PRODUCT MONOGRAPH

PrZEVALIN®

Ibritumomab tiuxetan

Kit for the preparation of ^{90}Y-ibritumomab tiuxetan

Therapeutic radiopharmaceutical

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Date of Revision:
March 05, 2020

Submission Control No.: 196723

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	Kit for the preparation of ^{90}Y-ibritumomab tiuxetan / 3.2 mg ibritumomab tiuxetan in 2 mL 0.9% sodium chloride solution (1.6 mg/mL)	Human serum albumin *For a complete listing see* **DOSAGE FORMS, COMPOSITION AND PACKAGING** *section.*

DESCRIPTION

The ZEVALIN (ibritumomab tiuxetan) kit provides the non-radioactive components for the radiolabeling of ibritumomab tiuxetan with yttrium-90 (^{90}Y). Each ZEVALIN kit contains the following components: one ZEVALIN vial containing 3.2 mg of ibritumomab tiuxetan (murine IgG_1 monoclonal antibody produced in a Chinese Hamster Ovary (CHO) cell line by recombinant DNA technology and conjugated to the chelating agent MX-DTPA) in 2 mL of 0.9% sodium chloride solution; one 50 mM sodium acetate vial; one formulation buffer vial; one empty reaction vial and four identification labels.

Physical Characteristics

Yttrium-90 decays by emission of beta particles, with a physical half-life of 64.1 hours (2.67 days). The product of radioactive decay is non-radioactive zirconium-90. The range of beta particles in soft tissue (χ_{90}) is 5 mm. Radiation emission data for ^{90}Y are summarized in Table 1.

Table 1: Principal ^{90}Y Radiation Emission Data

Radiation	Mean % per Disintegration	Mean Energy (keV)
Beta minus	100	750-935

External Radiation

The exposure rate for 37 MBq (1 mCi) of ^{90}Y is 8.3 x 10^{-3} Ci/kg/hr (32 R/hr) at the mouth of an open ^{90}Y vial. Adequate shielding should be used with this beta emitter, in accordance with institutional good radiation safety practices.

To allow correction for physical decay of ^{90}Y, the fractions that remain at selected intervals before and after the time of calibration are shown in Table 2.

Table 2: Physical Decay Chart: ^{90}Y Half-Life 2.67 Days (64.1 Hours)

Calibration Time (Hrs.)	Fraction Remaining	Calibration Time (Hrs.)	Fraction Remaining
-36	1.48	0	1.00
-24	1.30	1	0.99
-12	1.14	2	0.98
-8	1.09	3	0.97
-7	1.08	4	0.96
-6	1.07	5	0.95
-5	1.06	6	0.94
-4	1.04	7	0.93
-3	1.03	8	0.92
-2	1.02	12	0.88
-1	1.01	24	0.77
0	1.00	36	0.68

INDICATIONS AND CLINICAL USE

ZEVALIN (ibritumomab tiuxetan), as part of the ZEVALIN therapeutic regimen, is indicated for the treatment of patients with relapsed or refractory low-grade or follicular, CD20 positive, B-cell non-Hodgkin's lymphoma, including patients with rituximab-refractory follicular non-Hodgkin's lymphoma.

CONTRAINDICATIONS

ZEVALIN (ibritumomab tiuxetan) is contraindicated in patients with known type I hypersensitivity or anaphylactic reactions to murine proteins or to any component of the ZEVALIN therapeutic regimen, including yttrium chloride and rituximab. ZEVALIN is also contraindicated in pregnant or nursing women (see **WARNINGS AND PRECAUTIONS – Special Populations**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

^{90}Y-ZEVALIN (ibritumomab tiuxetan) is a radiopharmaceutical and should be used only by physicians and other professionals qualified by training and experienced in the safe use and handling of radionuclides (see **DOSAGE AND ADMINISTRATION – Instructions for Preparation and Use**).

Fatal infusion reactions with rituximab: Deaths have occurred within 24 hours of rituximab infusion, an essential component of the ZEVALIN therapeutic regimen. Approximately 80% of fatal infusion reactions occurred in association with the first rituximab infusion. These fatalities were associated with an infusion reaction symptom complex that included hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation or cardiogenic shock. Patients who develop severe infusion reactions should have rituximab and ^{90}Y-ZEVALIN infusions discontinued and receive medical treatment (see **WARNINGS AND PRECAUTIONS – Sensitivity/Resistance** and **ADVERSE REACTIONS**).

Prolonged and severe cytopenias: ^{90}Y-ZEVALIN administration can result in severe and prolonged cytopenias, especially when administered after prior radiation or multiple chemotherapies. The risk of hematological toxicity may be increased when ZEVALIN is administered shortly (< 4 months) after prior therapy with fludarabine-containing regimens (see **DRUG INTERACTIONS**). The ZEVALIN therapeutic regimen should not be administered to patients with ≥ 25% lymphoma marrow involvement and/or impaired bone marrow reserve (see **WARNINGS AND PRECAUTIONS – Hematologic** and **ADVERSE REACTIONS**).

Severe mucocutaneous reactions: Severe mucocutaneous reactions, some with fatal outcome, have been reported in association with the ZEVALIN therapeutic regimen, which includes rituximab and ^{90}Y-ZEVALIN. Patients who develop a severe mucocutaneous reaction should have rituximab and ^{90}Y-ZEVALIN infusions discontinued and receive medical treatment (see **WARNINGS AND PRECAUTIONS – Skin** and **ADVERSE REACTIONS**).

Dosing: The prescribed, measured and administered dose of ^{90}Y-ZEVALIN should not exceed the absolute maximum allowable dose of 32.0 mCi (1200 MBq) (see **DOSAGE AND ADMINISTRATION**).

General

^{90}Y-ZEVALIN should be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals (for radiopharmaceutical precautions see **DOSAGE AND ADMINISTRATION** – **Instructions for Preparation and Use**). Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

ZEVALIN may be received, used and administered only by authorized persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of local competent official organizations.

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

Because the ZEVALIN therapeutic regimen includes the use of rituximab (see DOSAGE AND ADMINISTRATION), please also consult the prescribing information for RITUXAN (rituximab) and follow instructions carefully.

The ZEVALIN therapeutic regimen is intended as a single course treatment. The safety and toxicity profile from multiple courses of the ZEVALIN therapeutic regimen or of other forms of therapeutic irradiation preceding, following or in combination with the ZEVALIN therapeutic regimen have not been established.

^{90}Y-ZEVALIN solution must not be administered to patients who are likely to develop life-threatening hematological toxicity signs.

Carcinogenesis and Mutagenesis

Out of 349 patients treated with the ZEVALIN therapeutic regimen, three cases of acute myelogenous leukemia and two cases of myelodysplastic syndrome have been reported following the ZEVALIN therapeutic regimen (see **ADVERSE REACTIONS**).

No long-term animal studies have been performed to establish the carcinogenic or mutagenic potential of the ZEVALIN therapeutic regimen. However, radiation is a potential carcinogen or mutagen.

Contamination

The contents of the ZEVALIN kit are not radioactive. However, during and after radiolabeling of ZEVALIN with ^{90}Y, care should be taken to minimize radiation exposure to patients and to medical personnel, consistent with institutional good radiation safety practices and patient management procedures.

General Disorders and Administration Site Conditions

Close monitoring for evidence of extravasation during the injection of ZEVALIN is required in order to avoid radiation-associated tissue damage. If any signs or symptoms of extravasation have occurred, the infusion should be immediately terminated and restarted in another vein. If possible extravasation is suspected, the physician should be informed.

Hematologic

The most common severe adverse events reported with the ZEVALIN therapeutic regimen were thrombocytopenia (61% of patients with platelet counts < 50,000 cells/mm^3) and neutropenia (57% of patients with absolute neutrophil count [ANC] < 1,000 cells/mm^3) in patients with ≥ 150,000 platelets/mm^3 prior to treatment. Both incidences of severe thrombocytopenia and neutropenia increased to 78% and 74% for patients with mild thrombocytopenia at baseline (platelet count of 100,000 to 149,000 cells/mm^3). For all patients, the median time to nadir was

seven to nine weeks and the median duration of cytopenias was 22-35 days. In < 5% of cases, patients experienced severe cytopenia that extended beyond the prospectively defined protocol treatment period of 12 weeks following administration of the ZEVALIN therapeutic regimen. Some of these patients eventually recovered from cytopenia, while others experienced progressive disease, received further anti-cancer therapy or died of their lymphoma without having recovered from cytopenia. The cytopenias may have influenced subsequent treatment decisions (see **ADVERSE REACTIONS**).

Hemorrhage, including fatal cerebral hemorrhage, and severe infections, some with fatal outcome, have occurred in a minority of patients in clinical studies and in post-marketing experience . Careful monitoring for and management of cytopenias and their complications (eg, febrile neutropenia, hemorrhage) for up to three months after use of the ZEVALIN therapeutic regimen are necessary. Caution should be exercised in treating patients with drugs that interfere with platelet function or coagulation (eg, ASA, NSAIDs and COX-2 inhibitors) following the ZEVALIN therapeutic regimen, and patients receiving such agents should be closely monitored.

The ZEVALIN therapeutic regimen should not be administered to patients with ≥ 25% lymphoma marrow involvement and/or impaired bone marrow reserve, eg, due to prior myeloablative therapies; platelet count < 100,000 cells/mm^3; neutrophil count < 1,500 cells/mm^3; hypocellular bone marrow (≤ 15% cellularity or marked reduction in bone marrow precursors) or to patients with a history of failed stem cell collection, as safety and efficacy have not been established.

The risk of hematological toxicity may be increased after prior therapy with fludarabine-containing regimens (for details see **DRUG INTERACTIONS – Drug-Drug Interactions**).

Special caution is required with respect to bone marrow depletion. In most patients administration of ZEVALIN (after pretreatment with rituximab) results in severe and prolonged cytopenia which is generally reversible (see **ADVERSE REACTIONS – Abnormal Hematologic and Clinical Chemistry Findings**). Complete blood cell and platelet counts must be monitored weekly following ZEVALIN treatment until levels recover or as clinically indicated.

Immune

The safety and efficacy of immunization with any vaccine, particularly live viral vaccines, following the ZEVALIN therapeutic regimen have not been studied. Due to the potential risk of developing viral infections, it is not recommended to administer live viral vaccines to patients who have recently received ZEVALIN (see **DRUG INTERACTIONS – Drug-Drug Interactions**). A potentially limited ability of patients to generate a primary or anamnestic humoral response to any vaccine following ZEVALIN treatment has to be taken into consideration.

Patients must not receive growth factor treatment such as G-CSF for 3 weeks prior to ZEVALIN administration as well as for 2 weeks following completion of the treatment in order to assess the adequate bone marrow reserve correctly and because of the potential sensitivity of rapidly dividing myeloid cells to radiation (see **DRUG INTERACTIONS – Drug-Drug Interactions**).

Neurologic

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

ZEVALIN could affect the ability to drive and to use machines, as dizziness has been reported as a common side effect.

Sensitivity/Resistance

Infusion reactions may occur during or following ZEVALIN administration after pretreatment with rituximab. Signs and symptoms of infusion reactions may include dizziness, cough, nausea, vomiting, rash, pruritus, tachycardia, asthenia, pyrexia, and rigors (see **ADVERSE REACTIONS**). In case of a potential severe infusion reaction, treatment must be stopped immediately.

Hypersensitivity reactions following ZEVALIN administration are commonly observed. Severe hypersensitivity reactions including anaphylaxis occur in less than 1% of patients (see **ADVERSE REACTIONS** – **Immunogenicity**). In case of hypersensitivity reactions, ZEVALIN infusion must be stopped immediately. Medications for the treatment of hypersensitivity reactions, eg, epinephrine, antihistamines and corticosteroids, should be available for immediate use in the event of an allergic reaction during administration of the ZEVALIN therapeutic regimen. Patients who have received murine-derived proteins before ZEVALIN treatment should be screened for human anti-mouse antibodies.

Patients with evidence of HAMA have not been studied and may be at increased risk of allergic or serious hypersensitivity reactions during ZEVALIN therapeutic regimen administration.

After the use of ZEVALIN, patients should generally be tested for HAMA before any further treatment with mouse-derived proteins.

Sexual Function/Reproduction

The ZEVALIN therapeutic regimen results in a significant radiation dose to the testes. The radiation dose to the ovaries has not been established. There have been no studies to evaluate whether the ZEVALIN therapeutic regimen causes hypogonadism, premature menopause, azoospermia and/or mutagenic alterations to germ cells. There is a potential risk that ionizing radiation by ^{90}Y-ZEVALIN could cause toxic effects on the male and female gonads. Therefore it is recommended that women of childbearing potential, as well as males, use effective contraceptive methods during and up to 12 months following the ZEVALIN therapeutic regimen. Patients planning to have children should be informed accordingly.

Skin

Severe mucocutaneous skin reactions of erythema multiforme (including Stevens-Johnson syndrome) have been reported postmarketing with the administration of ZEVALIN after pretreatment with rituximab. The onset of the reactions varied from days to months. Although the incidence is rare, the fatality associated with the administration of the ZEVALIN therapeutic regimen that included renal failure progressing to death (observed in one report of postmarketing experience) is clinically relevant. In patients experiencing a severe mucocutaneous reaction, treatment must be discontinued.

Special Populations

Pregnant Women: ^{90}Y-ZEVALIN can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. Since IgGs are known to cross the placenta and because of the significant risk associated with the use of radiation, ZEVALIN is contraindicated during pregnancy (see **CONTRAINDICATIONS**). Pregnancy must be excluded before the start of treatment in women.

Nursing Women: It is not known whether ZEVALIN is excreted in human milk. Since maternal IgGs are excreted in human milk and because of the unknown potential for absorption and immunosuppression in the infant, women must not breastfeed during treatment and for 12 months following treatment. Formula feeding should be substituted for breastfeeding.

Pediatrics (< 18 years of age): The safety and effectiveness of the ZEVALIN therapeutic regimen in children have not been established.

Geriatrics (> 65 years of age): Of 349 patients treated with the ZEVALIN therapeutic regimen in clinical studies, 38% (132 patients) were 65 years of age or over, while 12% (41 patients) were 75 years of age or over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Patients with CNS Lymphoma: Patients with follicular NHL may present with CNS involvement. These patients were excluded from clinical trials because they require different treatment modalities. Since ZEVALIN may not cross the blood brain barrier, the efficacy has not been established in these patients. The use of ZEVALIN is therefore not recommended in NHL patients with CNS involvement.

Patients with renal impairment: The safety and effectiveness in patients with renal impairment have not been established.

Patients with hepatic impairment: The safety and effectiveness in patients with hepatic impairment have not been established.

Monitoring and Laboratory Tests

Complete blood counts (CBCs) and platelet counts should be obtained weekly following the ZEVALIN therapeutic regimen and should continue until levels recover. CBCs and platelet

counts should be monitored more frequently in patients who develop severe cytopenia, or as clinically indicated.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Safety data, except where indicated, are based upon 349 patients treated in five clinical studies with the ZEVALIN (ibritumomab tiuxetan) therapeutic regimen (see **DOSAGE AND ADMINISTRATION**). Because the ZEVALIN therapeutic regimen includes the use of rituximab, please also consult the prescribing information for RITUXAN (rituximab) for adverse reactions observed with rituximab alone.

The most serious adverse reactions caused by the ZEVALIN therapeutic regimen include infections (predominantly bacterial in origin), allergic reactions (bronchospasm and angioedema), hemorrhage while thrombocytopenic (resulting in death), and severe and prolonged cytopenias. Severe mucocutaneous reactions were also reported in postmarketing surveillance. In addition, patients who have received the ZEVALIN therapeutic regimen have developed myeloid malignancies and dysplasias. Fatal infusion reactions have occurred following the infusion of rituximab. Please refer to the **WARNINGS AND PRECAUTIONS** section for detailed descriptions of these reactions.

The most common toxicities reported were neutropenia, thrombocytopenia, leukocytopenia, anemia, infections, fever, asthenia, chills, gastrointestinal symptoms (nausea, vomiting, abdominal pain and diarrhea), increased cough, dyspnea, dizziness, arthralgia, anorexia, anxiety and ecchymosis. Hematologic toxicity was often severe and prolonged, whereas most non-hematologic toxicity was mild in severity.

Clinical Trial Adverse Drug Reactions

Table 3 and Table 4 list adverse events that occurred in ≥ 5% of patients and in ≥ 1% and ≤ 5% of patients, respectively. A more detailed description of the incidence and duration of hematologic toxicities, according to baseline platelet count (as an indicator of bone marrow reserve), is provided in Table 5, Severe Hematologic Toxicity.

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 3: Incidence of Adverse Events in ≥ 5% of Patients Receiving the ZEVALIN Therapeutic Regimen[a] (N = 349)

	All Grades %	Grade 3/4 %
Any Adverse Event	**99**	**89**
Body as a whole	**80**	**12**
Asthenia	43	3
Infection	29	5
Chills	24	< 1
Fever	17	1
Abdominal pain	16	3
Pain	13	1
Headache	12	1
Throat irritation	10	0
Back pain	8	1
Flushing	6	0
Cardiovascular system	**17**	**3**
Hypotension	6	1
Digestive system	**48**	**3**
Nausea	31	1
Vomiting	12	0
Diarrhea	9	< 1
Anorexia	8	0
Abdominal enlargement	5	0
Constipation	5	0
Hemic and lymphatic system	**98**	**86**
Thrombocytopenia	95	63
Neutropenia	77	60
Anemia	61	17
Ecchymosis	7	< 1
Metabolic and nutritional disorders	**23**	**3**
Peripheral edema	8	1
Angioedema	5	< 1
Musculoskeletal system	**18**	**1**
Arthralgia	7	1
Myalgia	7	<1
Nervous system	**27**	**2**
Dizziness	10	< 1
Insomnia	5	0
Respiratory system	**36**	**3**
Dyspnea	14	2
Increased cough	10	0
Rhinitis	6	0
Bronchospasm	5	0
Skin and appendages	**28**	**1**
Pruritus	9	< 1
Rash	8	< 1
Special senses	**7**	< **1**
Urogenital system	**6**	< **1**

a Adverse events were followed for a period of 12 weeks following the first rituximab infusion of the ZEVALIN therapeutic regimen.

Note: All adverse events are included, regardless of causality.

The following adverse events were reported in ≥ 1% and < 5% of patients.

Table 4: Incidence of Adverse Events in ≥ 1% and < 5% of Patients Receiving the ZEVALIN Therapeutic Regimen[a] (N = 349)

	%
Body as a Whole	
Chest pain	4.3
Enlarged abdomen	2.9
Pain neck	2.6
Malaise	2.3
Allergic reaction	2.0
Cellulitis	1.7
Flu syndrome	1.7
Tumour pain	1.7
Sepsis	1.4
Moniliasis	1.1
Axilla pain	1.1
Injection site pain	1.1
Cardiovascular System	
Tachycardia	2.9
Hypertension	2.3
Palpitation	1.1
Digestive System	
Dyspepsia	3.7
Dry mouth	2.0
Melena	2.0
Gastrointestinal disorder	1.7
Stomatitis	1.7
Rectal hemorrhage	1.4
Oral moniliasis	1.4
Dysphagia	
Gastrointestinal hemorrhage	1.1
Gum hemorrhage	1.1
	1.1
Hemic and Lymphatic System	
Petechia	3.4
Febrile neutropenia	
Pancytopenia	2.6
Lymphadenopathy	2.0
	1.1
Metabolic and Nutritional Disorders	
Increased lactic dehydrogenase	3.7
Hyperglycemia	2.9
Dehydration	2.3
Increased SGOT	2.3
Increased BUN	2.0
Increased alkaline phosphatase	2.0
Hypocalcemia	1.7
Increased SGPT	1.7
Increased creatinine	1.4
Edema	1.4
Decreased weight	1.4
Hypokalemia	1.1
Hypoproteinemia	1.1
Musculoskeletal System	
Bone pain	2.6
Leg cramps	2.0

Table 4: Incidence of Adverse Events in ≥ 1% and < 5% of Patients Receiving the ZEVALIN Therapeutic Regimen[a] (N = 349)

	%
Myasthenia	1.4
Nervous System	
Anxiety	3.7
Hypesthesia	2.6
Paresthesia	2.6
Depression	2.3
Somnolence	2.0
Agitation	1.1
Vasodilation	1.1
Respiratory System	
Sinusitis	4.9
Epistaxis	2.9
Bronchitis	1.7
Pneumonia	1.7
Voice alteration	1.7
Pleural effusion	1.4
Pharyngitis	1.1
Skin and Appendages	
Urticaria	4.0
Sweats	3.7
Night sweats	3.2
Skin disorder	2.3
Herpes simplex	1.7
Herpes zoster	1.1
Special Senses	
Conjunctivitis	2.9
Alopecia	1.1
Abnormal vision	1.1
Urogenital System	
Dysuria	1.1
Urinary incontinence	1.1

a Adverse events were followed for a period of 12 weeks following the first rituximab infusion of the ZEVALIN therapeutic regimen.

Note: All adverse events are included, regardless of causality.

Severe or life-threatening adverse events occurring in 1% to 5% of patients consisted of pancytopenia (2%), allergic reaction (1%), gastrointestinal hemorrhage (1%), melena (1%), tumour pain (1%) and apnea (1%). The following severe or life-threatening events occurred in < 1% of patients: angioedema, tachycardia, urticaria, arthritis, lung edema, pulmonary embolus, encephalopathy, hematemesis, subdural hematoma and vaginal hemorrhage. Fatal outcome has been observed with the following events either in clinical trials or in postmarketing experience: anemia, pancytopenia, hemorrhage while thrombocytopenic, infection, pneumonia, sepsis, myelodysplastic syndrome/acute myelogenous leukemia, severe mucocutaneous skin reactions and intracranial hemorrhage while thrombocytopenic.

Abnormal Hematologic and Clinical Chemistry Findings

Hematologic toxicity was the most frequently observed adverse event in clinical trials and is dose-limiting. Thrombocytopenia, leukocytopenia, neutropenia and anemia have been reported

very commonly as adverse drug reactions. Also, febrile neutropenia, pancytopenia and lymphocytopenia have been reported as common adverse drug reactions. Table 5 presents the incidence and duration of severe hematologic toxicity for patients with a normal baseline platelet count (≥ 150,000 cells/mm^3) treated with the ZEVALIN therapeutic regimen and patients with mild thrombocytopenia (platelet count 100,000 to 149,000 cells/mm^3) at baseline who were treated with a modified ZEVALIN therapeutic regimen that included a lower specific activity ^{90}Y-ZEVALIN dose at 0.3 mCi/kg (11 MBq/kg).

Table 5: Severe Hematologic Toxicity Observed in Clinical Trials with ZEVALIN

	ZEVALIN Therapeutic Regimen Using 0.4 mCi/kg ^{90}Y Dose (15 MBq/kg)	**Modified ZEVALIN Therapeutic Regimen Using 0.3 mCi/kg ^{90}Y Dose (11 MBq/kg)**
ANC		
Median nadir (cells/mm^3)	800	600
Per patient incidence: ANC < 1,000 cells/mm^3	57%	74%
Per patient incidence: ANC < 500 cells/mm^3	30%	35%
Median duration (days)[a]: ANC < 1,000 cells/mm^3	22	29
Platelets		
Median nadir (cells/mm^3)	41,000	24,000
Per patient incidence: platelets < 50,000 cells/mm^3	61%	78%
Per patient incidence: platelets < 10,000 cells/mm^3	10%	14%
Median duration (days)[b]: platelets < 50,000 cells/mm^3	24	35

a Median duration of neutropenia for patients with ANC < 1,000 cells/mm^3 (date from last laboratory value showing ANC ≥ 1,000 cells/mm^3 to date of first laboratory value following nadir showing ANC ≥ 1,000 cells/mm^3, censored at initiation of next treatment or death).

b Median duration of thrombocytopenia for patients with platelets < 50,000 cells/mm3 (date from last laboratory value showing platelet count ≥ 50,000 cells/mm3 to date of first laboratory value following nadir showing platelet count ≥ 50,000 cells/mm3, censored at initiation of next treatment or death).

Median time to ANC nadir was 62 days, to platelet nadir, 53 days, and to hemoglobin nadir, 68 days. In clinical trials with the indication of relapsed and refractory NHL, grade 3 or 4 thrombocytopenia was reported with median times to recovery of 13 and 21 days and grade 3 or 4 neutropenia with median times to recovery of 8 and 14 days. Information on growth factor use and platelet transfusions is based on 211 patients for whom data were collected. Filgrastim was given to 13% of patients and erythropoietin to 8%. Platelet transfusions were given to 22% of patients and red blood cell transfusions to 20%.

Infections and Infestations

During the first three months after initiating the ZEVALIN therapeutic regimen, 29% of patients developed infections. Three percent of patients developed serious infections comprising urinary tract infection, febrile neutropenia, sepsis, pneumonia, cellulitis, colitis, diarrhea, osteomyelitis and upper respiratory tract infection. Life-threatening infections were reported in 2% of patients, including sepsis, empyema, pneumonia, febrile neutropenia, fever, and biliary stent-associated cholangitis. During follow-up from three months to four years after the start of treatment with ZEVALIN, 6% of patients developed infections. Two percent of patients had serious infections comprising urinary tract infection, bacterial or viral pneumonia, febrile neutropenia, perihilar infiltrate, pericarditis and intravenous drug-associated viral hepatitis. One percent of patients had life-threatening infections that included bacterial pneumonia, respiratory disease and sepsis.

Some of these infectious events have been associated with a fatal outcome. Infections may be bacterial, fungal or viral, including reactivation of latent viruses.

Secondary Malignancies

A total of 2% of patients developed secondary malignancies following the ZEVALIN therapeutic regimen. One patient developed a grade 1 meningioma, three developed acute myelogenous leukemia, and two developed a myelodysplastic syndrome. The onset of a second cancer was 8-34 months following the ZEVALIN therapeutic regimen and 4-14 years following the patients' diagnosis of NHL.

Immunogenicity

Hypersensitivity reactions following ZEVALIN administration are commonly observed. Severe (grade 3/4) hypersensitivity reactions including anaphylaxis occur in less than 1% of patients (see **WARNINGS AND PRECAUTIONS – Immune**).

Of 211 patients who received the ZEVALIN therapeutic regimen in clinical trials and who were followed for 90 days, there were eight (3.8%) patients with evidence of human anti-mouse antibodies (HAMA) (n = 5) or human anti-chimeric antibodies (HACA) (n = 4) at any time during the course of the study. Two patients had low titers of HAMA prior to initiation of the ZEVALIN therapeutic regimen; one remained positive without an increase in titer while the other had a negative titer post-treatment. Three patients had evidence of HACA responses prior to initiation of the ZEVALIN therapeutic regimen; one had a marked increase in HACA titer while the other two had negative titers post-treatment. Of the three patients who had negative HAMA or HACA titers prior to the ZEVALIN therapeutic regimen, two developed HAMA in absence of HACA titers, and one had both HAMA and HACA positive titers post-treatment. Evidence of immunogenicity may be masked in patients who are lymphopenic. There has not been adequate evaluation of HAMA and HACA at delayed timepoints, concurrent with the recovery from lymphopenia at 6-12 months, to establish whether masking of the immunogenicity at early timepoints occurs. The data reflect the percentage of patients whose test results were considered positive for antibodies to ibritumomab or rituximab using kinetic enzyme immunoassays to ibritumomab and rituximab. The observed incidence of antibody positivity in an assay is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors including sample handling and concomitant medications. Comparisons of the incidence of HAMA/HACA with the ZEVALIN therapeutic regimen to the incidence of antibodies with other products may be misleading.

Post-Market Adverse Drug Reactions

Skin and Subcutaneous Tissue Disorders

Severe mucocutaneous skin reactions of erythema multiforme (including Stevens-Johnson syndrome) have been reported (3 reports / 3757 commercially treated patients = 0.08%) with the administration of ZEVALIN after pretreatment with rituximab. Although the incidence is rare, the fatality associated with the administration of ZEVALIN after pretreatment with rituximab that included renal failure progressing to death (observed in one report of postmarketing experience) is clinically relevant.

General Disorders and Administration Site Conditions

Reports of extravasation with subsequent infusion site reaction, such as infusion site dermatitis, infusion site desquamation, and infusion site ulcer, have been received.

ZEVALIN-associated radiation might cause damage to lymphoma-surrounding tissue and complications due to lymphoma swelling.

DRUG INTERACTIONS

Drug-Drug Interactions

No formal drug interaction studies have been performed with ZEVALIN. Due to the frequent occurrence of severe and prolonged thrombocytopenia, the potential benefits of medications that interfere with platelet function and/or anticoagulation should be weighed against the potential increased risks of bleeding and hemorrhage. Patients receiving medications that interfere with platelet function or coagulation (eg, ASA, NSAIDs and COX-2 inhibitors) should have more frequent laboratory monitoring for thrombocytopenia. In addition, the transfusion practices for such patients may need to be modified given the increased risk of bleeding.

In a clinical trial it has been shown that the use of fludarabine-containing regimens within 4 months before ZEVALIN treatment may increase the risk of hematological toxicity (see also **WARNINGS AND PRECAUTIONS – Hematologic**).

Growth factor treatment such as G-CSF must not be given to patients for 3 weeks prior to ZEVALIN administration as well as for 2 weeks following completion of the treatment (see **WARNINGS AND PRECAUTIONS – Immune**).

The safety and efficacy of immunization with any vaccine, particularly live viral vaccines, following therapy with ZEVALIN have not been studied (see **WARNINGS AND PRECAUTIONS – Immune**).

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The prescribed, measured and administered dose of ^{90}Y-ZEVALIN must not exceed the absolute maximum allowable dose of 32.0 mCi (1,200 MBq), regardless of the patient's body weight. Do not give ^{90}Y-ZEVALIN to patients with a platelet count < 100,000/mm^3 (see WARNINGS AND PRECAUTIONS).

Recommended Dose and Dosage Adjustment

The ZEVALIN (ibritumomab tiuxetan) therapeutic regimen is administered in two steps: step 1 is a single intravenous infusion of 250 mg/m^2 of rituximab (not included in the ZEVALIN kit). Step 2 follows step 1 by seven to nine days and consists of a second infusion of 250 mg/m^2 of rituximab shortly (within 4 hours) prior to 0.4 mCi/kg of ^{90}Y-ZEVALIN administered as a ten-minute IV push.

ZEVALIN therapeutic regimen dose modification in patients with mild thrombocytopenia: The ^{90}Y-ZEVALIN dose should be reduced to 0.3 mCi/kg (11 MBq/kg) for patients with a baseline platelet count between 100,000 and 149,000 cells/mm^3.

Note that the dose of rituximab is lower when used as part of the ZEVALIN therapeutic regimen, as compared to the dose of rituximab when used as a single agent. Do not administer rituximab as an intravenous push or bolus.

Hypersensitivity reactions may occur. Premedication, consisting of acetaminophen and diphenhydramine, should be considered before each infusion of rituximab (see **WARNINGS AND PRECAUTIONS**).

ZEVALIN is supplied as a kit that contains all of the non-radioactive ingredients necessary to produce a single-unit dose of ZEVALIN for labeling with ^{90}Y for therapy.

^{90}Y chloride sterile solution will be shipped directly from the manufacturer upon placement of an order for the ZEVALIN kit. Rituximab must be ordered separately and is available through hospital pharmacies.

^{90}Y-ZEVALIN is a radiopharmaceutical and should be used only by physicians and other professionals qualified by training and experienced in the safe use and handling of radionuclides. **Changing the ratio of any of the reactants in the radiolabeling process may adversely affect therapeutic results and is not recommended. ^{90}Y-ZEVALIN should not be used in the absence of the rituximab pre-dose.**

Data on the retreatment of patients with ^{90}Y-ZEVALIN are not available.

Administration

The patient dose should be measured by a suitable radioactivity calibration system prior to administration.

The ^{90}Y-ZEVALIN solution must be prepared according to the section **DOSAGE AND ADMINISTRATION** – **Instructions for Preparation and Use.**

Before administration to the patient, the percent radioincorporation of the prepared ^{90}Y-ZEVALIN must be checked according to the procedure outlined in the section **DOSAGE AND ADMINISTRATION** – **Directions for Quality Control**.

If the average radiochemical purity is less than 95%, the preparation must not be administered.

The prepared infusion solution must be given as a slow intravenous administration over 10 minutes. The infusion must not be administered as an intravenous bolus.

No incompatibilities have been observed between ZEVALIN and infusion sets.

Step 1:

First rituximab infusion: Rituximab at a dose of 250 mg/m^2 should be administered intravenously at an initial rate of 50 mg/hr. Rituximab should not be mixed or diluted with other drugs. If hypersensitivity or infusion-related events 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 event develops, the infusion should be temporarily slowed or interrupted (see **WARNINGS AND PRECAUTIONS**). The infusion can continue at one-half the previous rate upon improvement of patient symptoms. Refer to the prescribing information of rituximab for detailed guidance on its use.

Step 2:

Step 2 of the ZEVALIN therapeutic regimen is initiated seven to nine days following step 1 administration.

Second rituximab infusion: Rituximab at a dose of 250 mg/m^2 is administered intravenously at an initial rate of 100 mg/hr (50 mg/hr if infusion-related events were documented during the first rituximab administration) and increased by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr, as tolerated.

^{90}Y-ZEVALIN injection: Within four hours following completion of the rituximab dose, ^{90}Y-ZEVALIN at a dose of 0.4 mCi/kg (15 MBq/kg) actual body weight for patients with a platelet count ≥150,000 cells/mm^3, and 0.3 mCi/kg (11 MBq/kg) actual body weight for patients with a platelet count of 100,000 to 149,000 cells/mm^3 is injected intravenously over a period of ten minutes. ^{90}Y- ZEVALIN may be infused directly by stopping the flow from an infusion bag and administering it directly into the line. A 0.2 or 0.22-micrometer low-protein-binding membrane filter should be in line between the syringe and the infusion port prior to injection of ^{90}Y-ZEVALIN. After injection, the line should be flushed with at least 10 mL of 0.9% sodium chloride solution. Precautions should be taken to avoid extravasation. A free-flowing intravenous line should be established prior to ^{90}Y-ZEVALIN injection. Close monitoring for evidence of extravasation during the injection of ^{90}Y-ZEVALIN is required. If any signs or symptoms of extravasation occur, the infusion should be immediately terminated and restarted in another vein.

Instructions for Preparation and Use

The ZEVALIN carton is to be used by a qualified specialist to prepare a single dose of ^{90}Y-ZEVALIN for therapy. **Changing the ratio of any of the reactants in the radiolabeling process may adversely affect therapeutic results and is not recommended. ZEVALIN must not be mixed with other drugs.**

Read all directions thoroughly and assemble all materials before starting the radiolabeling procedure.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration. The dose calibrator must be operated in accordance with the manufacturer's specifications and quality control for the measurement of ^{90}Y.

Proper aseptic technique and precautions for handling radioactive materials should be employed. Waterproof gloves should be utilized during the preparation and determination of radiochemical purity of ^{90}Y-ZEVALIN. Appropriate shielding should be used during radiolabeling and use of a syringe shield is recommended during administration to the patient. The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spills of urine, vomiting, etc. Radiation protection precaution in accordance with local regulations must therefore be taken. Any unused product or waste material should be disposed of in accordance with local requirements. Contaminated materials must be disposed of as radioactive waste by the authorized route.

The radiolabeling of ZEVALIN shall be done according to the following directions.

Required materials not supplied in the carton:

A. ^{90}Y chloride sterile solution (^{90}Y chloride)
B. Three sterile 1-mL syringes
C. One sterile 3-mL syringe
D. Two sterile 10-mL syringes with 18 - 20 G needles
E. Instant thin-layer chromatographic silica gel strips (ITLC-SG)
F. 0.9% sodium chloride aqueous solution for the chromatography solvent
G. Suitable radioactivity counting apparatus
H. Developing chamber for chromatography
I. Membrane filter, 0.22-micrometer, low-protein-binding
J. Vial and syringe shield

Method:

1. Sterile, pyrogen-free ^{90}Y chloride must be used for the preparation of ^{90}Y-ZEVALIN. The use of high purity ^{90}Y chloride is required.

2. Before radiolabeling, allow the contents of the refrigerated carton to reach room temperature. Note: The ZEVALIN vial contains a protein solution that may develop translucent particulates. These particulates will be removed by filtration prior to administration.

3. Clean the rubber stoppers of all of the vials in the kit and the ^{90}Y chloride vial with a suitable alcohol swab and allow to air-dry.

4. Place the empty reaction vial in a suitable dispensing shield (pre-warmed to room temperature). To avoid the build-up of excessive pressure during the procedure, use a 10-mL syringe to withdraw 10 mL of air from the reaction vial.

5. Prior to initiating the radiolabeling reaction, determine the amount of each component needed according to the directions below:

    a. Calculate the volume of ^{90}Y chloride that is equivalent to 40 mCi based on the activity concentration of the ^{90}Y chloride stock. Use the certificate of analysis provided by the manufacturer of the ^{90}Y chloride for this calculation.

    b. The volume of 50 mM sodium acetate solution needed is equal to the volume of ^{90}Y chloride solution determined in step 5.a. above, multiplied by a factor of 1.2. (The 50 mM sodium acetate is used to adjust the pH for the radiolabeling reaction.)

    c. Calculate the volume of formulation buffer needed to bring the reaction vial contents to a final volume of 10 mL. This is the volume of formulation buffer needed to protect the labeled product from radiolysis and to terminate the labeling reaction. For example: The volume of ibritumomab tiuxetan required is 1.3 mL. If the volume of ^{90}Y chloride equivalent to 40 mCi is calculated to be 0.5 mL, then 0.6 mL of sodium acetate (0.5 mL multiplied by a factor of 1.2) is required. Therefore, the amount of formulation buffer needed is 7.6 mL (ie, 10 mL – 1.3 mL – 0.5 mL – 0.6 mL).

6. With a sterile 1-mL syringe, transfer the calculated volume of 50 mM sodium acetate to the empty reaction vial. Coat the entire inner surface of the reaction vial by gentle inversion or rolling.

7. Transfer 40 mCi of ^{90}Y chloride to the reaction vial with a sterile 1-mL syringe. Mix the two solutions and coat the entire inner surface of the reaction vial by gentle inversion or rolling.

8. With a sterile 3-mL syringe, transfer 1.3 mL of ZEVALIN (ibritumomab tiuxetan) to the reaction vial. Coat the entire surface of the reaction vial by gentle inversion or rolling. **Do not shake or agitate the vial contents, since this will cause foaming and denaturation of the protein.**

9. Allow the labeling reaction to proceed at room temperature for five minutes. Allowing the labeling reaction to proceed for a longer or shorter time may result in inadequate labeling.

10. **Immediately** after the five-minute incubation period, using a sterile 10-mL syringe with

a large bore needle (18 G - 20 G), transfer the calculated volume of formulation buffer from step 5.c. to the reaction vial, terminating incubation. Gently add the formulation buffer down the side of the reaction vial. If necessary to normalize air pressure, withdraw an equal volume of air. Coat the entire inner surface of the reaction vial by gentle inversion or rolling. Do not shake or agitate the vial contents. Avoid foaming.

11. Using the supplied labels, record the patient identification information, the date and time of preparation, the total activity and volume, and the date and time of expiration, and affix these labels to the reaction vial and shielded reaction vial container.

12. Calculate the volume required for a ^{90}Y-ZEVALIN dose of 0.4 mCi/kg (15 MBq/kg) of actual body weight for patients with a normal platelet count, and 0.3 mCi/kg (11 MBq/kg) of actual body weight for patients with a platelet count of 100,000 - 149,000 cells/mm^3. **The prescribed, measured and administered dose of ^{90}Y-ZEVALIN must not exceed the absolute maximum allowable dose of 32.0 mCi (1,200 MBq), regardless of the patient's body weight.** Withdraw the required volume from the reaction vial contents into a sterile 10-mL syringe with a large bore needle (18 G - 20 G). Assay the syringe and contents in a dose calibrator. The dose calibrator must be operated in accordance with the manufacturer's specifications and quality control for the measurement of ^{90}Y. The syringe should contain the dose of ^{90}Y-ZEVALIN to be administered to the patient and should be within 10% of the actual prescribed dose of ^{90}Y-ZEVALIN, not to exceed a maximum dose of 32.0 mCi. Do not exceed ± 10% of the prescribed dose. Using the supplied labels, record the patient identification information, the date and time of preparation, the total activity and volume added, and the date and time of expiration, and affix these labels to the syringe and shielded unit dose container.

13. Determine radiochemical purity. See **Directions for Quality Control** that follow these **Instructions for Preparation and Use**.

14. ^{90}Y-ZEVALIN should be stored under refrigeration between 2°C and 8°C until use and administered within eight hours of radiolabeling.

15. See **DOSAGE AND ADMINISTRATION** – **Administration**, step 2.

16. Discard vials, needles and syringes in accordance with regulations governing radioactive and biohazardous waste.

^{90}Y-ZEVALIN is suitable for administration on an outpatient basis. Beyond the use of vial and syringe shields for preparation and injection, no special shielding is necessary.

Directions for Quality Control

Procedure for determining radiochemical purity (RCP)

1. At room temperature, place a small drop of ^{90}Y-ZEVALIN at the origin of an ITLC-SG strip.

2. Place the ITLC-SG strip into a chromatography chamber with the origin at the bottom and the solvent front at the top. Allow the solvent (0.9% NaCl) to migrate at least 5 cm from the bottom of the strip. Remove the strip from the chamber and cut the strip in half. Count each half of the ITLC-SG strip for one minute (CPM) with a suitable counting apparatus.

3. Calculate the percentage of RCP as follows:

$$\% \text{ RCP} = \frac{\text{CPM bottom half}}{\text{CPM bottom half + CPM top half}} \times 100$$

4. If the radiochemical purity is < 95%, the ITLC procedure should be repeated. If repeat testing confirms that radiochemical purity is < 95%, the preparation should not be administered.

RADIATION DOSIMETRY

Based upon dosimetry studies with ^{111}In-ZEVALIN, the estimated radiation dosimetry for individual organs following administration of ^{90}Y-ZEVALIN at activities of 15 MBq/kg and 11 MBq/kg was calculated according to Medical Internal Radiation Dosimetry (MIRD) (see Table 6). The estimated radiation-absorbed doses to normal organs were substantially below recognized upper safety limits. Individual patient dosimetry results were not predictive for ^{90}Y-ZEVALIN toxicity and, accordingly, general performance of dosimetry is not recommended.

Table 6: Estimated Radiation Absorbed Doses From ^{90}Y-ZEVALIN

Organ	^{90}Y-ZEVALIN mGy/MBq	
	Median	**Range**
Spleen[a]	9.4	1.8 - 20.0
Liver[a]	4.8	2.9 - 8.1
Lower large intestinal wall[a]	4.7	3.1 – 8.2
Upper large intestinal wall[a]	3.6	2.0 – 6.7
Heart wall[a]	2.9	1.5 - 3.2
Lungs[a]	2.0	1.2 - 3.4
Testes[a]	1.5	1.0 – 4.3
Small intestine[a]	1.4	0.8 – 2.1
Red marrow[b]	1.3	0.6 - 1.8
Urinary bladder wall[c]	0.9	0.7 - 1.3
Bone surfaces[b]	0.9	0.5 - 1.2
Ovaries[c]	0.4	0.3 - 0.5
Uterus[c]	0.4	0.3 - 0.5
Adrenals[c]	0.3	0.2 - 0.5
Brain[c]	0.3	0.2 - 0.5
Breasts[c]	0.3	0.2 - 0.5

Table 6: Estimated Radiation Absorbed Doses From ^{90}Y-ZEVALIN

Organ	^{90}Y-ZEVALIN mGy/MBq	
	Median	**Range**
Gallbladder wall[c]	0.3	0.2 - 0.5
Muscle[c]	0.3	0.2 - 0.5
Pancreas[c]	0.3	0.2 - 0.5
Skin[c]	0.3	0.2 - 0.5
Stomach[c]	0.3	0.2 - 0.5
Thymus[c]	0.3	0.2 - 0.5
Thyroid[c]	0.3	0.2 - 0.5
Kidneys[a]	0.1	0.0 - 0.3
Total body[c]	0.5	0.4 - 0.7

a Organ region of interest
b Sacrum region of interest
c Whole body region of interest

The effective dose equivalent for ^{90}Y in a 70 kg adult resulting from an intravenously injected activity of 1 GBq of unbound ^{90}Y is 700 mSv (worst case).

OVERDOSAGE

Doses as high as 0.52 mCi/kg (19.2 MBq/kg) of ^{90}Y-ZEVALIN (ibritumomab tiuxetan) were administered in ZEVALIN therapeutic regimen clinical trials and severe hematological toxicities were observed. No fatalities or second organ injury resulting from overdosage administrations were documented. However, single doses up to 50 mCi (1,850 MBq) of ^{90}Y-ZEVALIN and multiple doses of 20 mCi (740 MBq) followed by 40 mCi (1,480 MBq) of ^{90}Y-ZEVALIN were studied in a limited number of subjects. In these trials, some patients required autologous stem cell support to manage hematological toxicity. Patients recovered from these toxicity signs, and overdoses were not associated with serious or fatal outcome.

There is no known specific antidote for ^{90}Y-ZEVALIN overdosage. Treatment consists of discontinuation of ZEVALIN and supportive therapy, which may include growth factors. If available, autologous stem cell support should be administered to manage hematological toxicity.

ACTION AND CLINICAL PHARMACOLOGY

ZEVALIN (ibritumomab tiuxetan) is composed of a murine IgG_1 monoclonal antibody (ibritumomab) covalently bound to the chelating agent tiuxetan. Unlabeled ZEVALIN is chelated with ^{90}Y chloride sterile solution before intravenous administration to prepare

^{90}Y-ZEVALIN, the active therapeutic agent.

Mechanism of Action

Ibritumomab reacts specifically with the CD20 antigen, which is present in approximately 93% of patients with B-cell NHL. The CD20 antigen is found on the surface of both normal and malignant B lymphocytes, but not on hematopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissue.

The complementarity-determining regions of ibritumomab bind to the CD20 antigen on the target B lymphocytes, and the long β-energy pathlength of ^{90}Y (χ_{90} = 5 mm) allows neighbouring tumour cells in the range (100-200 cell diameters) of the β emissions to be killed without direct binding of the antibody. The binding of an anti-CD20 antibody combined with an effective cell-killing mechanism provides a highly selective method for the elimination of malignant B-cells and still allows the progenitor B-cells to regenerate the immune system normally.

Pharmacodynamics

In clinical studies, administration of the ZEVALIN therapeutic regimen resulted in sustained depletion of circulating B-cells. At four weeks, the median number of circulating B-cells was zero (range: 0 to 1,084 cells/mm^3). B-cell recovery began at approximately 12 weeks following treatment, and the median level of B-cells was within the normal range (32 to 341 cells/mm^3) by nine months after treatment. Median serum levels of IgG and IgA remained within the normal range throughout the period of B-cell depletion. Median IgM serum levels dropped below normal (median 49 mg/dL, range 13 to 3,990 mg/dL) after treatment and recovered to normal values by six months post-therapy.

Pharmacokinetics

The small quantities of ^{90}Y-ZEVALIN (approximately 2.1 mg) in a typical administration are not optimally targeted to tumours unless measures are taken to block or deplete CD20 binding sites, including those on circulating lymphocytes, and in normal or involved tissues with large numbers of B-cells and high blood flow (such as the spleen and liver). Rituximab administered prior to ZEVALIN treatment is used to optimize biodistribution. In patients in which an injection of ^{111}In-ZEVALIN (used for imaging purposes) was preceded by a single infusion of rituximab at either 100 mg/m^2 or 250 mg/m^2, known disease sites were imaged in both groups without accumulation of ^{111}In-ZEVALIN in normal organs. No substantial qualitative or quantitative differences in imaging were observed between the two rituximab doses, however the higher dose of 250 mg/m^2 was chosen since it would likely lead to an enhanced therapeutic effect.

In pharmacokinetic studies of patients receiving the ZEVALIN therapeutic regimen, the mean effective half-life for ^{90}Y activity in blood was 30 hours and the mean area under the fraction of injected activity (FIA) vs. time curve in blood was 39 hours. Over seven days, a median of 7.2% of the injected activity was excreted in urine.

Under conditions corresponding to the recommended treatment regimen, the kinetics of ZEVALIN fit a linear and noncompartmental model. The physical half-life of ^{90}Y is 64.1 hours (2.7 days), with rapid decay to stable and nontoxic zirconium-90. The minor amounts of unbound circulating radioactivity are eliminated in urine with a median effective half-life in blood of 27.1 hours and a median area under the curve (AUC) of 27.5 hours. Approximately

5.7% (range 3.2% to 8.9%) of the injected dose is eliminated in urine over a period of seven days, with 80% of this elimination complete within four days. This corresponds to a total urinary elimination of 2 mCi or less of the total radioisotope over a period of a few days.

Results of dosimetry measurements performed in 179 patients indicate that radiation doses delivered to normal organs and marrow by ^{90}Y-ZEVALIN at the recommended maximum dose of 0.4 mCi are significantly below exposure levels that would justify clinical concern (2,000 cGy to normal organs; 300 cGy to marrow).

The correlation between myelotoxicity and red marrow dose was examined by the use of scatter plots and correlation analyses, comparing the blood cell nadir (neutrophils or platelets) and the recovery time versus the radiation dose to marrow. These data demonstrate a poor correlation between radiation dose to marrow and hematologic toxicity.

STORAGE AND STABILITY

After radiolabeling, an immediate use is recommended. Chemical and physical in-use stability has been demonstrated for 8 hours at 2°C to 8°C and protected from light.

Store the ZEVALIN kit under refrigeration between 2°C and 8°C in its original packaging to protect from light. Do not freeze. Administer within 8 hours of radiolabeling.

SPECIAL HANDLING INSTRUCTIONS

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

DOSAGE FORMS, COMPOSITION AND PACKAGING

The ZEVALIN (ibritumomab tiuxetan) kit provides the non-radioactive components for the radiolabeling of ibritumomab tiuxetan with ^{90}Y.

^{90}Y chloride sterile solution will be shipped directly from the manufacturer upon placement of an order for the ZEVALIN kit. Rituximab must be ordered separately, and is available through hospital pharmacies.

Each ZEVALIN kit contains the following components:

- One vial (ZEVALIN vial) containing 3.2 mg of ibritumomab tiuxetan in 2 mL of normal saline solution. Supplied as a clear, colourless solution that may contain translucent particles.

- One vial (50 mM sodium acetate vial) containing 13.6 mg of sodium acetate trihydrate in 2 mL of Water for Injection. Supplied as a clear, colourless solution.

- One vial (formulation buffer vial) containing 750 mg of human serum albumin, 76 mg of

sodium chloride, 21 mg of sodium phosphate dibasic dodecahydrate, 4 mg of pentetic acid, 2 mg of potassium phosphate monobasic and 2 mg of potassium chloride in 10 mL of Water for Injection adjusted to pH 7.1 with either sodium hydroxide or hydrochloric acid. Supplied as a yellow to amber coloured solution.

- One empty reaction vial.

- Four identification labels.

The contents of all vials are sterile, pyrogen-free and contain no preservatives.

The final formulation after radiolabeling contains 2.08 mg ^{90}Y-ibritumomab tiuxetan in a total volume of 10 mL.

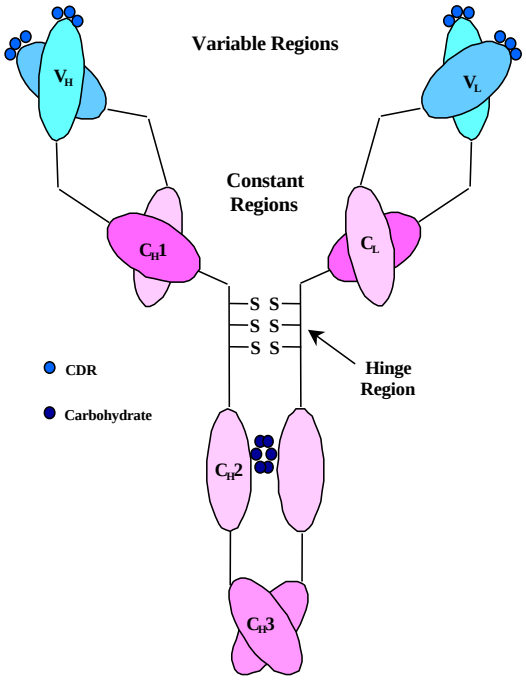
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

ZEVALIN (ibritumomab tiuxetan) is the immunoconjugate resulting from a stable thiourea covalent bond between the monoclonal antibody ibritumomab and the linker-chelator tiuxetan [N-[2-bis(carboxymethyl)amino]-3-(p-isothiocyanatophenyl)-propyl]-[N-[2-bis(carboxymethyl) amino]-2-(methyl)-ethyl]glycine. This linker-chelator provides a high affinity, conformationally restricted chelation site for ^{90}Y. The approximate molecular weight of ibritumomab tiuxetan is 148 kD.

The antibody moiety of ZEVALIN is ibritumomab, a murine IgG_1 kappa monoclonal antibody directed against the CD20 antigen, which is found on the surface of normal and malignant B lymphocytes. Ibritumomab is produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology and is composed of two murine gamma 1 heavy chains of 445 amino acids each and two kappa light chains of 213 amino acids each. The molecular structure is shown below.



CLINICAL TRIALS

The safety and efficacy of the ZEVALIN therapeutic regimen were evaluated in two multi-centre trials enrolling a total of 197 subjects. The ZEVALIN therapeutic regimen was administered in two steps. The activity and toxicity of a variation of the ZEVALIN therapeutic regimen employing a reduced dose of ^{90}Y-ZEVALIN was further defined in a third study enrolling a total of 30 patients who had mild thrombocytopenia (platelet count 100,000 to 149,000 cells/mm^3).

Study 1 was a single-arm study of 54 patients with relapsed follicular lymphoma refractory to rituximab treatment. Patients were considered refractory if their last prior treatment with rituximab did not result in a complete or partial response, or if time to disease progression (TTP) was < 6 months. The primary efficacy endpoint of the study was the overall response rate (ORR) using the International Workshop Response Criteria (IWRC). Secondary efficacy endpoints included time to disease progression (TTP) and duration of response (DR). In a secondary analysis comparing objective response to the ZEVALIN therapeutic regimen with that observed with the most recent treatment with rituximab, the median duration of response following the ZEVALIN therapeutic regimen was six vs. four months. Table 7 summarizes efficacy data from this study.

Study 2 was a randomized, controlled, multicentre study comparing the ZEVALIN therapeutic regimen to treatment with rituximab. The trial was conducted in 143 patients with relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma (NHL), or transformed B-cell NHL. A total of 73 patients received the ZEVALIN therapeutic regimen, and 70 patients received rituximab given as an intravenous infusion at 375 mg/m^2 weekly times four doses. The primary efficacy endpoint of the study was to determine the ORR using the IWRC (see Table 7). The ORR was significantly higher (80% vs. 56%, p = 0.002) for patients treated with the ZEVALIN therapeutic regimen. The secondary endpoints, duration of response and time to progression, were not significantly different between the two treatment arms.

Table 7: Summary of Efficacy Data[a] for Studies 1 and 2

	Study 1	**Study 2**	
	ZEVALIN Therapeutic Regimen N = 54	**ZEVALIN Therapeutic Regimen N = 73**	**Rituximab N = 70**
Overall response rate (%)	74	80	56
Complete response rate (%)	15	30	16
CRu Rate[b] (%)	0	4	4
Median DR[c,d] (Months) [Range[e]]	6.4 [0.5-24.9+]	13.9 [1.0-30.1+]	11.8 [1.2-24.5]
Median TTP[c,f] (Months) [Range[e]]	6.8 [1.1-25.9+]	11.2 [0.8-31.5+]	10.1 [0.7-26.1]

a IWRC: International Workshop Response Criteria
b CRu: Unconfirmed complete response
c Estimated with observed range
d Duration of response: interval from the onset of response to disease progression
e "+" indicates an ongoing response
f TTP: Time to disease progression: interval from the first infusion to disease progression

Study 3 was a single-arm study of 30 patients with relapsed or refractory low-grade, follicular or transformed B-cell NHL who had mild thrombocytopenia (platelet count 100,000 to 149,000 cells/mm^3). Excluded from the study were patients with ≥ 25% lymphoma marrow involvement and/or impaired bone marrow reserve. Patients were considered to have impaired bone marrow reserve if they had any of the following: prior myeloablative therapy with stem cell support; prior external beam radiation to > 25% of active marrow; a platelet count < 100,000 cells/mm^3; or neutrophil count < 1,500 cells/mm^3. In this study, a modification of the ZEVALIN therapeutic regimen with a lower specific activity ^{90}Y-ZEVALIN dose [^{90}Y-ZEVALIN at 0.3 mCi/kg (11 MBq/kg)] was used. Objective, durable clinical responses were observed [67% ORR (95% CI: 48-85%), 11.8 months median DR (range: 4-17 months)] (see Table 8) and resulted in a greater incidence of hematologic toxicity than in studies 1 and 2 (see **ADVERSE REACTIONS**).

Table 8: Summary of Efficacy Data for Study 3

	ZEVALIN (Reduced Dose Regimen[a]) N = 30
Overall response rate[b] (%)	67
Complete response rate[b] (%)	33
Median DR[c] (Months) [Range]	11.8 [4 - 17]

a Reduced dose: ^{90}Y-ZEVALIN at 0.3 mCi/kg (11 MBq/kg)
b Sponsor evaluation criteria
c Duration of response: interval from the onset of response to disease progression

DETAILED PHARMACOLOGY

Animal

Cynomolgus monkeys were given intravenous infusions of 30 mg/kg rituximab followed immediately by i.v. injections of 1.5 mg/kg of nonradioactive ^{89}Y labeled ibritumomab tiuxetan on days 1 and 8. Two weeks following injection the CD20+ lymphocytes were depleted in peripheral blood, spleen, lymph node and bone marrow tissue; variable B-cell recovery in these tissues was observed by day 55. In contrast, monkeys given ^{89}Y-labeled ibritumomab tiuxetan alone showed variable reductions of peripheral blood CD20+ lymphocytes, and the absolute number of CD20+ lymphocytes approached baseline levels by day 55. Higher plasma concentrations of ^{89}Y-labeled ibritumomab tiuxetan were observed in the sera of monkeys that received rituximab followed by ^{89}Y-labeled ibritumomab tiuxetan, relative to those receiving ^{89}Y-labeled ibritumomab tiuxetan alone.

Biodistribution studies with ^{90}Y-ibritumomab tiuxetan performed in normal mice showed low bone accumulation (1.3% of injected dose/g of tissue or less over ten days) compared with heart, lung, kidney, liver and spleen (1.7% to 30.8% of injected dose/g of tissue) over the same period. When ^{111}In-ibritumomab tiuxetan was administered to mice bearing CD20+ tumours, concentrations of the radiolabeled conjugate in the tumour increased steadily over 48 hours. The radioactivity level decreased in the blood and most other organs, but remained constant or increased slightly in the spleen, muscle, bone and intestine. Radiolabeled conjugate recovered in excreta increased over time throughout the 48-hour period. The linker chelate tiuxetan forms a stable complex with the radioisotopes yttrium-90 and indium-111 and only negligible degradation due to radiolysis is expected.

Human

Ibritumomab tiuxetan binds specifically to the CD20 antigen (human B-lymphocyte-restricted differentiation antigen, Bp35), a hydrophobic transmembrane protein with a molecular weight of approximately 35 kD located on pre-B and mature B lymphocytes and on established B-cell lines. The apparent affinity of ibritumomab tiuxetan for the CD20 antigen ranges between approximately 14 to 18 nM. The CD20 antigen is expressed on > 90% of B-cell non-Hodgkin's lymphomas (NHL), but is not found on hematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissues. The CD20 antigen may regulate one or more early steps in the activation process for cell cycle initiation and differentiation, and possibly functions as a calcium ion channel. The CD20 antigen is not shed from the cell surface and does not internalize upon antibody binding.

The complementarity-determining regions of ibritumomab bind to the CD20 antigen on B lymphocytes. The chelator tiuxetan, which tightly binds to ^{90}Y, is covalently linked to the amino groups of exposed lysines and arginines contained within the antibody. The beta emission from ^{90}Y induces cellular damage by the formation of free radicals in the target and neighbouring cells. Native ibritumomab induces apoptosis in CD20+ B-cell lines in vitro. It may also promote weak Fc-mediated phagocytosis of antigen-positive cells in vivo.

Ibritumomab tiuxetan binding was observed on lymphoid cells of the bone marrow, lymph node, thymus, red and white pulp of the spleen and lymphoid follicles of the tonsil, as well as lymphoid nodules of other organs such as the large and small intestines. No binding was observed in the non-lymphoid tissues or gonadal tissues.

Pharmacokinetic and biodistribution studies were performed using ^{111}In-ZEVALIN (5 mCi [185 MBq] of ^{111}In, 1.6 mg of ibritumomab tiuxetan) as an imaging agent. In a study designed to assess the need for pre-administration of unlabeled antibody, only 18% of known sites of disease were imaged when ^{111}In-ZEVALIN was administered without unlabeled ibritumomab. When preceded by unlabeled ibritumomab (1.0 mg/kg or 2.5 mg/kg), ^{111}In-ZEVALIN detected 56% and 92% of known disease sites, respectively.

TOXICOLOGY

Animal

Non-clinical data reveal no special hazard for humans based on studies of single and repeated dose toxicity. No long-term animal studies have been performed to evaluate carcinogenic or mutagenic potential or whether ZEVALIN (ibritumomab tiuxetan) affects fertility in males or females. Due to the exposure to ionizing radiation derived from the radiolabel, a risk of mutagenic and carcinogenic effects has to be taken into account.

Human

Studies on reproductive and developmental toxicity have not been performed. In clinical studies, the ^{90}Y- ZEVALIN after pretreatment with rituximab results in a significant radiation dose to the testes. The radiation dose to the ovaries has not been established. There is a potential risk that ^{90}Y- ZEVALIN after pretreatment with rituximab could cause toxic effects on the male and female gonads (see **WARNINGS AND PRECAUTIONS – Sexual Function/Reproduction)**.

REFERENCES

1. Anderson KC, Bates MP, Slaughenhoupt BL, Pinkus GS, Schlossman SF, Nadler LM. Expression of human B cell-associated antigens on leukemias and lymphomas: a model of human B cell differentiation. Blood 1984;63(6):1424-33.

2. Bubien JK, Zhou LJ, Bell PD, Frizzell RA, Tedder TF. Transfection of the CD20 cell surface molecule into ectopic cell types generates a Ca2+ conductance found constitutively in B lymphocytes. J Cell Biol 1993;121(5):1121-32.

3. Chakrabarti MC, Le N, Paik CH, De Graff WG, Carrasquillo JA. Prevention of radiolysis of monoclonal antibody during labeling. J Nucl Med 1996;37(8):1384-8.

4. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 1999;17(4):1244.

5. Einfeld DA, Brown JP, Valentine MA, Clark EA, Ledbetter JA. Molecular cloning of the human B cell CD20 receptor predicts a hydrophobic protein with multiple transmembrane domains. Embo J 1988;7(3):711-7.

6. Gordon LI, Molina A, Witzig T, Emmanouilides C, Raubtischek A, Darif M, et al. Durable responses after ibritumomab tiuxetan radioimmunotherapy for CD20+ B-cell lymphoma: long-term follow-up of a phase 1/2 study. Blood 2004;103(12):4429-31.

7. Kantarjian HM, Keating MJ. Therapy-related leukemia and myelodysplastic syndrome. Semin Oncol 1987;14(4):435-43.

8. Knox SJ, Goris ML, Trisler K, Negrin R, Davis T, Liles TM, et al. Yttrium-90-labeled anti-CD20 monoclonal antibody therapy of recurrent B-cell lymphoma. Clin Cancer Res 1996;2(3):457-70.

9. Wiseman GA, Gordon LI, Multani PS, Witzig TE, Spies S, Bartlett NL, et al. Ibritumomab tiuxetan radioimmunotherapy for patients with relapsed or refractory non-Hodgkin lymphoma and mild thrombocytopenia: a phase II multicenter trial. Blood 2002;99(12):4336-42.

10. Wiseman GA, Leigh BR, Dunn WL, Stabin MG, White CA. Additional radiation absorbed dose estimates for Zevalin radioimmunotherapy. Cancer Biother Radiopharm 2003;18(2):253-8.

11. Wiseman GA, White CA, Sparks RB, Erwin WD, Podoloff DA, Lamonica D, et al. Biodistribution and dosimetry results from a phase III prospectively randomized controlled trial of Zevalin radioimmunotherapy for low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. Crit Rev Oncol Hematol 2001;39(1-2):181-94.

12. Wiseman GA, White CA, Stabin M, Dunn WL, Erwin W, Dahlbom M, et al. Phase I/II ^{90}Y-Zevalin (yttrium-90 ibritumomab tiuxetan, IDEC-Y2B8) radioimmunotherapy

dosimetry results in relapsed or refractory non-Hodgkin's lymphoma. Eur J Nucl Med 2000;27(7):766-77.

13. Wiseman GA, White CA, Witzig TE, Gordon LI, Emmanouilides C, Raubitschek A, et al. Radioimmunotherapy of relapsed non-Hodgkin's lymphoma with zevalin, a 90Y-labeled anti-CD20 monoclonal antibody. Clin Cancer Res 1999;5(10 Suppl):3281s-3286s.

14. Wiseman GA, Witzig TE. Yttrium-90 (90Y) ibritumomab tiuxetan (Zevalin) induces long-term durable responses in patients with relapsed or refractory B-Cell non-Hodgkin's lymphoma. Cancer Biother Radiopharm 2005;20(2):185-8.

15. Witzig T, White C, Gordon L, Murray J, Wiseman G, Czuczman M. Prospective randomized controlled study of Zevalin™ (IDEC-Y2B8) radioimmunotherapy compared to rituximab immunotherapy for B-cell NHL: report of interim results. 1999.

16. Witzig TE. The use of ibritumomab tiuxetan radioimmunotherapy for patients with relapsed B-cell non-Hodgkin's lymphoma. Semin Oncol 2000;27(6 Suppl 12):74-8.

17. Witzig TE. Radioimmunotherapy for patients with relapsed B-cell non-Hodgkin lymphoma. Cancer Chemother Pharmacol 2001;48 Suppl 1:S91-5.

18. Witzig TE, Flinn IW, Gordon LI, Emmanouilides C, Czuczman MS, Saleh MN, et al. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. J Clin Oncol 2002;20(15):3262-9.

19. Witzig TE, Gordon LI, Cabanillas F, Czuczman MS, Emmanouilides C, Joyce R, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol 2002;20(10):2453-63.

20. Witzig TE, White CA, Gordon LI, Wiseman GA, Emmanouilides C, Murray JL, et al. Safety of yttrium-90 ibritumomab tiuxetan radioimmunotherapy for relapsed low-grade, follicular, or transformed non-hodgkin's lymphoma. J Clin Oncol 2003;21(7):1263-70.

21. Witzig TE, White CA, Wiseman GA, Gordon LI, Emmanouilides C, Raubitschek A, et al. Phase I/II trial of IDEC-Y2B8 radioimmunotherapy for treatment of relapsed or refractory CD20(+) B-cell non-Hodgkin's lymphoma. J Clin Oncol 1999;17(12):3793-803.

PART III: CONSUMER INFORMATION

PrZEVALIN®
Ibritumomab tiuxetan

This leaflet is part III of a three-part Product Monograph for ZEVALIN and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about ZEVALIN. Contact your doctor if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ZEVALIN is used to treat certain types of B-cell non-Hodgkin's lymphoma (NHL). This is a cancer of certain white blood cells called B lymphocytes (B-cells). ZEVALIN is used if an earlier treatment has not worked, or has stopped working.

What it does:
ZEVALIN is a type of targeted cancer therapy called radioimmunotherapy. ***Radioimmunotherapy*** refers to a treatment that combines a source of radiation, such as a radioisotope, with a component of the immune system, such as an antibody.

Antibodies are part of the body's natural defence system, the immune system. Antibodies circulate in the blood stream and are able to recognize and attach themselves to foreign substances that enter the body, such as bacteria. This alerts other parts of the immune system to help destroy and remove the foreign substance from the body. Scientists can now make antibodies that recognize and attach to specific targets. The antibody used in ZEVALIN is designed to recognize and attach to B-cells, including the cancerous B-cells in patients with B-cell NHL.

A ***radioisotope*** is an atom that gives off energy in the form of radiation. When ZEVALIN is combined with a radioisotope, it is said to be radiolabeled. For therapeutic purposes, ZEVALIN is combined with yttrium-90 (^{90}Y), which produces a type of radiation called beta emission.

As ZEVALIN enters the bloodstream, the antibody portion recognizes and attaches to a B-cell, allowing the energy emitted from the yttrium-90 to penetrate and damage or kill the cancerous B-cell. In what is called a "cross-fire" effect, the emitted energy can also reach and destroy neighbouring cancer cells.

When it should not be used:
You must not be given ZEVALIN:

- If you have an allergy (if you are hypersensitive) to the active ingredient (ibritumomab tiuxetan), to yttrium chloride, to rituximab, to mouse proteins or to any of the other ingredients in ZEVALIN (see below).
- If you are pregnant or nursing

What the medicinal ingredient is:
The medicinal ingredient is ibritumomab tiuxetan. Ibritumomab is a man-made antibody that can recognize and attach to B-cells.

What the important nonmedicinal ingredients are:
The other ingredients are human serum albumin, hydrochloric acid, pentetic acid, potassium chloride, potassium phosphate monobasic, sodium acetate trihydrate, sodium chloride, sodium hydroxide, sodium phosphate dibasic dodecahydrate and water for injection.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Because ZEVALIN is a radiopharmaceutical, it can only be given by doctors and other health professionals who are specially trained and experienced in the safe use and handling of radioisotopes.**
- **Deaths have occurred within 24 hours of receiving infusion with rituximab, an essential part of the ZEVALIN therapeutic regimen. Approximately 80% of fatal infusion reactions occurred in association with the first rituximab infusion. Patients who develop severe infusion reactions should have rituximab and ^{90}Y-ZEVALIN infusions stopped immediately and receive medical treatment (see WARNINGS AND PRECAUTIONS - Severe infusion reactions).**
- **Treatment with ZEVALIN can result in very low blood cell counts for a prolonged period of time (see SIDE EFFECTS AND WHAT TO DO ABOUT THEM).**
- **To ensure safe administration, the dose of ZEVALIN that you receive should not exceed the maximum allowable dose of 32 mCi (1200 MBq).**

BEFORE you receive the ZEVALIN therapeutic regimen, talk to your doctor if:

- You have an allergy to ibritumomab tiuxetan, yttrium chloride, rituximab, mouse proteins or to any of the other ingredients in ZEVALIN (see **ABOUT THIS MEDICATION: What the important nonmedicinal ingredients are**).
- You are pregnant or could be pregnant. You should not receive ZEVALIN if you are pregnant.

- You are breastfeeding. You must not receive ZEVALIN if you are breastfeeding.

Your doctor will need to think carefully whether to give you ZEVALIN in some cases:

- If a quarter or more of your bone marrow contains malignant abnormal cells.
- If you have a marked reduction in bone marrow cells.
- If the number of your platelets is less than 100,000/mm^3 or if the number of one type of white blood cells (called neutrophils) is less than 1,500/mm^3.
- If you have had a failed stem cell collection.

If you have had certain other types of antibody treatment before starting ZEVALIN, you may be more likely to have an allergic reaction (hypersensitivity). You may therefore need to be tested for special antibodies. Your doctor will tell you if this applies to you.

After treatment with ZEVALIN, and if your doctor plans to treat you with some other antibody, please tell your doctor about your treatment with ZEVALIN. This will help avoid a possible allergic reaction (hypersensitivity).

Severe infusion reactions:
Rituximab, a key part of the ZEVALIN therapeutic regimen, has been known to cause a severe allergic reaction in some patients. This severe allergic reaction does not occur often. When it does occur, it is usually during the first infusion of rituximab. In some patients, this severe allergic reaction has led to death within 24 hours of receiving rituximab. Symptoms of this severe allergic reaction include low blood oxygen levels, fluid in the lungs, severe difficulty in breathing, disturbances in heart rhythms, heart attack and disruption in bodily functions related to a sudden decline in heart function. Patients who develop symptoms of this severe type of allergic reaction should have their rituximab or ZEVALIN infusions stopped and receive medical treatment.

Prolonged low blood cell counts:
Treatment with ZEVALIN can result in very low blood cell counts for a prolonged period of time (see **SIDE EFFECTS AND WHAT TO DO ABOUT THEM**). The ZEVALIN therapeutic regimen should not be given to patients with 25% or more of their bone marrow cells affected by lymphoma and/or patients whose bone marrow may have difficulty recovering from therapy.

Skin and mucous membrane reactions:
If you notice a skin or mucous membrane reaction during or after ZEVALIN or rituximab treatment, inform your doctor immediately, because in rare instances such reactions have been reported to develop into severe cases, even with the possibility of death.

Secondary cancers:
Following treatment with the ZEVALIN therapeutic regimen, development of a second type of cancer involving blood cells has occurred in a small percentage of cancer patients (less than 2 in 100) participating in ZEVALIN studies. The risk of these secondary cancers occurring after certain cancer drugs called alkylating agents is already known to doctors. Previous treatment with alkylating agents is, however, widespread prior to ZEVALIN treatment. Therefore it is difficult to know whether ZEVALIN itself contributes to this risk of developing a secondary cancerous disease.

Immunization:
The safety of immunization with any vaccine, particularly live viral vaccines, following therapy with ZEVALIN has not been studied. The ability of the body to respond to any vaccine following ZEVALIN treatment has also not been studied.

Driving and using machines:
It is possible that ZEVALIN will affect your ability to drive and to operate any tools or machines as dizziness is a common side effect. Please take care, and do not try to drive or operate machines until you are sure you are not affected.

Children and adolescents:
The safety and effectiveness of ZEVALIN in children and adolescents have not yet been established.

Precautions to be taken <u>after</u> receiving ZEVALIN:
The amount of radiation that your body will be exposed to during the ZEVALIN therapeutic regimen is smaller than it would be during radiotherapy. With the type of radioactivity from ZEVALIN (pure beta emission) there is no direct effect of radiation outside the body. You are not exposing other people to radiation. The effects of ZEVALIN stay mainly within your body and bodily fluids, such as urine and blood. A small part of the radioactivity will leave your body through your urine. The remainder will break down within the body, leaving no radioactive remains.

Typically, there is no need to stay in the hospital or to avoid contact with family, friends or co-workers after treatment with ZEVALIN. However, it is advisable to observe some safety precautions for the week following treatment with the therapeutic dose of ZEVALIN, to minimize any potential radiation exposure to other people. If you have any questions concerning the precautions listed below or about participation in a particular activity, be sure to discuss them with your doctor.

Safety precautions to be followed for 7 days

- Wash your hands thoroughly after using the bathroom.
- Use a condom during sexual intercourse to avoid transfer of bodily fluids.

Pregnancy precautions

- **If you could get pregnant,** use reliable contraception. Pregnancy should be ruled out before you start treatment and must be avoided during treatment and for **one year** after treatment.
- **Men who have been given ZEVALIN** and who could become fathers must use reliable contraception during and for **one year** after treatment.

Breastfeeding

- **Talk to your doctor before starting breast-feeding** after the end of treatment as it is not known whether ZEVALIN is excreted in human milk. Some antibodies are excreted in human milk. Women must not breastfeed during and for **one year** after treatment.

After receiving ZEVALIN, follow your doctor's instructions and the guidelines included in this leaflet regarding going home and back to work.

INTERACTIONS WITH THIS MEDICATION

Please tell your doctor if you are taking or have recently taken any other medicines, even those you bought without a prescription.

If you take blood thinners or other medications that interfere with blood clotting, such as warfarin (Coumadin®), ASA (ASPIRIN®), nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen (Motrin®, Advil®) and naproxen (Naprosyn®), or COX-2 inhibitors like celecoxib (Celebrex®), your doctor will need to monitor your blood and platelet counts carefully during and after receiving ZEVALIN.

PROPER USE OF THIS MEDICATION

ZEVALIN will be given to you under the supervision of a health professional who is specially trained and experienced in the safe use of radiopharmaceuticals.

Do I need to make special preparations before beginning treatment with ZEVALIN?
In general, you do not need to make any special preparations before you begin treatment with the ZEVALIN therapeutic regimen. You can continue with your normal activities and your regular diet. You may also wear your regular clothes to receive your treatments. Your doctor or nurse may have some specific suggestions or recommendations for you to follow.

How is the ZEVALIN therapeutic regimen given?
The ZEVALIN therapeutic regimen is intended as a single course of treatment, consisting of two hospital visits, approximately one week apart.

On your first visit (day 1), you will receive treatment with rituximab, an antibody similar to the one used in ZEVALIN. Rituximab is given before ZEVALIN to allow ZEVALIN to better target the lymphoma cells within your body. Rituximab is administered by intravenous infusion, which means that the medicine is given by a drip into the vein. The infusion may take several hours to complete.

On your second visit (day 7, 8 or 9), you will receive a second rituximab infusion. Within four hours after receiving this second rituximab infusion, you will receive your ZEVALIN treatment. Radiolabeled ZEVALIN is administered by intravenous infusion over 10 minutes.

Important: You must receive rituximab before you can be given ZEVALIN. Please ask your doctor for the rituximab patient brochure for important information on this product.

How much ZEVALIN is given?
The doctor will calculate your individual dose. This depends on your body weight and the number of your blood platelets.

What kind of follow-up is needed after completing ZEVALIN treatment?
Your doctor will want to obtain complete blood cell counts and platelet counts weekly for at least 12 weeks following completion of the ZEVALIN therapeutic regimen. Some patients may need more frequent monitoring. Speak to your doctor concerning all details of your follow-up treatment.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, ZEVALIN can have side effects and most people receiving it are likely to get some of these. Because many side effects resemble the effects of the illness, it is not always clear if a reaction seen in clinical trials was due to ZEVALIN or not.

During treatment with the ZEVALIN therapeutic regimen:
The most common side effects during treatment included

weakness, nausea, infection, chills and fever, abdominal or general pain, shortness of breath, headache, vomiting, sore throat, cough and dizziness. If you experience any of these side effects, or any effects not mentioned here, tell a healthcare professional immediately.

Treatment with the ZEVALIN therapeutic regimen may cause a severe and potentially fatal allergic reaction. This severe reaction typically occurs with the first administration of rituximab. Ask your doctor for the rituximab patient information for important information on side effects with rituximab.

Following treatment with the ZEVALIN therapeutic regimen:
Following treatment with ZEVALIN, you will likely experience a period of decreased blood cell counts. For some patients, blood cell counts may become very low. Low white blood cell counts can decrease your ability to fight infections. Low red blood cell counts can cause fatigue. Low platelet counts can cause difficulty in forming blood clots, leading to increased bruising or bleeding. Low blood cell counts can occur up to two months following completion of the ZEVALIN therapeutic regimen and counts may remain low for a few weeks. Your body is usually able to recover normal blood counts within a few weeks after this period of decreased blood cell counts.

Very low blood counts may lead to serious or life-threatening complications, such as infections. Some patients have needed transfusions or have been given medications to help their blood counts recover faster. Your doctor may provide you with special instructions if your blood counts become very low.

Other side effects related to ZEVALIN treatment may occur, but are generally mild in severity. These may include nausea, vomiting, abdominal pain, diarrhea, increased cough, shortness of breath, dizziness, tiredness, loss of appetite, nervousness and bruising.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor	
		Only if severe	In all cases
Common (occurring between 1 and 10 of every 100 patients)	Allergic reactions		✓
	Black tarry stools		✓
	High fever		✓
	Infections		✓
	Prolonged pauses in breathing during sleep		✓
Uncommon (occurring between 1 and 10 of every 1000 patients)	Difficulty breathing		✓
	Hives or swelling beneath the skin		✓
	Rapid heart rate		✓
	Unusual vaginal bleeding (hemorrhage)		✓
	Vomiting of blood		✓
Rare (occurring between 1 and 10 of every 10,000 patients)	Skin or mucous membrane reactions		✓

This is not a complete list of side effects. If you have any unexpected effects after receiving ZEVALIN, contact your doctor.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online:	www.healthcanada.gc.ca/medeffect
Call toll-free at:	1-866-234-2345
Complete a Canada Vigilance Reporting Form and:	
Fax toll-free to:	1-866-678-6789, or
Mail to:	Canada Vigilance Program Health Canada Postal Locator 0701C Ottawa ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada website at: www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effect, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Servier Canada Inc. at: 1-800-363-6093

This leaflet was prepared by Servier Canada Inc.

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Last revised: March 05, 2020

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