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----------

Indications and Usage (1)	9/2009
Dosage and Administration (2)	9/2009
Warnings and Precautions (5)	9/2009

----------INDICATIONS AND USAGE----------

Zevalin is a CD20-directed radiotherapeutic antibody administered as part of the Zevalin therapeutic regimen indicated for the treatment of patients with:

- relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma (NHL) (1.1).
- previously untreated follicular NHL who achieve a partial or complete response to first-line chemotherapy (1.2).

----------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 (14.8 MBq per kg) Y-90 Zevalin IV.
  - If platelets ≥ 100,000 but ≤ 149,000/mm^3 in relapsed or refractory patients: Within 4 hours after rituximab infusion, administer 0.3 mCi/kg (11.1 MBq per kg) Y-90 Zevalin IV.

----------DOSAGE FORMS AND STRENGTHS----------

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

----------CONTRAINDICATIONS----------

None.

----------WARNINGS AND PRECAUTIONS----------

- **Serious Infusion Reactions:** Immediately stop and permanently discontinue rituximab, In-111 Zevalin, and Y-90 Zevalin. (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 or Zevalin infusions if patients develop severe cutaneous or mucocutaneous reactions. (5.3, 6.3)
- **Leukemia and Myelodysplastic Syndrome** (5.5, 6.1)
- **Embryo-fetal Toxicity:** May cause fetal harm if given during pregnancy. (5.6, 8.1)
- **Extravasation:** Monitor for extravasation and terminate infusion if it 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----------

Common adverse reactions (≥ 40%) in clinical trials were: neutropenia, leukopenia, thrombocytopenia, anemia, infection, asthenia, musculoskeletal symptoms and gastrointestinal symptoms. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Spectrum Pharmaceuticals at 1-866-298-8433 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: 9/2009

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

1.1 Relapsed or Refractory, Low-Grade or Follicular NHL

Zevalin is indicated for the treatment of relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma (NHL).

1.2 Previously Untreated Follicular NHL

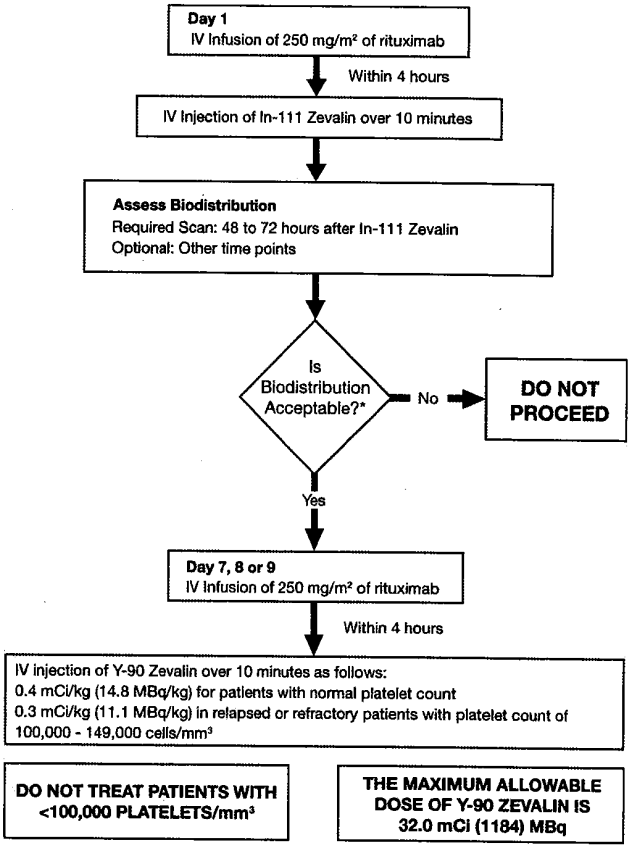
Zevalin is indicated for the treatment of previously untreated follicular NHL in patients who achieve a partial or complete response to first-line chemotherapy.

2 DOSAGE AND ADMINISTRATION

Recommended Dosing Schedule:

- Administer the Zevalin therapeutic regimen as outlined in Section 2.1.
- Initiate the Zevalin therapeutic regimen following recovery of platelet counts to ≥150,000/mm^3 at least 6 weeks, but no more than 12 weeks, following the last dose of first-line chemotherapy.

2.1 Overview of Dosing Schedule



* See IMAGE ACQUISITION AND INTERPRETATION

2.2 Zevalin Therapeutic Regimen Dosage and Administration

Day 1:

- Premedicate with acetaminophen 650 mg orally and diphenhydramine 50 mg orally prior to rituximab 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 the Zevalin therapeutic regimen *[see Boxed Warning* 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 in-line filter 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)]*.

- Premedicate with acetaminophen 650 mg orally and diphenhydramine 50 mg orally prior to rituximab 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. Use a 0.22 micron low-protein-binding in-line filter between the syringe and the infusion port. After injection, flush the line with at least 10 mL of normal saline.
  - **If platelet count ≥150,000/mm^3**, administer Y-90 Zevalin over 10 minutes as an intravenous injection at a dose of Y-90 0.4 mCi per kg (14.8 MBq per kg) actual body weight.
  - **If platelet count 100,000-149,000/mm^3**, in relapsed or refractory patients, administer Y-90 Zevalin over 10 minutes as an intravenous injection at a dose of Y-90 0.3 mCi per kg (11.1 MBq per kg) actual body weight.
  - **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)]*.

2.3 Directions for Preparation of Radiolabeled 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 Mallinckrodt /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 (ITLC-SG)
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 the 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 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 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. Developing chamber for chromatography
H. Suitable radioactivity counting apparatus
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 (1184 MBq)**. 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

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 Biodistribution

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

Organ	Y-90 Zevalin cGy /mCi (mGy/MBq)		In-111 Zevalin cGy/mCi (mGy/MBq)	
	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 ibritumomab tiuxetan per 2 mL, 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 reactions may include urticaria, 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 Warning* and *Dosage and Administration (2.2)]*.

5.2 Prolonged and Severe 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)]*.

Do not administer the Zevalin therapeutic regimen to patients with ≥ 25% lymphoma marrow involvement and/or impaired bone marrow reserve. 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 Warning* 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 (2.5)]*.

5.5 Leukemia and Myelodysplastic Syndrome

Myelodysplastic syndrome (MDS) and/or acute myelogenous leukemia (AML) were reported in 5.2% (11/211) of patients with relapsed or refractory NHL 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)]*.

Among 204 patients receiving Y-90 Zevalin following first-line chemotherapy, two patients (1%) were diagnosed with AML within 3 years of receiving Zevalin.

5.6 Embryo-Fetal Toxicity

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 patients 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 serious adverse reactions are discussed in greater detail in other sections of the label:

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

The most common adverse reactions of Zevalin are cytopenias, fatigue, abdominal pain, nausea, nasopharyngitis, asthenia, diarrhea, cough and pyrexia.

The most serious adverse reactions of Zevalin are prolonged and severe cytopenias (thrombocytopenia, anemia, lymphopenia, neutropenia) and secondary malignancies.

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 reported safety data reflects exposure to Zevalin in 349 patients with relapsed or refractory, low-grade, follicular or transformed NHL across 5 trials (4 single arm and 1 randomized) and in 206 patients with previously untreated follicular NHL in a randomized trial (Study 4) who received any portion of the Zevalin therapeutic regimen. The safety data reflect exposure to Zevalin in 270 patients with relapsed or refractory NHL with platelet counts ≥150,000/ mm^3 who received 0.4 mCi/kg (14.8 MBq/kg) of Y-90 Zevalin (Group 1 in Table 4), 65 patients with relapsed or refractory NHL with platelet counts of 100,000 to 149,000/mm^3 who received 0.3 mCi/kg (11.1 MBq/kg) of Y-90 Zevalin (Group 2 in Table 4), and 204 patients with previously untreated NHL with platelet counts ≥150,000/ mm^3 who received 0.4 mCi/kg (14.8 MBq/kg) of Y-90 Zevalin; all patients received a single course of Zevalin.

Table 2 displays selected adverse reaction incidence rates in patients who received any portion of the Zevalin therapeutic regimen (n=206) or no further therapy (n=203) following first-line chemotherapy (Study 4).

Table 2.
Per-Patient Incidence (%) of Selected* Adverse Reactions Occurring in ≥ 5% of Patients with Previously Untreated Follicular NHL Treated with the Zevalin Therapeutic Regimen

	Zevalin (n=206)		Observation (n=203)	
	All Grades**	Grade** 3-4	All Grades**	Grade** 3-4
	%	%	%	%
Gastrointestinal Disorders				
Abdominal pain	17	2	13	<1
Diarrhea	11	0	3	0
Nausea	18	0	2	0
Body as a Whole				
Asthenia	15	1	8	<1
Fatigue	33	1	9	0
Influenza-like illness	8	0	3	0
Pyrexia	10	3	4	0
Musculoskeletal				
Myalgia	9	0	3	0
Metabolism				
Anorexia	8	0	2	0
Respiratory, Thoracic & Media				
Cough	11	<1	5	0
Pharyngolaryngeal pain	7	0	2	0
Epistaxis	5	2	<1	0
Nervous System				
Dizziness	7	0	2	0
Vascular				
Hypertension	7	3	2	<1
Skin & Subcutaneous				
Night sweats	8	0	2	0
Petechiae	8	2	0	0
Pruritus	7	0	1	0
Rash	7	0	<1	0
Infections & Infestations				
Bronchitis	8	0	3	0
Nasopharyngitis	19	0	10	0
Rhinitis	8	0	2	0
Sinusitis	7	<1	<1	0
Urinary tract infection	7	<1	3	0
Blood and Lymphatic System				
Thrombocytopenia	62	51	1	0
Neutropenia	45	41	3	2
Anemia	22	5	4	0
Leukopenia	43	36	4	1
Lymphopenia	26	18	9	5

*Between-group difference of ≥5%
**NCI CTCAE version 2.0

Table 3 shows hematologic toxicities in 349 Zevalin-treated patients with relapsed or refractory, low-grade, follicular or transformed B-cell NHL. Grade 2-4 hematologic toxicity occurred in 86% of Zevalin-treated patients.

Table 3.
Per-Patient Incidence (%) of Hematologic Adverse Reactions in Patients with Relapsed or Refractory Low-grade, Follicular or Transformed B-cell NHL†
(N = 349)

	All Grades %	Grade 3-4 %
Thrombocytopenia	95	63
Neutropenia	77	60
Anemia	61	17
Ecchymosis	7	<1

†Occurring within the 12 weeks following the first rituximab infusion of the Zevalin therapeutic regimen

Prolonged and Severe Cytopenias
Patients in clinical studies were not permitted to receive hematopoietic growth factors beginning 2 weeks prior to administration of the Zevalin therapeutic regimen.

The incidence and duration of severe hematologic toxicity in previously treated NHL patients (N=335) and in previously untreated patients (Study 4) receiving Y-90 Zevalin are shown in Table 4.

Table 4.
Severe Hematologic Toxicity in Patients Receiving Zevalin

Baseline Platelet Count	**Group 1 (n=270) ≥ 150,000/mm³**	**Group 2 (n=65) 100,000 to 149,000/mm³**	**Study 4 (n=204) ≥ 150,000/mm³**
Y-90 Zevalin Dose	**0.4 mCi/kg (14.8 MBq/kg)**	**0.3 mCi/kg (11.1 MBq/kg)**	**0.4 mCi/kg (14.8 MBq/kg)**
ANC			
Median nadir (per mm³)	800	600	721
Per Patient Incidence ANC <1000/mm³	57%	74%	65%
Per Patient Incidence ANC <500/mm³	30%	35%	26%
Median Duration (Days)* ANC <1000/mm³	22	29	29
Median Time to Recovery**	12	13	15
Platelets			
Median nadir (per mm³)	41,000	24,000	42,000
Per Patient Incidence Platelets <50,000/mm³	61%	78%	61%
Per Patient Incidence Platelets <10,000/mm³	10%	14%	4%
Median Duration (Days)# Platelets <50,000/mm³	24	35	26
Median Time to Recovery**	13	14	14

* Day from last ANC ≥1000/mm³ to first ANC ≥1000/mm³ following nadir, censored at next treatment or death
**Day from nadir to first count at level of Grade 1 toxicity or baseline
Day from last platelet count ≥50,000/mm³ to day of first platelet count ≥50,000/mm³ following nadir, censored at next treatment or death

Cytopenias were more severe and more prolonged among eleven (5%) patients who received Zevalin after first-line fludarabine or a fludarabine-containing chemotherapy regimen as compared to patients receiving non-fludarabine-containing regimens. Among these eleven patients, the median platelet nadir was 13,000/mm³ with a median duration of platelets below 50,000/mm³ of 56 days and the median time for platelet recovery from nadir to Grade 1 toxicity or baseline was 35 days. The median ANC was 355/ mm³, with a median duration of ANC below 1,000/mm³ of 37 days and the median time for ANC recovery from nadir to Grade 1 toxicity or baseline was 20 days.

The median time to cytopenia was similar across patients with relapsed/refractory NHL and those completing first-line chemotherapy, with median ANC nadir at 61-62 days, platelet nadir at 49-53 days, and hemoglobin nadir at 68-69 days after Y-90-Zevalin administration.

Information on hematopoietic growth factor use and platelet transfusions is based on 211 patients with relapsed/refractory NHL and 206 patients following first- line chemotherapy. Filgrastim was given to 13% of patients and erythropoietin to 8% with relapsed or refractory disease; 14% of patients receiving Zevalin following first-line chemotherapy received granulocyte-colony stimulating factors and 5% received erythopoiesis-stimulating agents. Platelet transfusions were given to approximately 22% of all Zevalin-treated patients. Red blood cell transfusions were given to 20% of patients with relapsed or refractory NHL and 2% of patients receiving Zevalin following first-line chemotherapy.

Infections
In relapsed or refractory NHL patients, infections occurred in 29% of 349 patients during the first 3 months after initiating the Zevalin therapeutic regimen and 3% developed serious infections (urinary tract infection, febrile neutropenia, sepsis, pneumonia, cellulitis, colitis, diarrhea, osteomyelitis, and upper respiratory tract infection). Life-threatening infections were reported in 2% (sepsis, empyema, pneumonia, febrile neutropenia, fever, and biliary stent-associated cholangitis). From 3 months to 4 years after Zevalin treatment, 6% of patients developed infections; 2% were serious (urinary tract infection, bacterial or viral pneumonia, febrile neutropenia, perihilar infiltrate, pericarditis, and intravenous drug-associated viral hepatitis) and 1% were life-threatening infections (bacterial pneumonia, respiratory disease, and sepsis).

When administered following first-line chemotherapy (Table 2), Grade 3-4 infections occurred in 8% of Zevalin treated patients and in 2% of controls and included neutropenic sepsis (1%), bronchitis, catheter sepsis, diverticulitis, herpes zoster, influenza, lower respiratory tract infection, sinusitis, and upper respiratory tract infection.

Leukemia and Myelodysplastic Syndrome
Among 746 patients with relapsed/refractory NHL, 19 (2.6%) patients developed MDS/AML 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).

Among 204 patients receiving Y-90-Zevalin following first-line treatment, 2 (1%) developed AML at approximately 2 and 3.3 years after Zevalin administration, respectively.

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 Warning* 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 of Zevalin have not been established in pediatric patients.

8.5 Geriatric Use

Of 349 patients with relapsed/refractory NHL 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.

Of 414 patients enrolled in Study 4 (Zevalin following first-line chemotherapy) 206 patients received Zevalin. Of these patients 14% (29 patients) were 65 years and over, while 2% (4 patients) were 75 years and older. In the control arm, 10% (21 patients) were 65 years or over and 0% (0 patients) were 75 years or older.

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 (1184 MBq).

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 2 mL 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 5.

Table 5.
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 x 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 6.

Table 6.
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 7.

Table 7.
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 x 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 8.

Table 8.
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 months 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 therapeutic regimen have not been conducted. Because the Zevalin therapeutic regimen includes the use of rituximab, also see prescribing information for rituximab.

14 CLINICAL STUDIES

14.1 Relapsed or Refractory, Low-grade or Follicular Lymphoma

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 main efficacy outcome measure of the study was the overall response rate (ORR) using the International Workshop Response Criteria (IWRC). Other efficacy outcome measures included time-to-disease-progression (TTP) and duration of response (DR). Table 9 summarizes efficacy data from Study 1.

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 main efficacy outcome measure of the study was ORR using the IWRC. 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 9 summarizes efficacy data from Study 2.

Table 9.
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+]

1 IWRC: International Workshop response criteria
2 CRu and CR: Unconfirmed and confirm complete response
3 Estimated with observed range
4 Duration of response: interval from the onset of response to disease progression
5 "+" indicates an ongoing response
6 Time 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 Y-90 Zevalin [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)].

14.2 Follicular, B-Cell NHL Upon Completion of First-Line Chemotherapy

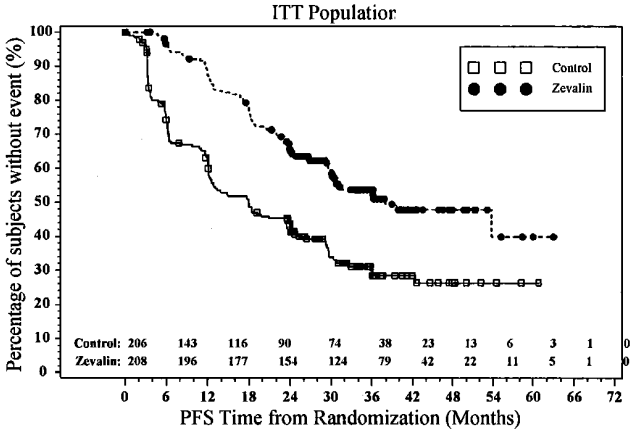
Study 4 was a multi-center, randomized, open-label study conducted in patients with follicular NHL with a partial (PR) or complete response (CR/CRu) upon completion of first-line chemotherapy. Randomization was stratified by center and response to first-line therapy (CR or PR). Key eligibility criteria were <25% bone marrow involvement, no prior external beam radiation or myeloablative therapy, and recovery of platelets to normal levels. Patients were randomized to receive Zevalin (n=208) or no further therapy (n=206). Y-90 Zevalin was administered at least 6 weeks but no more than 12 weeks following the last dose of chemotherapy. The main efficacy outcome measure was progression-free survival (PFS) assessed by study investigators using the International Workshop to Standardize Response Criteria for non-Hodgkin's Lymphoma (1999).

Among the 414 patients, 49% were male, 99% were Caucasian, 12% were ≥65 years old, 83% had a WHO performance status of 0, and 65% had Stage IV disease. Thirty-nine (9.5%) patients received single agent chlorambucil, 22 (5%) patients received fludarabine or a fludarabine-containing regimen, 294 (71%) patients received cyclophosphamide-containing combination chemotherapy [CHOP (31%); CHOP-like (15%); CVP/COP (26%)] and 59 (14%) patients received rituximab-containing combination chemotherapy as first-line treatment.

Progression-free survival was significantly prolonged among Zevalin-treated patients compared to those receiving no further treatment [median PFS 38 months vs. 18 months; HR 0.46 (95% CI: 0.35, 0.60) p<0.0001 Cox model stratified by response to first-line therapy and initial treatment strategy (immediate vs. watch-and-wait)]. The number of patients who died was too small to permit a reliable comparison of survival.

The results for PFS are presented in Figure 1.

Figure 1.
Study 4: Kaplan-Meier Estimator for Investigator-Assessed Progression Free Survival Time



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 68152-104-04) and one for preparation of Y-90 radiolabeled Zevalin (NDC 68152-103-03). 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 Mallinckrodt/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 and Genentech USA) 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 Dosage and Administration (2.2)* and *Warnings and Precautions (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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