non-Hodgkin's lymphoma who are under treatment with Zytux in combination with CHOP chemotherapy(cyclophosphamide ,doxorubicin, vincristine and prednisone) is higher than those under treatment with only CHOP chemotherapy that is shown in table below.

Table 2:Possible grade 3 and 4 adverse events that may occur in patients under treatment with CHOP or R-CHOP

Organ class	Adverse Events
Infections and Infestations	Neutropenic infection,Sepsis,Urinary tract infection
Blood and lymphatic system	Neutropenia*,Leukopenia,Thrombocytopenia,Febrile

	neutropenia ,Hematotoxicity,Anemia
Immune system	Hypersensitivity*
metabolism ,nutritional disorders	Hyperglycemia
Nervous system	Sensory disorders
Cardio vascular system	Cardiological disorders*
Respiratory ,thoracic and/or sternal disorders	Dyspnea
Gastrointestinal tract	Nausea*,Vomiting,Abdominal pain,Diarrhea,Constipation*,Stomatitis*
Skin and subcutaneous tissue	Hair loss*,Skin changes*
Skeletal muscle,connective tissue,bone	Back pain*
General disorders and reactions at the administration site	Asthenia,Pyrexia

*The incidence of these adverse events is higher in patients under treatment with Zytux plus CHOP than in patients with only CHOP.

IF patients responded to the initial treatment mentioned above, Zytux can be used for them as maintenance therapy. Zytux maintenance therapy consists of a single infusion of Zytux 375 mg/ m^2 every 3 months and for a maximum of 2 years or untill disease progression.

The incidence of some grade 3 and 4 adverse events is higher in patients under treatment with Zytux maintenance therapy than follow-up patients that is shown in table below.

Table 3: Possible Grade 3 and 4 adverse events in patients on Zytux maintenance therapy or follow up.

Organ class	Adverse event
Infections and Infestations	Pneumonia*,Airway infections*
Blood and lymphatic system	Neutropenia*,Leukopenia*,Hematotoxicity
Nervous system	Sensory disorders
Cardio vascular system	Cardiological disorders*
Vascular system	Hypertension
Skin and subcutaneous tissue	Hair loss*
General disorders and reactions at the	Asthenia

administration site

* The incidence of these grade 3 and 4 adverse events is higher in the Zytux maintenance therapy group than follow-up group.

Infusion-related reactions:

During maintenance therapy with Zytux, non-serious signs and symptoms indicative of infusion-related reactions frequently occur in kind of general disorders including asthenia, fever, flu-like symptoms and pain.

In a few number of patients these infusion-related reactions are considered as immune system disorders(hypersensitivity).Severe infusion-related reactions in patients receiving Zytux maintenance therapy is very rare.

Infections:

The incidence of grade 1 to 4 infections in patients receiving Zytux maintenance therapy is higher than patients of follow-up group.In few cases infections like:pneumonia,airway infections,febrile infections,and herpes zoster occurs in patients receiving Zytux maintenance therapy.

Hematological events:

The incidence of leukopenia and grade 3 and 4 neutropenia is a little higher in patients receiving Zytux maintenance therapy than patients of follow-up group. Grade 3 and 4 thrombocytopenia may occur in few cases.

Cardiological disorders:

The incidence of grade 3 and 4 cardiological disorders is similar in patients with Zytux maintenance therapy and those of follow-up group. Serious cardiac disorders that may occur are consisted of: atrial fibrillation, myocardial infarction, left heart failure, myocardial ischemia.

IgG levels:

After induction therapy median IgG levels in both follow up and Zytux maintenance therapy groups are below the lower limit of normal(<7 g/l).In the follow-up group median IgG levels then increase to values above the lower limit of normal while remaining unchanged on Zytux treatment.

Zytux in combination with CHOP chemotherapy

The following table lists grade 3 and 4 adverse events(including grade 2 infections) occurring in patients on either treatment groups(Zytux plus CHOP or only CHOP).

Table 4: Possible Grade 3 and 4 adverse events(including grade 2 infections) in patients on either treatment groups(Zytux plus CHOP or only CHOP)

Organ class	Adverse event
Infections and Infestations	Bronchitis*,Unirary tract infections,Pneumonia,Sepsis,Herpes zoster*,Septic shock,Implant infections,Staphylococal septicemia,Pulmonary super infection,Acute bronchitis*,Pulmonary infections,Sinusitis*
Blood and lymphatic system	Febrile neutropenia, neutropenia ,Anemia
Endocrine disease	Inadequate diabetic control
Metabolism, nutritional disorders	Anorexia
Psychiatric disease	Confusion
Nervous system	Paresthesia
Investigations	Abnormal ejection fraction,Positive blood cultures
Cardiovascular system	Heart failure ,Atrial fibrillation*,pulmonary edema
Vascular disorders	Deep vein thrombosis of the limbs,Hypotension,Hypertension*,Venous thrombosis
Respiratory ,thoracic and/or sternal disorders	Dyspnea*,Cough,Rhinitis,Rhinorrhea
Gastrointestinal tract	Vomiting,Abdominal pain*,Constipation,Nause,Diarrhea
Skeletal muscle,connective tissue	Back pain
General disorders and reactions at the administration site	Fever,Prostration,Genral physical health deterioration,Mucosal inflammation,Chills*,Chest pain,Flu-like illness,Fall,Malaise,Multiorgan

	failure,Asthenia,Lower limb edema

*The incidence of these adverse events is higher in R-CHOP group than CHOP group.

Infusion-related reactions

Grade 3 and 4 infusion-related reactions occurs in approximately 9% of patients during the first R-CHOP treatment cycle. The incidence of all-grade infusion-related reactions decreases gradually during next treatment cycles. The signs and symptoms are consistent with those observed during monotherapy with Zytux and are consisted of fever ,chills, hypotension, ,tachycardia, dyspnea, bronchospasm, nausea, vomiting, pain and the features of tumor lysis syndrome.

Infections

The incidence of grade 2 to 4 fungal infections is higher in patients under treatment with R-CHOP than patients with CHOP. The incidence of herpes zoster infection, including ophthalmic herpes zoster, is higher in patients under treatment with R-CHOP than in CHOP group.

Hematologicaly:

After each treatment cycle, leukopenia and neutropenia occurs more frequently in the R-CHOP group than in the CHOP group. No difference is found between the two treatment groups in grade 3 and 4 anemia or thrombocytopenia. The time to recovery from all hematological abnormalities is similar in both treatment groups.

Cardiac events

The incidence of grade 3 and 4 cardiac arrhythmias, predominantly supraventricular arrhythmias such as tachycardia and atrial flutter/fibrillation, is higher in the R-CHOP group than in the CHOP group. All these arrhythmias either occurs in conjunction with Zytux infusion or are associated with predisposing factors such as fever, infection, acute myocardial infarction or pre-existing respiratory and cardiovascular disease. There is no difference between the R-CHOP group and CHOP group in the incidence of other grade 3 and 4 cardiac evevnts,including heart failure,myocardial disease and overt coronary artery disease.

Neurological events

In rare cases, there is risk of thromboembolic cerebrovascular accidents in patients with cardiovascular risk factors during treatment with R-CHOP or CHOP. There is no difference between the treatment two groups in the incidence of thromboembolic events.

RHEUMATOID ARTHRITIS

The most frequent adverse events attributed to the administration of Zytux 2×1000 mg,in patients with rheumatoid arthritis are acute infusion-related reactions that is more during the first infusion and decreases markedly in the second infusion.

Table 5:Possible adverse events in patients with rheumatoid arthritis under treatment with Zytux

Organ class	Adverse event
Acute infusion-related reactions*	Hypertension, Nausea, Skin rash, Pyrexia, Pruritis, Urticaria, Rhinitis, Throat irritation, Hot flash, Hypotension, Chills.
Infections and Infestations	All infections, Unirary tract infections, Upper airway infection, lower airway infection/pneumonia
General symptoms	Asthenia
Gastrointestinal tract	Dyspepsia, Epigrastic pain
Metabolism,nutritional disorders	Hypercholesterolemia
Skeletal muscle,connective tissue,bone	Joint pain/locomotor pain, muscle cramps, osteoarthritis
Nervous system	Paresthesia, Migraine

*Reactions occurring up to 24 hours after infusion.

In addition to the adverse events listed above,in rare cases, in patients under treatment with Zytux following medically relevant signs and symptoms may occur that are classified as potential reactions to treatment:

General symptoms: Generalised edema

Airway disorders : Bronchospasm, wheezing, laryngeal edema

Skin and subcutaneous tissue disorders: Angioneurotic edema, generalised pruritus

Immune system disorders : Anaphylaxis ,anaphylactoid reaction

Several treatment cycles

The adverse events profile after several treatment cycles is similar to that after first exposure. The incidence of acute infusion reactions after repeated treatment cycles is generally lower than after the first Zytux infusion.

Acute infusion-related reactions

Symptoms indicative of an acute infusion reaction (pruritus ,fever, urticaria/rash, chills, pyrexia,sneezing,angioneurotic edema,throat irritation,cough and bronchospasm-with or without concomitant hypertension or hypotension) are possible to occur after first exposure to Zytux. Premedication with a glucocorticoid administered IV decreases the incidence and severity of these reactions.

Infections

The incidence of infection in patients under treatment with Zytux is rare. Upper airway and urinary tract infections occurs most frequently.

SPECIAL REMARKS

Incompatibilities

No incompatibilities is observed between Zytux and polyvinyl chloride or polyethylene bags or infusion sets.

Interference with diagnostic methods

Possible effects on vaccination response and on diagnostic procedures based on antibody detection have not so far been studied.

Stability

This medicinal product must not be used after the expiry date(EXP) shown on the packaging.

SPECIAL INSTRUCTIONS FOR STORAGE

Store vials at 2-8˚C (in the refrigerator). Keep the container in the outer carton to protect it from light.

The prepared infusion solution of Zytux is physically and chemically stable for 24 hours at 2-8˚C and for 12 hours at 15˚C-25˚C. As Zytux contains no antimicrobial preservative ,the ready-to use preparation must,for microbiological reasons,be used immediately after dilution unless it has been prepared under controlled and validated aseptic conditions.

INSTRUCTIONS FOR HANDLING AND DISPOSAL

Zytux is a clear colorless liquid presented in sterile single use ,preservative and pyrogen-free vials.

Aseptically withdraw the necessary amount of Zytux and dilute to calculate rituximab concentration of 1 mg/ml in an infusion bag containing sterile pyrogrn free 0.9% aquous sodium chloride solution or 5% aquous glucose solution. To mix the solution , gently invert the bag to avoid foaming. Since the medicinal product does not contain any antimicrobial preservative or bacteriostatic agents,aseptic technique must be observed. Parenetral medicinal products should be inspected visually for particulate matter or discolouration prior to administration. After completion of treatment or expiry,unused medicinal product should be disposed of in accordance with local regulations.

PACKS

Vials of 10 ml(10 mg/ml):2 in each small package

Vials of 50 ml(10 mg/ml):1 in each small package

ATTENTION

This is a medicament which affects your health,and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor’s prescription ,the method of use and the instructions of the pharmacist who sold the medicament.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine :keep out of reach of children.