Final Draft Approved MAR 25 2008

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Zevalin safely and effectively. See full prescribing information for Zevalin.

Zevalin (ibritumomab tiuxetan)
Injection for intravenous use
Initial U.S. Approval: 2002

WARNING: SERIOUS INFUSION REACTIONS, PROLONGED AND SEVERE CYTOPENIAS, and SEVERE CUTANEOUS AND MUCOCUTANEOUS REACTIONS

See full prescribing information for complete boxed warning.

- **Serious Infusion Reactions, some fatal, may occur within 24 hours of rituximab infusion. (5.1)**
- **Prolonged and Severe Cytopenias occur in most patients. (5.2)**
- **Severe Cutaneous and Mucocutaneous Reactions, some fatal, reported with Zevalin therapeutic regimen. (5.3, 6.3).**
- **Do not administer Y-90 Zevalin to patients with altered biodistribution. (5.4)**
- **Do not exceed 32 mCi (1184 MBq) of Y-90 Zevalin. (2.2)**

RECENT MAJOR CHANGES

Warnings and Precautions: Extravasation (5.7)	11/2007
Indications (1)	3/2008

INDICATIONS AND USAGE

Zevalin is a CD20-directed, radiotherapeutic antibody indicated as part of the Zevalin therapeutic regimen for treatment of relapsed or refractory, low-grade or follicular B-cell Non-Hodgkin's Lymphoma, including patients with rituximab refractory follicular Non-Hodgkin's Lymphoma. (1, 14)

DOSAGE AND ADMINISTRATION

- **Day 1**: Administer rituximab 250 mg/m^2 IV . Within 4 hours after rituximab infusion, administer 5 mCi In-111 Zevalin IV. (2.2)
- **Day 7, 8, or 9**:
  Administer rituximab 250 mg/m^2 IV infusion (2.2).
  - If platelets ≥ 150,000/mm^3: Within 4 hours after rituximab infusion, administer 0.4 mCi/kg Y-90 Zevalin IV.
  - If platelets ≥ 100,000 but ≤ 149,000/mm3: Within 4 hours after rituximab infusion, administer 0.3 mCi/kg Y-90 Zevalin IV.

DOSAGE FORMS AND STRENGTHS

3.2 mg per 2mL, single-use vial (3)

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

- **Infusion Reactions:** Immediately stop and permanently discontinue rituximab, In-111 Zevalin, and Y-90 Zevalin for serious infusion reactions. (5.1, 6.1)
- **Prolonged and Severe Cytopenias:** Do not administer Zevalin to patients with ≥ 25% lymphoma marrow involvement or impaired bone marrow reserve. (5.2, 6.1)
- **Severe Cutaneous and Mucocutaneous Reactions:** Discontinue rituximab, In-111 Zevalin, and Y-90 Zevalin infusions if patients develop severe cutaneous or mucocutaneous reactions. (5.3, 6.3)
- **Secondary Leukemia, Myelodysplastic Syndrome (MDS)** (5.5, 6.1)
- **Embryofetal toxicity:** May cause fetal harm when administered to a pregnant woman. (5.6, 8.1)
- **Extravasation:** Monitor for extravasation and terminate infusion if extravasation occurs. Resume infusion in another limb. (5.7, 6.3)
- **Immunization** : Do not administer live viral vaccines to patients who recently received Zevalin. (5.8)
- **Laboratory Monitoring:** Obtain complete blood counts (CBC) and platelet counts at least weekly. (5.9)

ADVERSE REACTIONS

The most common adverse reactions (≥ 40%) are neutropenia, thrombocytopenia, anemia, asthenia, and gastrointestinal symptoms. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Biogen Idec at 1-877-866-4332 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

- Monitor patients receiving medications that interfere with platelet function or coagulation more frequently for thrombocytopenia and bleeding (7)

USE IN SPECIFIC POPULATIONS

- Nursing Mother: Discontinue nursing. (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: March/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFUSION REACTIONS, PROLONGED AND SEVERE CYTOPENIAS, and SEVERE CUTANEOUS AND MUCOCUTANEOUS REACTIONS

Serious Infusion Reactions: Deaths have occurred within 24 hours of rituximab infusion, an essential component of the Zevalin therapeutic regimen. These fatalities were associated with hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Most (80%) fatalities occurred with the first rituximab infusion [*see Warnings and Precautions (5.1)* and *Adverse Reactions (6.1)*]. **Discontinue rituximab, In-111 Zevalin, and Y-90 Zevalin infusions in patients who develop severe infusion reactions.**

Prolonged and Severe Cytopenias: Y-90 Zevalin administration results in severe and prolonged cytopenias in most patients. Do not administer the Zevalin therapeutic regimen to patients with ≥ 25% lymphoma marrow involvement and/or impaired bone marrow reserve [*see Warnings and Precautions (5.2)* and *Adverse Reactions (6.1)*].

Severe Cutaneous and Mucocutaneous Reactions: Severe cutaneous and mucocutaneous reactions, some fatal, can occur with the Zevalin therapeutic regimen. Discontinue rituximab, In-111 Zevalin, and Y-90 Zevalin infusions in patients experiencing severe cutaneous or mucocutaneous reactions [*see Warnings and Precautions (5.3)* and *Adverse Reactions (6.3)*].

Dosing: The dose of Y-90 Zevalin should not exceed 32.0 mCi (1184 MBq). Do not administer Y-90 Zevalin to patients with altered biodistribution as determined by ~~imaging with In-111 Zevalin~~ [*see Dosage and Administration (2.2)*].

1 INDICATIONS AND USAGE

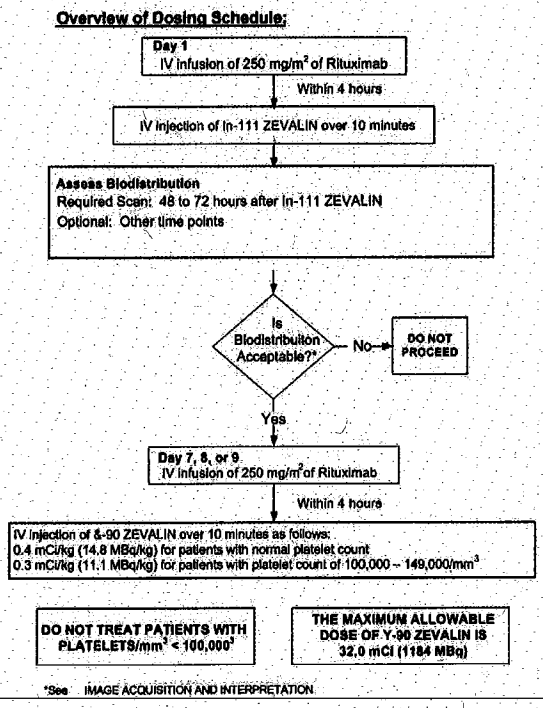
Non-Hodgkin's lymphoma

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

The Zevalin therapeutic regimen has been given accelerated approval for the treatment of relapsed or refractory, rituximab-naïve, low-grade and follicular NHL based on studies that have shown durable objective overall response rates, a surrogate endpoint for progression-free survival [*see Clinical Studies (14.2)]*. Studies to determine whether the Zevalin therapeutic regimen confers an effect on progression-free survival are ongoing.

2 DOSAGE AND ADMINISTRATION

2.1 Overview of Dosing Schedule



2.2 Zevalin Therapeutic Regimen Dosage and Administration

Day 1:

- Premedication with acetaminophen 650 mg orally and diphenhydramine 50 mg orally may be administered prior to ritixumab infusion
- Administer rituximab 250 mg/m^2 intravenously at an initial rate of 50 mg/hr. In the absence of infusion reactions, escalate the infusion rate in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. Do not mix or dilute rituximab with other drugs.
- Immediately stop the rituximab infusion for serious infusion reactions and discontinue Zevalin therapeutic regimen [*see Boxed Warnings* and *Warnings and Precautions (5.1)*].
- Temporarily slow or interrupt the rituximab infusion for less severe infusion reactions. If symptoms improve, continue the infusion at one-half the previous rate.

- Administer 5 mCi In-111 Zevalin over 10 minutes as an intravenous injection within 4 hours following completion of the rituximab infusion. Use a 0.22 micron low-protein-binding filter in-line between the syringe and the infusion port. After injection, flush the line with at least 10 mL of normal saline.

Day 7, 8 or 9:

Verify that expected biodistribution is present. [*see Dosage and Administration (2.5)*].

- Premedication with acetaminophen 650 mg orally and diphenhydramine 50 mg orally may be administered prior to ritixumab infusion
- Administer rituximab 250 mg/m^2 intravenously at an initial rate of 100 mg/hr. Increase rate by 100 mg/hr increments at 30 minute intervals, to a maximum of 400 mg/hr, as tolerated. If infusion reactions occurred during rituximab infusion on Day 1 of treatment, administer rituximab at an initial rate of 50 mg/hr and escalate the infusion rate in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.

- Administer Y-90 Zevalin injection through a free flowing intravenous line within 4 hours following completion of rituximab infusion.
  - If platelet count ≥150,000/mm^3, administer Y-90 Zevalin over 10 minutes as an intravenous injection at a dose of 0.4 mCi per kg (14.8 MBq per kg) actual body weight

- If platelet count 100,000-149,000/mm^3 administer Y-90 Zevalin 0.3 mCi per kg (11.1 MBq per kg) actual body weight over 10 minutes as an intravenous injection.
- **Do not administer more than 32 mCi (1184 MBq) Y-90 Zevalin dose regardless of the patient's body weight**

- Monitor patients closely for evidence of extravasation during the injection of Y-90 Zevalin. Immediately stop infusion and restart in another limb if any signs or symptoms of extravasation occur *[see Warnings and Precautions (5.7)]*.
- After injection, flush the line with at least 10 mL of normal saline.

2.3 Directions for Preparation of the In-111 and Y-90 Zevalin Doses

Two separate and distinctly-labeled kits are required for preparation of Indium-111 (In-111) Zevalin and Yttrium-90 (Y-90) Zevalin. Follow the detailed instructions for the preparation of radiolabeled Zevalin *[see Dosage and Administration (2.4)]*. The procedures are different for the preparation of In-111 Zevalin and of Y-90 Zevalin.

Directions for Preparation of Radiolabeled In-111 Zevalin Dose

Required materials not supplied in the kit:

A. Indium-111 Chloride Sterile Solution (In-111 Chloride) from GE Healthcare, or Covidien.
B. Three sterile 1 mL plastic syringes
C. One sterile 3 mL plastic syringe
D. Two sterile 10 mL plastic syringes with 18-20 G needles
E. Instant thin-layer chromatographic silica gel strips
F. 0.9% Sodium Chloride aqueous solution for the chromatography solvent
G. Developing chamber for chromatography
H. Suitable radioactivity counting apparatus
I. Filter, 0.22 micrometer, low-protein-binding
J. Appropriate lead shielding for reaction vial and syringe for In-111

Method:

1. Allow contents of the refrigerated In-111 Zevalin kit (Zevalin vial, 50 mM sodium acetate vial, formulation buffer vial, and empty reaction vial) to reach room temperature.

2. Place the empty reaction vial in an appropriate lead shield.

3. Determine the amount of each component needed:

   a. Calculate volume of In-111 Chloride equivalent to 5.5 mCi based on the activity concentration of the In-111 Chloride stock.

   b. The volume of 50 mM Sodium Acetate solution needed is 1.2 times the volume of In-111 Chloride solution determined in step 3.a., above.

   c. Calculate volume of formulation buffer needed to bring the reaction vial contents to a final volume of 10 mL.

4. Transfer the calculated volume of 50 mM of Sodium Acetate to the empty reaction vial. Coat entire inner surface of the reaction vial by gentle inversion or rolling.

5. Transfer 5.5 mCi of In-111 Chloride to the reaction vial using a lead shielded syringe. Mix the two solutions by gentle inversion or rolling.

6. Transfer 1 mL of Zevalin (ibritumomab tiuxetan) to the reaction vial. **Do not shake or agitate the vial contents.**

7. Allow the labeling reaction to proceed at room temperature for 30 minutes. A shorter or longer reaction time may adversely alter the final labeled product.

8. **Immediately** after the 30-minute incubation period, transfer the calculated volume of formulation buffer from step 3c. to the reaction vial. Gently add the formulation buffer down the side of the reaction vial. If necessary, withdraw an equal volume of air to normalize pressure.

9. Measure the final product for total activity using a radioactivity calibration system suitable for the measurement of In-111.

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

11. Patient Dose: Calculate the volume required for an In-111 Zevalin dose of 5 mCi. Withdraw the required volume from the reaction vial into a sterile syringe. Assay the syringe in a dose calibrator suitable for the measurement of In-111. Using the supplied labels, record patient identifier, total activity and volume and the date and time of expiration, and affix these labels to the syringe and shielded unit dose container.

12. Determine Radiochemical purity [*see Dosage and Administration (2.4)*].

13. Store Indium-111 Zevalin at 2-8°C (36-46°F) until use and administer within 12 hours of radiolabeling. Immediately prior to administration assay the syringe and contents using an appropriate radioactivity calibration system.

Directions for Preparation of Radiolabeled Y-90 Zevalin Dose

Required materials not supplied in the kit:

A. Yttrium-90 Chloride Sterile Solution from MDS Nordion
B. Three sterile 1 mL plastic syringes
C. One sterile 3 mL plastic syringe
D. Two sterile 10 mL plastic 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. Filter, 0.22 micrometer, low-protein-binding
J. Appropriate acrylic shielding for reaction vial and syringe for Y-90

Method:

1. Allow contents of the refrigerated Y-90 Zevalin kit (Zevalin vial, 50 mM sodium acetate vial, and formulation buffer vial) to reach room temperature.

2. Place the empty reaction vial in an appropriate acrylic shield.

3. Determine the amount of each component needed:

   a. Calculate volume of Y-90 Chloride equivalent to 40 mCi based on the activity concentration of the Y-90 Chloride stock.

   b. The volume of 50 mM Sodium Acetate solution needed is 1.2 times the volume of Y-90 Chloride solution determined in step 3.a, above.

   c. Calculate the volume of formulation buffer needed to bring the reaction vial contents to a final volume of 10 mL.

4. 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.

5. Transfer 40 mCi of Y-90 Chloride to the reaction vial using an acrylic shielded syringe. Mix the two solutions by gentle inversion or rolling.

6. Transfer 1.3 mL of Zevalin (ibritumomab tiuxetan) to the reaction vial. **Do not shake or agitate the vial contents.**

7. Allow the labeling reaction to proceed at room temperature for 5 minutes. A shorter or longer reaction time may adversely alter the final labeled product.

8. **Immediately** after the 5-minute incubation period, transfer the calculated volume of formulation buffer from step 3.c. to the reaction vial. Gently add the formulation buffer down the side of the reaction

vial. If necessary, withdraw an equal volume of air to normalize pressure.

9. Measure the final product for total activity using a radioactivity calibration system suitable for the measurement of Y-90.

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

11. Patient Dose: Calculate the volume required for a Y-90 Zevalin dose *(see Dosage and Administration [2.2])*. Withdraw the required volume from the reaction vial. Assay the syringe in the dose calibrator suitable for the measurement of Y-90. The measured dose must be within 10% of the prescribed dose of Y-90 Zevalin and **must not exceed 32 mCi**. Using the supplied labels, record the patient identifier, total activity and volume and the date and time of expiration and affix these labels to the syringe and shielded unit dose container.

12. Determine Radiochemical Purity [*see Dosage and Administration (2.4)*].

13. Store Yttrium-90 Zevalin at 2-8°C (36-46°F) until use and administer within 8 hours of radiolabeling. Immediately prior to administration, assay the syringe and contents using a radioactivity calibration system suitable for the measurement of Y-90.

2.4 Procedure for Determining Radiochemical Purity (RCP)

Use the following procedures for radiolabeling both In-111 Zevalin and Y-90 Zevalin:

A. Place a small drop of either In-111 Zevalin or Y-90 Zevalin at the origin of an ITLC-SG strip.

B. 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.

C. Calculate the percent RCP as follows:

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

D. Repeat the ITLC procedure if the radiochemical purity is <95%. If repeat testing confirms that radiochemical purity is <95%, do not administer the In-111 or Y-90 Zevalin dose.

2.5 Image Acquisition and Interpretation of Biodistributation

Assess the biodistribution of In-111 Zevalin by a visual evaluation of whole body planar view anterior and posterior gamma images obtained at 48 - 72 hours after injection. Images at additional time points may be necessary to resolve ambiguities. Acquire whole body anterior/posterior planar images using a large field-of-view gamma camera and medium energy collimators. Suggested gamma camera settings: 256 x 1024 matrix; dual energy photopeaks set at 172 and 247 keV; 15% symmetric window; scan speed of 10 cm/min for the 48-72 hour scan, and 7-10 cm/min for subsequent scans.

Expected Biodistribution

- Activity in the blood pool areas (heart, abdomen, neck, and extremities) may be faintly visible.
- Moderately high to high uptake in normal liver and spleen.
- Moderately low or very low uptake in normal kidneys, urinary bladder, and normal (uninvolved) bowel.
- Non-fixed areas within the bowel lumen that change position with time; delayed imaging as described above may be necessary to confirm gastrointestinal clearance.
- Focal fixed areas of uptake in the bowel wall (localization to lymphoid aggregates in bowel wall).

Tumor uptake may be visualized however tumor visualization on the In-111 Zevalin scan is not required for Y-90 Zevalin therapy.

Altered Biodistribution

The criteria for altered biodistribution are met if any of the following is detected on visual inspection of the required gamma images:

- Intense localization of radiotracer in the liver and spleen and bone marrow indicative of reticuloendothelial system uptake.
- Increased uptake in normal organs (not involved by tumor) such as:
  - Diffuse uptake in normal lung more intense than the liver.
  - Kidneys have greater intensity than the liver on the posterior view.
  - Fixed areas (unchanged with time) of uptake in the normal bowel greater than uptake in the liver.
  - In less than 0.5% of patients receiving In-111 Zevalin, prominent bone marrow uptake was observed, characterized by clear visualization of the long bones and ribs.

Consider bone marrow involvement by lymphoma, increased marrow activity due to recent hematopoietic growth factor administration, and increased reticuloendothelial uptake in patients with HAMA and HACA, as possible causes of prominent bone marrow uptake. Re-assess biodistribution after correction of underlying factors.

2.6 Radiation Dosimetry

Estimations of radiation-absorbed doses for In-111 Zevalin and Y-90 Zevalin were performed using sequential whole body images and the MIRDOSE 3 software program. The estimated radiation absorbed doses to organs and marrow from a course of the Zevalin therapeutic regimen are summarized in Table 1. Absorbed dose estimates for the lower large intestine, upper large intestine, and small intestine have been modified from the standard MIRDOSE 3 output to account for the assumption that activity is within the intestine wall rather than the intestine contents.

Table 1.
Estimated Radiation Absorbed Doses From Y-90 Zevalin and In-111 Zevalin

	Y-90 Zevalin cGy /mCi (mGy/MBq)		In-111 Zevalin cGy/mCi (mGy/MBq)	
Organ	**Median**	**Range**	**Median**	**Range**
Spleen[1]	34.78 (9.4)	6.66 - 74.00 (1.8 – 20.0)	3.33 (0.9)	0.74 - 6.66 (0.2 - 1.8)
Liver[1]	17.76 (4.8)	10.73 - 29.97 (2.9 - 8.1)	2.59 (0.7)	1.48 - 4.07 (0.4 - 1.1)
Lower Large Intestinal Wall[1]	17.39 (4.7)	11.47 - 30.34 (3.1 - 8.2)	1.48 (0.4)	0.74 - 2.22 (0.2 - 0.6)
Upper Large Intestinal Wall[1]	13.32 (3.6)	7.40 - 24.79 (2.0 – 6.7)	1.11 (0.3)	0.74 - 2.22 (0.2 - 0.6)
Heart Wall[1]	10.73 (2.9)	5.55 - 11.84 (1.5 - 3.2)	1.48 (0.4)	0.74 - 1.85 (0.2 - 0.5)
Lungs[1]	7.4 (2)	4.44 - 12.58 (1.2 - 3.4)	0.74 (0.2)	0.74 - 1.48 (0.2 - 0.4)
Testes[1]	5.55 (1.5)	3.70 - 15.91 (1.0 – 4.3)	0.37 (0.1)	0.37 - 1.11 (0.1 - 0.3)
Small Intestine[1]	5.18 (1.4)	2.96 - 7.77 (0.8 – 2.1)	0.74 (0.2)	0.74 - 1.11 (0.2 - 0.3)
Red Marrow[2]	4.81 (1.3)	2.22 - 6.66 (0.6 - 1.8)	0.74 (0.2)	0.37 - 0.74 (0.1 - 0.2)
Urinary Bladder Wall[3]	3.33 (0.9)	2.59 - 4.81 (0.7 – 1.3)	0.74 (0.2)	0.37 - 0.74 (0.1 - 0.2)
Bone Surfaces[2]	3.33 (0.9)	1.85 - 4.44 (0.5 - 1.2)	0.74 (0.2)	0.37 - 0.74 (0.1 - 0.2)

Organ	Y-90 Zevalin cGy /mCi (mGy/MBq)		In-111 Zevalin cGy/mCi (mGy/MBq)	
	Median	Range	Median	Range
Total Body[3]	1.85 (0.5)	1.48 - 2.59 (0.4 - 0.7)	0.37 (0.1)	0.37 - 0.74 (0.1 - 0.2)
Ovaries[3]	1.48 (0.4)	1.11 - 1.85 (0.3 - 0.5)	0.74 (0.2)	0.74 - 0.74 (0.2 - 0.2)
Uterus[3]	1.48 (0.4)	1.11 - 1.85 (0.3 - 0.5)	0.74 (0.2)	0.37 - 0.74 (0.1 - 0.2)
Adrenals[3]	1.11 (0.3)	0.74 - 1.85 (0.2 - 0.5)	0.74 (0.2)	0.74 - 1.11 (0.2 - 0.3)
Brain[3]	1.11 (0.3)	0.74 - 1.85 (0.2 - 0.5)	0.37 (0.1)	0.00 - 0.37 (0.0 - 0.1)
Breasts[3]	1.11 (0.3)	0.74 - 1.85 (0.2 - 0.5)	0.37 (0.1)	0.37 - 0.37 (0.1 - 0.1)
Gallbladder Wall[3]	1.11 (0.3)	0.74 - 1.85 (0.2 - 0.5)	1.11 (0.3)	0.74 - 1.48 (0.2 - 0.4)
Muscle[3]	1.11 (0.3)	0.74 - 1.85 (0.2 - 0.5)	0.37 (0.1)	0.37 - 0.37 (0.1 - 0.1)
Pancreas[3]	1.11 (0.3)	0.74 - 1.85 (0.2 - 0.5)	0.74 (0.2)	0.74 - 1.11 (0.2 - 0.3)
Skin[3]	1.11 (0.3)	0.74 - 1.85 (0.2 - 0.5)	0.37 (0.1)	0.00 - 0.37 (0.0 - 0.1)
Stomach[3]	1.11 (0.3)	0.74 - 1.85 (0.2 - 0.5)	0.74 (0.2)	0.37 - 0.74 (0.1 - 0.2)
Thymus[3]	1.11 (0.3)	0.74 - 1.85 (0.2 - 0.5)	0.37 (0.1)	0.37 - 0.74 (0.1 - 0.2)
Thyroid[3]	1.11 (0.3)	0.74 - 1.85 (0.2 - 0.5)	0.37 (0.1)	0.00 - 0.37 (0.0 - 0.1)
Kidneys[1]	0.37 (0.1)	0.00 - 1.11 (0.0 - 0.3)	0.74 (0.2)	0.37 - 0.74 (0.1 - 0.2)

1 Organ region of interest
2 Sacrum region of interest
3 Whole body region of interest

3 DOSAGE FORMS AND STRENGTHS

3.2 mg ibritumumab tiuxetan per 2mL, single-use vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infusion Reactions

See also prescribing information for rituximab.

Rituximab, alone or as a component of the Zevalin therapeutic regimen, can cause severe including fatal infusion reactions. These reactions typically occur during the first rituximab infusion with time to onset of 30 to 120 minutes. Signs and symptoms of severe infusion reaction may include uriticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Temporarily slow or interrupt the rituximab infusion for less severe infusion reactions. Immediately stop rituximab, In-111 Zevalin, or Y-90 Zevalin administration for severe infusion reactions *[see Boxed Warnings* and *Dosage and Administration (2.2)]*.

5.2 Cytopenias

Cytopenias with delayed onset and prolonged duration, some complicated by hemorrhage and severe infection, are the most common severe adverse reactions of the Zevalin therapeutic regimen. When used according to recommended doses, the incidences of severe thrombocytopenia and neutropenia are greater in patients with mild baseline thrombocytopenia (100,000 to 149,000 /mm^3) compared to those with normal pretreatment platelet counts. Severe cytopenias persisting more than 12 weeks following administration can occur *[see Boxed Warning* and *Adverse Reactions (6.1)]*.

Monitor patients for cytopenias and their complications (e.g., febrile neutropenia, hemorrhage) for up to 3 months after use of the Zevalin therapeutic regimen. Avoid using drugs which interfere with platelet function or coagulation following the Zevalin therapeutic regimen.

5.3 Severe Cutaneous and Mucocutaneous Reactions

Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous dermatitis, and exfoliative dermatitis, some fatal, were reported in post-marketing experience. The time to onset of these reactions was variable, ranging from a few days to 4 months after administration of the Zevalin therapeutic regimen. Discontinue the Zevalin therapeutic regimen in patients experiencing a severe cutaneous or mucocutaneous reaction [*see Boxed Warnings and Adverse Reactions (6.3)]*.

5.4 Altered Biodistribution

Do not administer Y-90 Zevalin to patients with altered biodistribution of In-111 Zevalin. In a post-marketing registry designed to collect biodistribution images and other information in reported cases of altered biodistribution, there were 12 (1.3%) patients reported to have altered biodistribution among 953 patients registered. For descriptions of expected and altered biodistribution image characteristics [*see Dosage and Administration (2.4)*].

5.5 Secondary Leukemia and Myelodysplastic Syndrome

Myelodysplastic syndrome (MDS) and/or acute myelogenous leukemia (AML) were reported in 5.2% (11/211) of patients enrolled in clinical studies and 1.5% (8/535) of patients included in the expanded-access trial, with median follow-up of 6.5 and 4.4 years, respectively. Among the 19 reported cases, the median time to the diagnosis of MDS or AML was 1.9 years following treatment with the Zevalin therapeutic regimen; however, the cumulative incidence continues to increase [*see Adverse Reactions (6.1)*].

5.6 Embryo-Fetal Toxicity (Pregnancy Category D)

Based on its radioactivity, Y-90 Zevalin may cause fetal harm when administered to a pregnant woman. If the Zevalin therapeutic regimen is administered during pregnancy, the patient should be apprised of the potential hazard to a fetus. [*see Use in Specific Populations (8.1)*].

5.7 Extravasation

Monitor patents closely for evidence of extravasation during Zevalin infusion. Immediately terminate the infusion if signs or symptoms of extravasation occur and restart in another limb. *[see Dosage and Administration (2.2)]*.

5.8 Immunization

The safety of immunization with live viral vaccines following the Zevalin therapeutic regimen has not been studied. Do not administer live viral vaccines to patients who have recently received Zevalin. The ability to generate an immune response to any vaccine following the Zevalin therapeutic regimen has not been studied.

5.9 Laboratory Monitoring

Monitor complete blood counts (CBC) and platelet counts following the Zevalin therapeutic regimen weekly until levels recover or as clinically indicated.

5.10 Radionuclide Precautions

During and after radiolabeling Zevalin with In-111 or Y-90, minimize radiation exposure to patients and to medical personnel, consistent with institutional good radiation safety practices and patient management procedures

5.11 Creutzfeldt-Jakob Disease (CJD)

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

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Serious Infusion Reactions [*see Boxed Warnings, Warnings and Precautions (5.1)]*.
- Prolonged and Severe Cytopenias [*see Boxed Warnings* and *Warnings and Precautions (5.2)]*.
- Severe Cutaneous and Mucocutaneous Reactions [*see Boxed Warnings* and *Warnings and Precautions (5.3)]*.
- Secondary Leukemia and Myelodysplastic Syndrome [*see Warnings and Precautions (5.5)*].

The most common adverse reactions of the Zevalin therapeutic regimen are neutropenia, thrombocytopenia, anemia, gastrointestinal symptoms (nausea, vomiting, abdominal pain, and diarrhea), increased cough, dyspnea, dizziness, arthralgia, anorexia, anxiety, and ecchymosis.

The most serious adverse reactions of the Zevalin therapeutic regimen are prolonged and severe cytopenias, infections (predominantly bacterial in origin), hemorrhage while thrombocytopenic, severe cutaneous and mucocutaneous reactions, infusion reactions (bronchospasm and angioedema), myeloid malignancies and myelodysplasias. Because the Zevalin therapeutic regimen includes the use of rituximab, see prescribing information for rituximab.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data below reflect exposure to the Zevalin therapeutic regimen in 349 patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma treated with a single course at the recommended dose and schedule. The safety population included patients enrolled on the following clinical trials: a dose escalation Phase 1 trial, a Phase 2 open label trial, a randomized Phase 3 trial, and an open label expanded access trial. Patients on these trials were required to have acceptable hematologic, renal and hepatic function, less than 25% bone marrow involvement by NHL, prior external beam radiation therapy not to exceed 25% of the bone marrow, and no prior history of myeloablative therapy/autologous bone marrow transplantation. Patients were not permitted to receive hematopoietic growth factors beginning 2 weeks prior to administration of the Zevalin therapeutic regimen.

Table 2 lists adverse reactions that occurred in ≥ 5% of patients. A more detailed description of hematologic toxicities, is provided in Table 3.

Table 2.
Incidence of Adverse Reactions in ≥ 5 % of Patients Receiving the Zevalin therapeutic regimen[†]
(N = 349)

	All Grades %	Grade 3/4 %
Any Adverse Reaction	**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**

[†]Adverse reactions were captured for a period of 12 weeks following the first rituximab infusion of the Zevalin therapeutic regimen

The following adverse reactions (except for those noted in Table 7) occurred in between 1 and 4% of patients: urticaria (4%), anxiety (4%), dyspepsia (4%), sweats (4%), petechiae (3%), epistaxis (3%), allergic reaction (2%), and melena (2%).

Severe or life-threatening adverse reactions occurring in 1-5% of patients included pancytopenia (2%), infusion reaction (1%), gastrointestinal hemorrhage (1%), melena (1%), tumor pain (1%), and apnea (1%). The following severe or life-threatening reactions occurred in <1% of patients: angioedema, tachycardia, urticaria, arthritis, lung edema, pulmonary embolus, encephalopathy, hematemesis, subdural hematoma, and vaginal hemorrhage.

Hematologic Reactions

Hematologic toxicity was the most frequently observed adverse reaction in clinical trials. Patients in clinical studies were not permitted to receive hematopoietic growth factors beginning 2 weeks prior to administration of the Zevalin therapeutic regimen. Table 3 presents the incidence and duration of severe hematologic toxicity for patients with normal baseline platelet count

(≥ 150,000/mm^3) treated with the Zevalin therapeutic regimen and patients with mild thrombocytopenia (platelet count 100,000 to 149,000/mm^3) at baseline who were treated with a modified Zevalin therapeutic regimen that included a lower Y-90 Zevalin dose at 0.3 mCi per kg (11.1 MBq per kg).

Table 3.
Severe Hematologic Toxicity

Baseline Platelet Count	**≥ 150,000mm^3**	**100,000 to 149,000/mm^3**
Y-90 Zevalin Dose	**0.4 mCi/kg (14.8 MBq/kg)**	**0.3 mCi/kg (11.1 MBq/kg)**
ANC		
Median nadir (per mm^3)	800	600
Per Patient Incidence ANC <1000/mm^3	57%	74%
Per Patient Incidence ANC <500/mm^3	30%	35%
Median Duration (Days)* ANC <1000/mm^3	22	29
Platelets		
Median nadir (per mm^3)	41,000	24,000
Per Patient Incidence Platelets <50,000/mm^3	61%	78%
Per Patient Incidence Platelets <10,000/mm^3	10%	14%
Median Duration (Days)# Platelets <50,000/mm^3	24	35

*Day from last ANC ≥1000/mm^3 to first ANC ≥1000/mm^3 following nadir, censored at next treatment or death
Day from last platelet count ≥50,000/mm^3 to day of first platelet count ≥50,000/mm^3 following nadir, censored at next treatment or death

Median time to ANC nadir was 62 days, to platelet nadir was 53 days, and to hemoglobin nadir was 68 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
During the first 3 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 for 2% of patients that included sepsis, empyema, pneumonia, febrile neutropenia, fever, and biliary stent-associated cholangitis. During follow-up from 3 months to 4 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.

Secondary Leukemia and Myelodysplastic Syndrome
There were 19 cases of MDS/AML reported among 746 (2.6%) patients included in clinical studies and the expanded access programs, with a median follow-up of 4.4 years. The overall incidence of MDS/AML among the 211 patients included in the clinical studies was 5.2% (11/211), with a median follow-up of 6.5 years and median time to development of MDS/AML of 2.9 years. The cumulative Kaplan-Meier estimated incidence of MDS/secondary leukemia in this patient population was 2.2% at 2 years and 5.9% at 5 years. The incidence of MDS/AML among the 535 patients in the expanded access programs was 1.5% (8/535) with a median follow-up of 4.4 years and median time to development of MDS/AML of 1.5 years. Multiple cytogenetic abnormalities were described, most commonly involving chromosomes 5 and/or 7. The risk of MDS/AML was not associated with the number of prior treatments (0-1 versus 2-10).

6.2 Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparisons of the incidence of HAMA/HACA to the Zevalin therapeutic regimen with the incidence of antibodies to other products may be misleading.

HAMA and HACA response data on 446 patients from 8 clinical studies conducted over a 10-year time period are available. Overall, 11/446 (2.5%) had evidence of either HAMA formation (N=8) or HACA formation (N=4). Six of these patients developed HAMA/HACA after treatment with Zevalin and 5 were HAMA/HACA positive at baseline. Of the 6 who were HAMA/HACA positive, only one was positive for both. Furthermore, in 6 of the 11 patients, the HAMA/HACA reverted to negative within 2 weeks to 3 months. No patients had increasing levels of HAMA/HACA at the end of the studies.

Only 6/446 patients (1.3%) had developed evidence of antibody formation after treatment with Zevalin, and of these, many either reverted to negative or decreased over time. This data demonstrates that HAMA/HACA develop infrequently, are typically transient, and do not increase with time.

6.3 Post-Marketing Experience
The following adverse reactions have been identified during post-approval use of the Zevalin therapeutic regimen in hematologic malignancies. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to the Zevalin therapeutic regimen.

- Cutaneous and mucocutaneous reactions: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous dermatitis, and exfoliative dermatitis *[see Boxed Warnings* and *Warnings and Precautions (5.3)]*.
- Infusion site erythema and ulceration following extravasation *[see Warnings and Precautions (5.7)]*.
- Radiation injury in tissues near areas of lymphomatous involvement within a month of Zevalin administration.

7 DRUG INTERACTIONS
No formal drug interaction studies have been performed with Zevalin. Patients receiving medications that interfere with platelet function or coagulation should have more frequent laboratory monitoring for thrombocytopenia.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Teratogenic Effects: Category D [*see Warnings and Precautions* (5.6)]: Based on its radioactivity, Y-90 Zevalin may cause fetal harm when administered to a pregnant woman. Immunoglobulins are known to cross the placenta. There are no adequate and well-controlled studies in pregnant women. Animal reproductive toxicology studies of Zevalin have not been conducted.

Advise women of childbearing potential to use adequate contraception. Inform women who become pregnant while receiving Zevalin of the potential fetal risks. [*see Patient Counseling Information (17)]*

8.3 Nursing Mothers
Because human IgG is excreted in human milk, it is expected that Zevalin would be present in human milk. Because of the potential for adverse reactions in nursing infants from Y-90 or In-111 Zevalin , a decision should be made to discontinue nursing or not administer the Zevalin therapeutic regimen, taking into account the importance of the drug to the mother.

8.4 Pediatric Use
The safety and effectiveness have not been established in pediatric patients.

8,5 Geriatric Use

Of 349 patients treated with the Zevalin therapeutic regimen in clinical studies, 38% (132 patients) were age 65 years and over, while 12% (41 patients) were age 75 years and 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.

10 OVERDOSAGE

Severe cytopenias which may require stem cell support have occurred at doses higher than the recommended maximum total dose of 32 mCi.

11 DESCRIPTION

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 Indium-111 or Yttrium-90. 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.

Ibritumomab tiuxetan is a clear, colorless, sterile, pyrogen-free, preservative-free solution that may contain translucent particles. Each single-use vial includes 3.2 mg of ibritumomab tiuxetan in 2mL of 0.9% Sodium Chloride.

Physical/Radiochemical Characteristics of In-111

Indium-111 decays by electron capture, with a physical half-life of 67.3 hours (2.81 days). The product of radioactive decay is non-radioactive Cadmium-111. Radiation emission data for In-111 are summarized in Table 4.

Table 4.
Principal In-111 Radiation Emission Data

Radiation	Mean % per Disintegration	Mean Energy (keV)
Gamma-2	90.2	171.3
Gamma-3	94.0	245.4

External Radiation

The exposure rate constant for 1 mCi (37 MBq) of In-111 is 8.3×10^{-4} C/kg/hr (3.2 R/hr) at 1 cm.

To allow correction for physical decay of In-111, the fractions that remain at selected intervals before and after the time of calibration are shown in Table 5.

Table 5.
Physical Decay Chart: In-111
Half-life 2.81 Days (67.3 Hours)

Calibration Time (Hrs.)	Fraction Remaining
-48	1.64
-42	1.54
-36	1.45
-24	1.28
-12	1.13
-6	1.06
0	1.00
6	0.94
12	0.88
24	0.78
36	0.69
42	0.65
48	0.61

Physical/Radiochemical Characteristics of Y-90

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 Y-90 are summarized in Table 6.

Table 6.
Principal Y-90 Radiation Emission Data

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

External Radiation

The exposure rate for 1 mCi (37 MBq) of Y-90 is 8.3×10^{-3} C/kg/hr (32 R/hr) at the mouth of an open Y-90 vial.

To allow correction for physical decay of Y-90, the fractions that remain at selected intervals before and after the time of calibration are shown in Table 7.

Table 7.
Physical Decay Chart: Y-90
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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ibritumomab tiuxetan binds specifically to the CD20 antigen (human B-lymphocyte-restricted differentiation antigen, Bp35). The apparent affinity (K_D) of ibritumomab tiuxetan for the CD20 antigen ranges between approximately 14 to 18 nM. The CD20 antigen is expressed on pre-B and mature B lymphocytes and on > 90% of B-cell non-Hodgkin's lymphomas (NHL). The CD20 antigen is not shed from the cell surface and does not internalize upon antibody binding.

The chelate tiuxetan, which tightly binds In-111 or Y-90, is covalently linked to ibritumomab. The beta emission from Y-90 induces cellular damage by the formation of free radicals in the target and neighboring cells.

Ibritumomab tiuxetan binding was observed *in vitro* 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.

12.2 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, 0-1084/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/mm^3) by 9 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 13-3990 mg/dL) after treatment and recovered to normal values by 6-month post therapy.

12.3 Pharmacokinetics

Pharmacokinetic and biodistribution studies were performed using In-111 Zevalin (5 mCi [185 MBq] In-111, 1.6 mg ibritumomab tiuxetan). In an early study designed to assess the need for pre-administration of unlabeled antibody, only 18% of known sites of disease were imaged when In-111 Zevalin was administered without unlabeled ibritumomab. When preceded by unlabeled ibritumomab (1.0 mg/kg or 2.5 mg/kg), In-111 Zevalin detected 56% and 92% of known disease sites, respectively. These studies were conducted with a Zevalin therapeutic regimen that included unlabeled ibritumomab.

In pharmacokinetic studies of patients receiving the Zevalin therapeutic regimen, the mean effective half-life for Y-90 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 7 days, a median of 7.2% of the injected activity was excreted in urine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity and mutogenicity studies have not been conducted. However, radiation is a potential carcinogen and mutagen. No animal studies have been performed to determine the effects of Zevalin on fertility in males or females. In clinical studies, the Zevalin therapeutic regimen results in a significant radiation dose to the testes; the radiation dose to the ovaries has not been established [*see Dosage and Administration (2.6)*]. There is a potential risk that the Zevalin therapeutic regimen could cause toxic effects on the male and female gonads. Effective contraceptive methods should be used during treatment and for up to 12 months following the Zevalin therapeutic regimen [*see Patient Counseling Information (17)*]

13.2 Animal Toxicology and/or Pharmacology

Animal reproductive toxicology studies of the Zevalin regimen have not been conducted. Because the Zevalin therapeutic regimen includes the use of rituximab, also see prescribing information for rituximab.

14 CLINICAL STUDIES

The safety and efficacy of the Zevalin therapeutic regimen were evaluated in 2 multi-center trials, enrolling a total of 197 subjects and a third study enrolling a total of 30 subjects.

14.1 Relapsed Follicular Lymphoma Refractory to Rituximab

Study 1 was a single arm study of 54 patients with relapsed follicular lymphoma, who were refractory to rituximab treatment. Patients had a World Health Organization (WHO) Performance Status (PS) 0-2, <25% bone marrow involvement by NHL, no prior bone marrow transplantation, and acceptable hematologic, renal, and hepatic function. Refractoriness to rituximab was defined as failure to achieve a complete or partial response or time to disease progression (TTP) of < 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). Table 8 summarizes efficacy data from Study 1.

14.2 Relapsed or Refractory, Rituximab-Naïve, Low-Grade or Follicular NHL

Study 2 was a randomized (1:1), open-label, multicenter study comparing the Zevalin therapeutic regimen with rituximab. The trial was conducted in 130 patients with relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma (NHL); no patient had received prior rituximab. Patients had histologically confirmed NHL requiring therapy, a WHO PS 0-2, <25% bone marrow involvement by NHL, no prior bone marrow transplantation, and acceptable hematologic function. Sixty-four patients received the Zevalin therapeutic regimen, and 66 patients received rituximab given as an IV infusion at 375 mg per m^2 weekly times 4 doses. The primary efficacy endpoint of the study was ORR using the IWRC (see Table 8). The ORR was significantly higher for patients receiving the Zevalin therapeutic regimen (83% vs. 55%, p<0.001). Time-to-disease-progression was not significantly different between study arms..

Table 8.
Summary of Efficacy Data[1]

	Study 1	Study 2	
	Zevalin therapeutic regimen N = 54	**Zevalin therapeutic regimen N = 64**	**Rituximab N = 66**
Overall Response Rate (%)	74	83	55
Complete Response Rate[2] (%)	15	38	18
Median DR[3,4] (Months) [Range[5]]	6.4 [0.5-49.9+]	14.3 [1.8-47.6+]	11.5 [1.2-49.7+]
Median TTP[3,6] (Months) [Range[5]]	6.8 [1.1-50.9+]	12.1 [2.1-49.0+]	10.1 [0.7-51.3+]

1IWRC: International Workshop response criteria

2CRu and CR: Unconfirmed and confirm complete response

3Estimated with observed range

4Duration of response: interval from the onset of response to disease progression

5"+" indicates an ongoing response

6Time to Disease Progression: interval from the first infusion to disease progression

Study 3 was a single arm study of 30 patients of whom 27 had relapsed or refractory low-grade, follicular NHL and a platelet count 100,000 to 149,000/mm^3. Patients with ≥ 25% lymphomatous marrow involvement, prior myeloablative therapy with stem cell support, prior external beam radiation to > 25% of active marrow or neutrophil count <1,500/mm^3 were ineligible for Study 3 All patients received [0.3 mCi per kg (11.1 MBq per kg). Objective, durable clinical responses were observed [89% ORR (95% CI: 70-97%) with a median duration of response of 11.6 months (range: 1.0-42.4+ months)].

16 HOW SUPPLIED/STORAGE AND HANDLING

There are two kits necessary for preparation of the Zevalin therapeutic regimen: one for preparation of In-111 radiolabeled Zevalin (NDC 60553-0104-04) and one for preparation of Y-90 radiolabeled Zevalin (NDC 60553-0103-03). The contents of all vials are sterile, pyrogen-free, contain no preservatives, and are not radioactive. Each kit contains four identification labels and the following four vials:

(1) One (1) Zevalin vial containing 3.2 mg ibritumomab tiuxetan in 2 mL 0.9% Sodium Chloride as a clear, colorless solution.
(2) One (1) 50 mM Sodium Acetate Vial containing 13.6 mg Sodium Acetate trihydrate in 2 mL Water for Injection, USP as a clear, colorless solution.
(3) One (1) Formulation Buffer Vial containing 750 mg Albumin (Human), 76 mg Sodium Chloride, 28 mg Sodium Phosphate Dibasic Dodecahydrate, 4 mg Pentetic Acid, 2 mg Potassium Phosphate Monobasic and 2 mg Potassium Chloride in 10 mL Water for Injection, pH 7.1 as a clear yellow to amber colored solution.
(4) One (1) empty Reaction Vial.

Indium-111 Chloride Sterile Solution (In-111 Chloride) must be ordered separately from either GE Healthcare, or Covidien.

Yttrium-90 Chloride Sterile Solution is shipped directly from MDS Nordion upon placement of an order for the Y-90 Zevalin kit.

Rituximab (Rituxan®, Biogen Idec, Inc. and Genetech USA Inc.) must be ordered separately.

Storage
Store kits at 2-8°C (36-46°F). Do not freeze.

17 PATIENT COUNSELING INFORMATION

Advise patients:

- To contact a healthcare professional for severe signs and symptoms of infusion reactions
- To take premedications as prescribed [*see Warnings and Precautions (2.2) and (5.1)]*.
- To report any signs or symptoms of cytopenias (bleeding, easy bruising, petechiae or purpura, pallor, weakness or fatigue)
- To avoid medications that interfere with platelet function, except as directed by a healthcare professional [*see Warnings and Precautions (5.2)]*.
- To seek prompt medical evaluation for diffuse rash, bullae, or desquamation of the skin or oral mucosa
- To immediately report symptoms of infection (e.g. pyrexia). [*see Adverse Reactions (6.3)]*.
- That immunization with live viral vaccines is not recommended for 12 months following the Zevalin therapeutic regimen. *[see Warnings and Precautions (5.8)]*.
- To use effective contraceptive methods during treatment and for a minimum of 12 months following Zevalin therapy
- To discontinue nursing during and after Zevalin treatment. *[see Use In Special Populations (8.3)]*.

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