PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

ZEVALIN®

Ibritumomab tiuxetan

Sterile solution, 3.2 mg (1.6 mg/mL) single use vial, for intravenous infusion

Kit for the preparation of yttrium (^{90}Y) ibritumomab tiuxetan

Therapeutic Radiopharmaceutical Kit

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ZEVALIN® [kit for the preparation of yttrium (^{90}Y) ibritumomab tiuxetan solution for injection], as part of the Zevalin therapeutic regimen, is indicated for the treatment of patients with relapsed or refractory low-grade or follicular, CD20 positive, B-cell non-Hodgkin's lymphoma, including patients with rituximab-refractory follicular non-Hodgkin's lymphoma.

1.1 Pediatrics

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

1.2 Geriatrics

Geriatrics (> 65 years of age): No overall differences in safety or efficacy were observed between patients ≥65 years and those younger than 65 years, but greater sensitivity of some older individuals cannot be ruled out.

2 CONTRAINDICATIONS

Zevalin (ibritumomab tiuxetan) is contraindicated in patients with known type I hypersensitivity or anaphylactic reactions to murine proteins or to any component of the Zevalin therapeutic regimen, including yttrium (^{90}Y) chloride, rituximab, non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING. Zevalin is also contraindicated in pregnant or nursing women (see 7 WARNINGS AND PRECAUTIONS).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Radiopharmaceuticals should be used only by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in or on humans.
- Fatal infusion reactions with rituximab: Deaths have occurred within 24 hours of rituximab infusion, an essential component of the Zevalin therapeutic regimen. Approximately 80% of fatal infusion reactions occurred in association with the first rituximab infusion. These fatalities were associated with an infusion reaction symptom complex that included hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation or cardiogenic shock. Patients who develop severe infusion reactions should have rituximab and yttrium (^{90}Y) ibritumomab tiuxetan infusions discontinued and receive medical treatment (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS).

- Prolonged and severe cytopenias: Yttrium (^{90}Y) ibritumomab tiuxetan administration can result in severe and prolonged cytopenias, especially when administered after prior radiation or multiple chemotherapies. The risk of hematological toxicity may be increased when Zevalin is administered shortly (< 4 months) after prior therapy with fludarabine-containing regimens (see 9 DRUG INTERACTIONS). The Zevalin therapeutic regimen should not be administered to patients with ≥25% lymphoma marrow involvement and/or impaired bone marrow reserve (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS).
- Severe mucocutaneous reactions: Severe mucocutaneous reactions, some with fatal outcome, have been reported in association with the Zevalin therapeutic regimen, which includes rituximab and yttrium (^{90}Y) ibritumomab tiuxetan. Patients who develop a severe mucocutaneous reaction should have rituximab and yttrium (^{90}Y) ibritumomab tiuxetan infusions discontinued and receive medical treatment (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS).
- Dosing: The prescribed, measured and administered dose of yttrium (^{90}Y) ibritumomab tiuxetan should not exceed the absolute maximum allowable dose of 32.0 mCi (1200 MBq) (see 4. DOSAGE AND ADMINISTRATION).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Do not give yttrium (^{90}Y) ibritumomab tiuxetan to patients with a platelet count < 100,000/mm^3 (see 7 WARNINGS AND PRECAUTIONS).

Premedication

Hypersensitivity reactions may occur. Premedication, consisting of acetaminophen and diphenhydramine, should be considered before each infusion of rituximab (see 7 WARNINGS AND PRECAUTIONS).

Yttrium (^{90}Y) ibritumomab tiuxetan should not be used in the absence of rituximab pre-dose.

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

The Zevalin (ibritumomab tiuxetan) therapeutic regimen is administered in two steps:

Step 1 is a single intravenous infusion of 250 mg/m^2 of rituximab (not included in the Zevalin kit).

Step 2 follows step 1 by 7-9 days and consists of a second infusion of 250 mg/m^2 of rituximab shortly (within 4 hours) prior to 0.4 mCi/kg (14.8 MBq/kg) of yttrium (^{90}Y) ibritumomab tiuxetan

administered as a ten-minute intravenous infusion.

The prescribed, measured and administered dose of yttrium (^{90}Y) ibritumomab tiuxetan must not exceed the absolute maximum allowable dose of 32.0 mCi (1200 MBq), regardless of the patient's body weight.

Dosage Adjustment

Patients with mild thrombocytopenia

The yttrium (^{90}Y) ibritumomab tiuxetan dose should be reduced to 0.3 mCi/kg (11 MBq/kg) for patients with a baseline platelet count between 100,000 and 149,000 cells/mm^3.

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

Special Population

Renal/hepatic impairment

The safety and efficacy in patients with renal or hepatic impairment have not been established.

Pediatric patients (below 18 years)

The safety and efficacy of yttrium (^{90}Y) ibritumomab tiuxetan in pediatric patients below 18 years have not been established.

Geriatric patients (65 years of age and above)

No overall differences in safety or efficacy of yttrium (^{90}Y) ibritumomab tiuxetan were observed between patients ≥65 years and those younger than 65 years, but greater sensitivity of some older individuals cannot be ruled out.

4.4 Administration

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

After radiolabeling, yttrium (^{90}Y) ibritumomab tiuxetan solution should be administered by intravenous infusion over 10 minutes.

The total radioactivity in the syringe should be verified with a dose calibrator immediately before and after yttrium (^{90}Y) ibritumomab tiuxetan administration to the patient. The dose calibrator must be calibrated and comply with international standards.

Before administration to the patient, the percent radiochemical purity of the prepared yttrium

(^{90}Y) ibritumomab tiuxetan must be verified. If the average radiochemical purity is less than 95%, the preparation must not be administered (see 4.7 Instructions for Preparation and Use).

Step 1:

First rituximab infusion: Rituximab at a dose of 250 mg/m^2 should be administered intravenously at an initial infusion rate of 50 mg/h. Rituximab should not be mixed or diluted with other drugs. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h. If hypersensitivity or an infusion-related event develops, the infusion should be temporarily slowed or interrupted (see 7 WARNINGS AND PRECAUTIONS). The infusion can continue at one-half the previous rate upon improvement of patient symptoms. Refer to rituximab Product Monograph for detailed guidance on its use.

Step 2:

Step 2 of the Zevalin therapeutic regimen is initiated 7-9 days (day 7, 8, or 9) following step 1 administration.

- Second rituximab infusion: Rituximab at a dose of 250 mg/m^2 is administered intravenously at an initial infusion rate of 100 mg/h (50 mg/h if infusion-related events were documented during the first rituximab administration) and increased by 100 mg/h increments at 30-minute intervals, to a maximum of 400 mg/h, as tolerated.
- Yttrium (^{90}Y) ibritumomab tiuxetan injection: Within four hours following completion of the rituximab dose, yttrium (^{90}Y) ibritumomab tiuxetan at a dose of 0.4 mCi/kg (15 MBq/kg) body weight for patients with a platelet count ≥150,000 cells/mm^3, and 0.3 mCi/kg (11 MBq/kg) body weight for patients with a platelet count of 100,000 to 149,000 cells/mm^3 is injected intravenously over a period of ten minutes. Yttrium (^{90}Y) ibritumomab tiuxetan may be infused directly by stopping the flow from an infusion bag and administering it directly into the line. A 0.2 or 0.22-micrometer low-protein-binding membrane filter should be in line between the syringe and the infusion port prior to injection of yttrium (^{90}Y) ibritumomab tiuxetan. After injection, the line should be flushed with at least 10 mL of 0.9% sodium chloride solution. Precautions should be taken to avoid extravasation. A free-flowing intravenous line should be established prior to yttrium (^{90}Y) ibritumomab tiuxetan injection. Close monitoring for evidence of extravasation during the injection of yttrium (^{90}Y) ibritumomab tiuxetan is required. If any signs or symptoms of extravasation occur, the infusion should be immediately terminated and restarted in another vein.

4.7 Instructions for Preparation and Use

General

- The Zevalin carton is to be used by a qualified specialist to prepare a single dose of

yttrium (^{90}Y) ibritumomab tiuxetan for therapy. Changing the ratio of any of the reactants in the radiolabeling process may adversely affect therapeutic results and is not recommended. Zevalin must not be mixed with other drugs.

- Read all directions thoroughly and assemble all materials before starting the radiolabeling procedure.
- The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration. The dose calibrator must be operated in accordance with the manufacturer's specifications and quality control for the measurement of yttrium-90.
- Proper aseptic technique and precautions for handling radioactive materials should be employed. Waterproof gloves should be utilized during the preparation and determination of radiochemical purity of yttrium (^{90}Y) ibritumomab tiuxetan. Appropriate shielding should be used during radiolabeling and use of a syringe shield is recommended during administration to the patient. The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spills of urine, vomiting, etc. Radiation protection precaution in accordance with local regulations must therefore be taken. Any unused product or waste material should be disposed of in accordance with local requirements. Contaminated materials must be disposed of as radioactive waste by the authorized route.
- Zevalin is supplied as a kit that contains non-radioactive ingredients necessary to produce a single-unit dose of Zevalin for labeling with yttrium-90 for therapy.
- Yttrium-90 chloride sterile solution will be shipped directly from the manufacturer upon placement of an order for the Zevalin kit. Rituximab must be ordered separately and is available through hospital pharmacies.

The radiolabeling of Zevalin shall be done according to the following directions.
Each Zevalin kit contains the following components:

- One vial: Zevalin vial.
- One vial: 50 mM sodium acetate vial.
- One vial: formulation buffer vial.
- One empty reaction vial.
- Four identification labels.

Required materials not supplied in the carton:

- Yttrium (^{90}Y) chloride sterile solution
- Three sterile 1-mL syringes
- One sterile 3-mL syringe
- Two sterile 10-mL syringes with 18 - 20 G needles

- Instant thin-layer chromatographic silica gel strips (ITLC-SG)
- 0.9% sodium chloride aqueous solution for the chromatography solvent
- Suitable radioactivity counting apparatus
- Developing chamber for chromatography
- Membrane filter, 0.22-micrometer, low-protein-binding
- Vial and syringe shield

Step 1: Radiolabeling and Incubation

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

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

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

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

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

    a. Calculate the volume of yttrium (^{90}Y) chloride that is equivalent to 40 mCi based on the activity concentration of the yttrium (^{90}Y) chloride stock. Use the certificate of analysis provided by the manufacturer of the yttrium (^{90}Y) chloride for this calculation.
    b. The volume of 50 mM sodium acetate solution needed is equal to the volume of yttrium (^{90}Y) chloride solution determined in step 5.a. above, multiplied by a factor of 1.2 (The 50 mM sodium acetate is used to adjust the pH for the radiolabeling reaction).
    c. Calculate the volume of formulation buffer needed to bring the reaction vial contents to a final volume of 10 mL. This is the volume of formulation buffer needed to protect the labeled product from radiolysis and to terminate the labeling reaction. For example: The volume of ibritumomab tiuxetan required is 1.3 mL. If the volume of yttrium (^{90}Y) chloride equivalent to 40 mCi is calculated to be 0.5 mL, then 0.6 mL of 50 mM sodium acetate (0.5 mL multiplied by a factor of 1.2) is required. Therefore, the amount of formulation buffer needed is 7.6 mL (i.e., 10 mL – 1.3 mL – 0.5 mL – 0.6 mL).

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

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

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

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

10. Immediately after the five-minute incubation period, using a sterile 10-mL syringe with a large bore needle (18 G - 20 G), transfer the calculated volume of formulation buffer from step 5.c. to the reaction vial, terminating incubation. Gently add the formulation buffer down the side of the reaction vial. If necessary to normalize air pressure, withdraw an equal volume of air. Coat the entire inner surface of the reaction vial by gentle inversion or rolling. Do not shake or agitate the vial contents to avoid foaming.

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

12. Calculate the volume required for yttrium (90Y) ibritumomab tiuxetan dose. Withdraw the required volume from the reaction vial contents into a sterile 10-mL syringe with a large bore needle (18 G - 20 G). Assay the syringe and contents in a dose calibrator. The syringe should contain the dose of yttrium (90Y) ibritumomab tiuxetan to be administered to the patient and should be within ±10% of the actual prescribed dose. Using the supplied labels, record the patient identification information, the date and time of preparation, the total activity and volume added, and the date and time of expiration, and affix these labels to the syringe and shielded unit dose container.

13. Determine radiochemical purity (see Step 2 below).

14. Yttrium (90Y) ibritumomab tiuxetan should be stored upright in a shielded container under refrigeration between 2°C and 8°C until use and administered within 8 hours of radiolabeling.

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

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

Step 2: Specifications and Quality Control

Procedure for determining radiochemical purity (RCP)

1. At room temperature, place a small drop of yttrium (^{90}Y) ibritumomab tiuxetan at the origin of an ITLC-SG strip.
2. Place the ITLC-SG strip into a chromatography chamber with the origin at the bottom and the solvent front at the top. Allow the solvent, 0.9% sodium chloride, to migrate at least 5 cm from the bottom of the strip. Remove the strip from the chamber and cut the strip in half. Count each half of the ITLC-SG strip for one minute (CPM) with a suitable counting apparatus.
3. Calculate the percentage of RCP as follows:

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

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

Step 3: Administration

- Aseptic technique and radiation shielding should be used when withdrawing and administering yttrium (^{90}Y) ibritumomab tiuxetan solution of injection (see 4 DOSAGE AND ADMINISTRATION).
- Prior to use, visually inspect behind a lead glass shield the prepared yttrium (^{90}Y) ibritumomab tiuxetan solution for injection. Only clear, colorless, and without undissolved matter solution should be used.
- A 0.2 or 0.22-micrometer low-protein-binding membrane filter should be in line between the syringe and the infusion port prior to injection of yttrium (^{90}Y) ibritumomab tiuxetan.
- The total radioactivity in the syringe should be verified with a dose calibrator immediately before and after yttrium (^{90}Y) ibritumomab tiuxetan administration to patient (see 4 DOSAGE AND ADMINISTRATION).

4.8 Radiation Dosimetry

Based upon dosimetry studies with indium (^{111}In) ibritumomab tiuxetan, the estimated radiation dosimetry for individual organs following administration of yttrium (^{90}Y) ibritumomab tiuxetan at activities of 15 MBq/kg and 11 MBq/kg was calculated according to Medical Internal Radiation Dosimetry (MIRD) (see Table 1). The estimated radiation-absorbed doses to normal organs were substantially below recognized upper safety limits. Individual patient dosimetry results were not predictive for yttrium (^{90}Y) ibritumomab tiuxetan toxicity and, accordingly, general performance of dosimetry is not recommended.

Table 1: Estimated median radiation absorbed doses of yttrium (^{90}Y) ibritumomab tiuxetan

Organ	Yttrium (^{90}Y) ibritumomab tiuxetan (mGy/MBq)	
	Median	**Range**
Spleen[a]	9.4	1.8 - 20.0
Liver[a]	4.8	2.9 - 8.1
Lower large intestinal wall[a]	4.7	3.1 – 8.2
Upper large intestinal wall[a]	3.6	2.0 – 6.7
Heart wall[a]	2.9	1.5 - 3.2
Lungs[a]	2.0	1.2 - 3.4
Testes[a]	1.5	1.0 – 4.3
Small intestine[a]	1.4	0.8 – 2.1
Red marrow[b]	1.3	0.6 - 1.8
Urinary bladder wall[c]	0.9	0.7 - 1.3
Bone surfaces[b]	0.9	0.5 - 1.2
Ovaries[c]	0.4	0.3 - 0.5
Uterus[c]	0.4	0.3 - 0.5
Adrenals[c]	0.3	0.2 - 0.5
Brain[c]	0.3	0.2 - 0.5
Breasts[c]	0.3	0.2 - 0.5
Gallbladder wall[c]	0.3	0.2 - 0.5
Muscle[c]	0.3	0.2 - 0.5
Pancreas[c]	0.3	0.2 - 0.5
Skin[c]	0.3	0.2 - 0.5
Stomach[c]	0.3	0.2 - 0.5
Thymus[c]	0.3	0.2 - 0.5
Thyroid[c]	0.3	0.2 - 0.5
Kidneys[a]	0.1	0.0 - 0.3
Total body[c]	0.5	0.4 - 0.7

[a] Organ region of interest

[b] Sacrum region of interest

[c] Whole body region of interest

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

Results of dosimetry measurements performed in 179 patients indicate that radiation doses delivered to normal organs and marrow by yttrium (^{90}Y) ibritumomab tiuxetan at the

recommended maximum dose of 0.4 mCi are significantly below exposure levels that would justify clinical concern (2,000 cGy to normal organs; 300 cGy to marrow).

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

5 OVERDOSAGE

Doses as high as 0.52 mCi/kg (19.2 MBq/kg) of yttrium (^{90}Y) ibritumomab tiuxetan were administered in Zevalin therapeutic regimen clinical trials and severe hematological toxicities were observed. No fatalities or second organ injury resulting from overdosage administrations were documented. However, single doses up to 50 mCi (1850 MBq) of yttrium (^{90}Y) ibritumomab tiuxetan and multiple doses of 20 mCi (740 MBq) followed by 40 mCi (1480 MBq) of yttrium (^{90}Y) ibritumomab tiuxetan were studied in a limited number of subjects. In these trials, some patients required autologous stem cell support to manage hematological toxicity. Patients recovered from these toxicity signs, and overdoses were not associated with serious or fatal outcome.

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	Kit for the preparation of yttrium (^{90}Y) ibritumomab tiuxetan Vial contains: 3.2 mg ibritumomab tiuxetan	sodium acetate trihydrate, human serum albumin, sodium chloride, sodium phosphate dibasic dodecahydrate, pentetic acid, potassium phosphate monobasic, and potassium chloride

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

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

Each Zevalin kit contains the following components:

- One vial (Zevalin vial) containing 3.2 mg of ibritumomab tiuxetan in 2 mL of normal saline solution. Supplied as a clear, colourless solution that may contain translucent particles.
- One vial (50 mM sodium acetate vial) containing 13.6 mg of sodium acetate trihydrate in 2 mL of Water for Injection. Supplied as a clear, colourless solution.
- One vial (formulation buffer vial) containing 750 mg of human serum albumin, 76 mg of sodium chloride, 21 mg of sodium phosphate dibasic dodecahydrate, 4 mg of pentetic acid, 2 mg of potassium phosphate monobasic and 2 mg of potassium chloride in 10 mL of Water for Injection adjusted to pH 7.1 with either sodium hydroxide or hydrochloric acid. Supplied as a yellow to amber coloured solution.
- One empty reaction vial.
- Four identification labels.

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

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

6.1 Physical Characteristics

Yttrium-90 decays to a stable zirconium-90 by emission of beta particles, with a physical half-life of 64.1 hours (2.67 days). The range of beta particles in soft tissue (c90) is 5 mm. Radiation emission data for yttrium-90 are summarized in Table 3.

Table 3: Principal yttrium-90 Radiation Emission properties

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

6.2 External Radiation

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

To allow correction for physical decay of yttrium-90, the fractions that remain at selected intervals before and after the time of calibration are shown in Table 4.

Table 4: Physical Decay Chart: yttrium-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

Calibration Time (Hrs.)	Fraction Remaining	Calibration Time (Hrs.)	Fraction Remaining
-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

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Yttrium (^{90}Y) ibritumomab tiuxetan should be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

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

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

Because the Zevalin therapeutic regimen includes the use of rituximab (see 4 DOSAGE AND ADMINISTRATION), healthcare professionals should consult the rituximab Product Monograph and follow instructions carefully.

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

Yttrium (^{90}Y) ibritumomab tiuxetan solution must not be administered to patients who are likely to develop life- threatening hematological toxicity signs.

Carcinogenesis and Mutagenesis

Out of 349 patients treated with the Zevalin therapeutic regimen, three cases of acute myelogenous leukemia and two cases of myelodysplastic syndrome have been reported following the yttrium (^{90}Y) ibritumomab tiuxetan therapeutic regimen (see 8 ADVERSE REACTIONS).

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

Contamination

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

General Disorders and Administration Site Conditions

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

Hematologic

The most common severe adverse events reported with the Zevalin therapeutic regimen were thrombocytopenia (61% of patients with platelet counts < 50,000 cells/mm^3) and neutropenia (57% of patients with absolute neutrophil count [ANC] < 1,000 cells/mm^3) in patients with ≥ 150,000 platelets/mm^3 prior to treatment. Both incidences of severe thrombocytopenia and neutropenia increased to 78% and 74% for patients with mild thrombocytopenia at baseline (platelet count of 100,000 to 149,000 cells/mm^3). For all patients, the median time to nadir was seven to nine weeks and the median duration of cytopenias was 22-35 days. In < 5% of cases, patients experienced severe cytopenia that extended beyond the prospectively defined protocol treatment period of 12 weeks following administration of the Zevalin therapeutic regimen. Some of these patients eventually recovered from cytopenia, while others experienced progressive disease, received further anti-cancer therapy or died of their lymphoma without having recovered from cytopenia. The cytopenias may have influenced subsequent treatment decisions (see 8 ADVERSE REACTIONS).

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

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

The risk of hematological toxicity may be increased after prior therapy with fludarabine-containing regimens (see 9 DRUG INTERACTIONS).

Special caution is required with respect to bone marrow depletion. In most patients administration of Zevalin (after pretreatment with rituximab) results in severe and prolonged cytopenia which is generally reversible (see 8 ADVERSE REACTIONS). Complete blood cell and platelet counts must be monitored weekly following Zevalin treatment until levels recover or as clinically indicated.

Immune

The safety and efficacy of immunization with any vaccine, particularly live viral vaccines, following the Zevalin therapeutic regimen have not been studied. Due to the potential risk of developing viral infections, it is not recommended to administer live viral vaccines to patients who have recently received Zevalin (see 9 DRUG INTERACTIONS). A potentially limited ability of patients to generate a primary or anamnestic humoral response to any vaccine following Zevalin treatment has to be taken into consideration.

Patients must not receive growth factor treatment such as G-CSF for 3 weeks prior to Zevalin administration as well as for 2 weeks following completion of the treatment in order to assess the adequate bone marrow reserve correctly and because of the potential sensitivity of rapidly dividing myeloid cells to radiation (see 9 DRUG INTERACTIONS).

Neurologic

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

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

Reproductive health: Female and Male Potential

The Zevalin therapeutic regimen results in a significant radiation dose to the testes. The radiation dose to the ovaries has not been established. There have been no studies to evaluate

whether the Zevalin therapeutic regimen causes hypogonadism, premature menopause, azoospermia and/or mutagenic alterations to germ cells. There is a potential risk that ionizing radiation by yttrium (^{90}Y) ibritumomab tiuxetan could cause toxic effects on the male and female gonads. Therefore, it is recommended that women of childbearing potential, as well as males, use effective contraceptive methods during and up to 12 months following the Zevalin therapeutic regimen. Patients planning to have children should be informed accordingly.

Sensitivity/Resistance

Infusion reactions may occur during or following Zevalin administration after pretreatment with rituximab. Signs and symptoms of infusion reactions may include dizziness, cough, nausea, vomiting, rash, pruritus, tachycardia, asthenia, pyrexia, and rigors (see 8 ADVERSE REACTIONS). In case of a potential severe infusion reaction, treatment must be stopped immediately.

Hypersensitivity reactions following Zevalin administration are commonly observed. Severe hypersensitivity reactions (Grade 3/4) including anaphylaxis occur in less than 1% of patients (see 8 ADVERSE REACTIONS). In case of hypersensitivity reactions, Zevalin infusion must be stopped immediately. Medications for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines and corticosteroids, should be available for immediate use in the event of an allergic reaction during administration of the Zevalin therapeutic regimen. Patients who have received murine-derived proteins before Zevalin treatment should be screened for human anti-mouse antibodies.

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

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

Skin

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

7.1 Special Populations

7.1.1 Pregnant Women

Yttrium (^{90}Y) ibritumomab tiuxetan can cause fetal harm when administered to a pregnant

woman. There are no adequate and well-controlled studies in pregnant women. Since IgGs are known to cross the placenta and because of the significant risk associated with the use of radiation, Zevalin is contraindicated during pregnancy (see 2 CONTRAINDICATIONS). Pregnancy must be excluded before the start of treatment in women.

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

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

7.1.4 Geriatrics

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

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

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Safety data, except where indicated, are based upon 349 patients treated in five clinical studies with the Zevalin (ibritumomab tiuxetan) therapeutic regimen.

The most serious adverse reactions caused by the Zevalin therapeutic regimen include infections (predominantly bacterial in origin), allergic reactions (bronchospasm and angioedema), hemorrhage while thrombocytopenic (resulting in death), and severe and prolonged cytopenias. Severe mucocutaneous reactions were also reported in post-marketing surveillance. In addition, patients who have received the Zevalin therapeutic regimen have developed myeloid malignancies and dysplasias. Fatal infusion reactions have occurred following the infusion of rituximab. Please refer to the 7 WARNINGS AND PRECAUTIONS section

for detailed descriptions of these reactions.

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

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful for identifying and approximating rates of adverse drug reactions in real-world use.

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

Table 5 and Table 6 list adverse events that occurred in ≥ 5% of patients and in ≥ 1% and < 5% of patients, respectively. A more detailed description of the incidence and duration of hematologic toxicities, according to baseline platelet count (as an indicator of bone marrow reserve), is provided in Table 7.

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

Adverse Events	All Grades %	Grade 3 to 4 %
Any Adverse Event	**99**	**89**
General disorders and administration site conditions.	**80**	**12**
Asthenia	43	3
Chills	24	< 1
Fever	17	1
Pain	13	1
Infections and infestations		
Infections	29	5
Vascular Disorders	**17**	**3**
Hypotension	6	1
Flushing	6	0

Adverse Events	All Grades %	Grade 3 to 4 %
Gastrointestinal disorders	**48**	**3**
Nausea	31	1
Vomiting	12	0
Diarrhea	9	< 1
Anorexia	8	0
Abdominal enlargement	5	0
Constipation	5	0
Abdominal pain	16	3
Blood and lymphatic system disorders	**98**	**86**
Thrombocytopenia	95	63
Neutropenia	77	60
Anemia	61	17
Ecchymosis	7	< 1
Metabolic and nutrition disorders	**23**	**3**
Peripheral edema	8	1
Immune system disorders		
Angioedema	5	< 1
Musculoskeletal and connective tissue disorders	**18**	**1**
Arthralgia	7	1
Myalgia	7	<1
Back pain	8	1
Nervous system disorders	**27**	**2**
Dizziness	10	< 1
Headache	12	1
Psychiatric disorders		
Insomnia	5	0
Respiratory, thoracic and mediastinal disorders	**36**	**3**
Dyspnea	14	2
Increased cough	10	0
Rhinitis	6	0
Bronchospasm	5	0
Throat irritation	10	0
Skin and subcutaneous tissue disorders	**28**	**1**
Pruritus	9	< 1
Rash	8	< 1
Special senses	**7**	< **1**
Renal and urinary disorders	**6**	< **1**

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

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

Table 6: Incidence of Adverse Events in ≥ 1% and < 5% of Patients Receiving the Zevalin Therapeutic Regimen[a] (N = 349)

Adverse events	Zevalin Therapeutic Regimen %
General disorders and administration site conditions.	
Malaise	2.3
Flu syndrome	1.7
Moniliasis	1.1
Axilla pain	1.1
Injection site pain	1.1
Edema	1.4
Cardiac disorders	
Chest pain	4.3
Tachycardia	2.9
Palpitation	1.1
Vascular Disorders	
Hypertension	2.3
Gastrointestinal disorders	
Dyspepsia	3.7
Dry mouth	2.0
Melena	2.0
Gastrointestinal disorder	1.7
Stomatitis	1.7
Rectal hemorrhage	1.4
Oral moniliasis	1.4
Dysphagia	1.1
Gastrointestinal hemorrhage	1.1
Enlarged abdomen	2.9
Gum hemorrhage	1.1
Blood and lymphatic system disorders	
Petechia	3.4
Febrile neutropenia	2.6
Pancytopenia	2.0
Lymphadenopathy	1.1
Metabolic and Nutrition Disorders	
Hyperglycemia	2.9
Dehydration	2.3
Hypocalcemia	1.7
Hypokalemia	1.1
Musculoskeletal and connective tissue disorders	
Bone pain	2.6
Leg cramps	2.0
Pain neck	2.6
Nervous System Disorders	
Somnolence	2.0
Vasodilation	1.1
Myasthenia	1.4
Respiratory, thoracic and mediastinal disorders	
Epistaxis	2.9
Bronchitis	1.7
Pneumonia	1.7
Voice alteration	1.7
Pleural effusion	1.4

Adverse events	Zevalin Therapeutic Regimen %
Skin and subcutaneous tissue disorders	
Urticaria	4.0
Sweats	3.7
Night sweats	3.2
Skin disorder	2.3
Herpes simplex	1.7
Alopecia	1.1
Renal and urinary disorders	
Dysuria	1.1
Urinary incontinence	1.1
Hypoproteinemia	1.1
Immune system disorders	
Allergic reaction	2.0
Infections and infestations	
Cellulitis	1.7
Sepsis	1.4
Hypesthesia	2.6
Paresthesia	2.6
Sinusitis	4.9
Pharyngitis	1.1
Herpes zoster	1.1
Conjunctivitis	2.9
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Tumor pain	1.7
Hepatobiliary disorders	
Increased lactic dehydrogenase	3.7
Investigations	
Increased SGOT	2.3
Increased BUN	2.0
Increased alkaline phosphatase	2.0
Increased SGPT	1.7
Increased creatinine	1.4
Decreased weight	1.4
Psychiatric disorders	
Anxiety	3.7
Psychiatric disorders	
Depression	2.3
Agitation	1.1
Eye Disorders	
Abnormal vision	1.1

[a] Adverse events were followed for a period of 12 weeks following the first rituximab infusion ofthe Zevalin therapeutic regimen.

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

Adverse Reactions of Special Interest

Infections and Infestations

During the first three months after initiating the Zevalin therapeutic regimen, 29% of patients developed infections. Three percent of patients developed serious infections comprising urinary tract infection, febrile neutropenia, sepsis, pneumonia, cellulitis, colitis, diarrhea,

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

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

Secondary Malignancies

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

8.3 Less Common Clinical Trial Adverse Reactions

There is no comprehensive data accessible for adverse events in <1% of patients.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Hematologic toxicity was the most frequently observed adverse event in clinical trials and is dose-limiting. Thrombocytopenia, leukocytopenia, neutropenia and anemia have been reported very commonly as adverse drug reactions. Also, febrile neutropenia, pancytopenia and lymphocytopenia have been reported as common adverse drug reactions. Table 7 presents the incidence and duration of severe hematologic toxicity for patients with a normal baseline platelet count (≥ 150,000 cells/mm^3) treated with the Zevalin therapeutic regimen and patients with mild thrombocytopenia (platelet count 100,000 to 149,000 cells/mm^3) at baseline who were treated with a modified Zevalin therapeutic regimen that included a lower specific activity yttrium (^{90}Y) ibritumomab tiuxetan dose at 0.3 mCi/kg (11 MBq/kg).

Table 7: Severe Hematologic Toxicity Observed in Clinical Trials with Zevalin

	Zevalin Therapeutic Regimen 0.4 mCi/kg (15 MBq/kg) Dose	Modified Zevalin Therapeutic Regimen 0.3 mCi/kg (11 MBq/kg) Dose
Absolute neutrophils count (ANC)		
Median nadir (cells/mm^3)	800	600
Per patient incidence (%): ANC < 1,000 cells/mm^3	57%	74%

Per patient incidence (%): ANC < 500 cells/mm^3	30%	35%
Median duration (days)[a]: ANC < 1,000 cells/mm^3	22	29
Platelets		
Median nadir (cells/mm^3)	41,000	24,000
Per patient incidence (%): platelets < 50,000 cells/mm^3	61%	78%
Per patient incidence (%): platelets < 10,000 cells/mm^3	10%	14%
Median duration (days)[b]: platelets < 50,000 cells/mm^3	24	35

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

[b] Median duration of thrombocytopenia for patients with platelets < 50,000 cells/mm^3 (date from last laboratory value showing platelet count ≥ 50,000 cells/mm^3 to date of first laboratory value following nadir showing platelet count ≥ 50,000 cells/mm^3, censored at initiation of next treatment or death).

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

8.5 Post-Market Adverse Reactions

Skin and Subcutaneous Tissue Disorders

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

General Disorders and Administration Site Conditions

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

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

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

No formal drug interaction studies have been performed with Zevalin. Due to the frequent

occurrence of severe and prolonged thrombocytopenia, the potential benefits of medications that interfere with platelet function and/or anticoagulation should be weighed against the potential increased risks of bleeding and hemorrhage. Patients receiving medications that interfere with platelet function or coagulation (e.g., Acetylsalicylic Acid (ASA), Non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors) should have more frequent laboratory monitoring for thrombocytopenia. In addition, the transfusion practices for such patients may need to be modified given the increased risk of bleeding.

In a clinical trial it has been shown that the use of fludarabine-containing regimens within 4 months before Zevalin treatment may increase the risk of hematological toxicity (see 7 WARNINGS AND PRECAUTIONS).

Growth factor treatment such as G-CSF must not be given to patients for 3 weeks prior to Zevalin administration as well as for 2 weeks following completion of the treatment (see 7 WARNINGS AND PRECAUTIONS).

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

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

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

imaging were observed between the two rituximab doses, however the higher dose of 250 mg/m^2 was chosen since it would likely lead to an enhanced therapeutic effect.

10.2 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 to 1,084 cells/mm^3). B-cell recovery began at approximately 12 weeks following treatment, and the median level of B-cells was within the normal range (32 to 341 cells/mm^3) by nine months after treatment. Median serum levels of IgG and IgA remained within the normal range throughout the period of B-cell depletion. Median IgM serum levels dropped below normal (median 49 mg/dL, range 13 to 3,990 mg/dL) after treatment and recovered to normal values by six months post-therapy.

10.3 Pharmacokinetics

The pharmacokinetics parameters in dosimetry study of yttrium (^{90}Y) ibritumomab tiuxetan solution for injections has been characterized in 179 patients with relapsed or refractory, low- or intermediate-grade non-Hodgkin's lymphoma (NHL). Under conditions corresponding to the recommended treatment regimen, the kinetics of Zevalin fit a linear and noncompartmental model.

Table 8: Summary of Zevalin pharmacokinetic parameters

	C_{max}	T_{max}	$T_{1/2}$(Hours)	AUC_{inf} (Hours)[#]	CL (%)[†]	V_d
Dosimetry Study	ND[*]	ND [*]	27.1	27.5	7.2	ND[‡]

[*] ND: Not determined, C_{max} and T_{max} values were not part of the study design.

[#] AUC_{inf}: Median area under the FIA (Fraction of Injected Activity) versus time curve from 0 till infinity.

[†] CL: Clearance expressed as median percent radioactivity excreted in the urine over seven days.

[‡] ND: Volume of distribution was not determined.

Absorption

yttrium (^{90}Y) ibritumomab tiuxetan is administered intravenously and is immediately and completely bioavailable.

Distribution

In all patients, median estimated indium-111 radiation absorbed dose was highest to the spleen with a median of 14.9 cGy (range: 3.0 – 75.0 cGy).

Metabolism

Only 3.2 – 8.5% of ^{90}Y is detected in the urine during the first week, indicating that the byproduct of antibody metabolism, thought to be yttrium (^{90}Y) tiuxetan bound to a short chain of amino acids, is excreted at low levels. These data provide evidence that antibody is not

rapidly metabolized.

Elimination

Over seven days, a median of 7.2% (range: 3.2-8.5%) of the injected radioactivity was excreted in urine.

Half-life

The mean effective half-life for yttrium-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 in patients receiving the Zevalin therapeutic regimen. The physical half-life of yttrium-90 is 64.1 hours (2.7 days), with rapid decay to stable and nontoxic zirconium-90.

The minor amounts of unbound circulating radioactivity are eliminated in urine with a median effective half-life in blood of 27.1 hours.

Special Population and Conditions

- **Renal/hepatic insufficiency:** The safety and efficacy in patients with renal or hepatic impairment have not been established.

11 STORAGE, STABILITY AND DISPOSAL

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

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

12 SPECIAL HANDLING INSTRUCTIONS

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

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Ibritumomab tiuxetan

Chemical name: Ibritumomab is a conjugated murine IgG1 kappa monoclonal antibody consists of two gamma heavy chains and two kappa light chain of 445 and 213 amino acids each, respectively. Ibritumomab is linked through a stable thiourea covalent bond tiuxetan chelator [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 yttrium-90.

Molecular formula: $C_{6382}H_{9830}N_{1672}O_{1979}S_{54}$

Molecular mass: 148 kDa

Structural formula: a conjugated antibody

Physicochemical properties: clear, colorless solution that may contain translucent particles. 3.2 mg soluble in 0.9% sodium chloride with pH between 6.0-8.0.

Product Characteristics

Zevalin is supplied as a single-dose 4-vials kit which contain non-radioactive ingredients needed for the radiopharmaceutical preparation of yttrium (^{90}Y) ibritumomab tiuxetan solution for injection (see 6 DOSAGE FORMS, STRENGHTS, COMPOSITION AND PACKAGING). Zevalin contains four type 1 glass vials closed with a rubber stopper and crimp sealed.
Before reconstitution, the content of Zevalin is not radioactive. After reconstitution, effective radiation shielding of the yttrium (^{90}Y) ibritumomab tiuxetan solution for injection should be maintained.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 9: Summary of patient demographics in clinical trials for patients with non-Hodgkin's lymphoma

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
Study 1 - 10606	Single-arm, multicenter study	Two steps IV infusion Zevalin therapeutic regimen	54	54 years (34 - 73 years)	51% female 49% male
Study 2 - 10604	Randomized, open-label, multicenter study	Two steps IV infusion Zevalin therapeutic regimen or rituximab IV infusion at 375 mg/m^2 weekly times four doses	Total: 143 Zevalin: 73 Rituximab: 70	60 years (29 – 80 years) Rituximab: 57 years (36 - 78 years)	51% female 49% male

Study 3 - 10605	Single-arm study	Reduced Zevalin dose 0.3 mCi/kg	30	61 years (29 – 85 years)	40 % female 60% male

The safety and efficacy of the Zevalin therapeutic regimen were evaluated in two multi-centre trials (Study 1 and Study 2) enrolling a total of 197 subjects. The Zevalin therapeutic regimen was administered in two steps as IV infusion.

Study 1 included adult patients with relapsed follicular lymphoma refractory to rituximab treatment. Patients were considered refractory if their last prior treatment with rituximab did not result in a complete or partial response, or if time to disease progression (TTP) was < 6 months. The study excluded patients with prior bone marrow transplantation. Patients had <25% bone marrow involvement by NHL and acceptable renal, hepatic, and hematological function. The median age was 54 years; 95% Caucasian; 4% Hispanic; 2% African-American; 94.7% had World Health Organization (WHO) Performance Status (PS) 0-1; 5.3% had WHO PS2. All patients had received at least one prior chemotherapy regimen. The main efficacy outcome measure 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).

Study 2 included adult patients with relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma (NHL), or transformed B-cell NHL. Patients had <25% bone marrow involvement by NHL and acceptable renal, hepatic, and hematological function. Patients were randomized 1:1 to receive either Zevalin therapeutic regimen (N=73) or rituximab (N=70) IV infusion at 375 mg/m^2 weekly times four doses. Demographics and baseline disease characteristics in Study 2 were balanced between the treatment arms. The median age was 60 years and 57 years; 93% and 90% Caucasian; 3% and 3% Hispanic; 3% and 4% African-American; 98.6% and 97.1% had WHO PS 0-1; 1.4% and 2.9% had WHO PS2 for Zevalin therapeutic regimen and rituximab, respectively. The main efficacy outcome measure of the study was the ORR using the IWRC.

Study 3 included patients with relapsed or refractory low-grade, follicular or transformed B-cell NHL who had mild thrombocytopenia (platelet count 100,000 to 149,000 cells/mm^3). The study excluded patients with ≥25% lymphoma marrow involvement and/or impaired bone marrow reserve. Patients were considered to have impaired bone marrow reserve if they had any of the following: prior myeloablative therapy with stem cell support; prior external beam radiation to > 25% of active marrow; a platelet count < 100,000 cells/mm^3; or neutrophil count < 1,500 cells/mm^3. The activity and toxicity of a variation of the Zevalin therapeutic regimen employing a reduced dose of yttrium (^{90}Y) ibritumomab tiuxetan was defined in Study 3. The median age was 61 years; 96.7% Caucasian; 3.3% Asian; 96.7% had WHO PS 0-1; 3.3% had WHO PS2.

14.2 Study Results

Study 1

Efficacy results are summarized in Table 10. In a secondary analysis comparing objective response to the Zevalin therapeutic regimen with that observed with the most recent treatment with rituximab, the median duration of response following the Zevalin therapeutic regimen was six vs. four months for rituximab.

Study 2

The ORR was significantly higher (80% vs. 56%, p = 0.002) for patients treated with the Zevalin therapeutic regimen. The secondary endpoints, duration of response and time to progression, were not significantly different between the two treatment arms.
Efficacy results are summarized in Table 10.

Table 10: Summary of Efficacy Data[a] for Studies 1 and 2

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

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

Study 3

In this study, a modification of the Zevalin therapeutic regimen with a lower specific activity yttrium (^{90}Y) ibritumomab tiuxetan dose [0.3 mCi/kg (11 MBq/kg)] was used. Objective, durable clinical responses were observed [67% ORR (95% CI: 48-85%), 11.8 months median duration of response (range: 4-17 months)] (see Table 11) and resulted in a greater incidence of hematologic toxicity than in studies 1 and 2.

Table 11: Summary of Efficacy Data for Study 3

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

[a] Reduced dose: yttrium (^{90}Y) ibritumomab tiuxetan at 0.3 mCi/kg (11 MBq/kg)
[b] Sponsor evaluation criteria
[c] DR: duration of response defined as the interval from the onset of response to disease progression

14.4 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay.

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

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

<u>Repeat Dose Study</u>

In a 2 week (14 days) repeat dose study, non-radioactive yttrium conjugated anti-CD20 antibody2B8 (^{89}Y-2B8-MX-DTPA) was administered to adult cynomolgus monkeys once every 48 hours at a dose of 0.003 mg/kg, 0.03 mg/kg, and 0.3 mg/kg for 7 doses. The objective of this study was to evaluate possible pharmacotoxic effects and to assess the *in vivo* toxicity associated with administration of multiple doses of the antibody. Other than a decreased lymphocyte count, no significant abnormalities were found in any clinical parameter evaluated that were related to the administration of the yttrium conjugated anti-CD20 antibody 2B8 (^{89}Y-2B8-MX-DTPA) test material under the conditions of the study.

A single dose of 10 mg/kg of murine hybridoma-expressed ibritumomab antibody was also administered to two cynomolgus monkeys for evaluation of the antibody's half-life. No significant toxic effects or mortality were noted in any clinical parameter evaluated during or

following the study that were related to the administration of ibritumomab antibody. The half-life value calculated from serum antibody concentration was approximately 4.5 days.

Carcinogenicity and Genotoxicity

No long-term animal studies have been performed to evaluate carcinogenic or mutagenic potential or whether Zevalin (ibritumomab tiuxetan) affects fertility in males or females. Due to the exposure to ionizing radiation derived from the radiolabel, a risk of mutagenic and carcinogenic effects cannot be ruled out.

Reproductive and Developmental Toxicology

For information on reproductive toxicity, see 7 WARNINGS AND PRECAUTIONS

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

ZEVALIN®
Ibritumomab tiuxetan, kit for radiopharmaceutical preparation of yttrium (^{90}Y) ibritumomab tiuxetan solution for injection

Read this carefully before you start taking **ZEVALIN®**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Zevalin®**.

Serious Warnings and Precautions

- Zevalin should be used by health professionals who are appropriately trained in the use of radiopharmaceuticals.
- Deaths associated with infusion reaction symptoms have occurred within 24 hours of receiving infusion with rituximab, an essential part of the Zevalin therapeutic regimen. Approximately 80% of fatal infusion reactions occurred in association with the first rituximab infusion. Symptoms may include low body oxygen (hypoxia), pus/blood build up in lungs (pulmonary infiltrates), fluids build up in lungs and shortness of beath (acute respiratory distress syndrome), heart attack (myocardial infarction), irregular heartbeats (ventricular fibrillation), or heart shock (cardiogenic shock). Patients who develop severe infusion reactions should have rituximab and yttrium (^{90}Y) ibritumomab tiuxetan infusions stopped immediately and should receive appropriate medical treatment.
- Treatment with Zevalin can result in very low blood cell counts for a prolonged period of time. The risk of low blood count may be increased when Zevalin therapeutic regimen is given shortly (<4 months) after prior therapy with fludarabine-containing regimen.
- Nail, skin, hair, and mucosal changes (mucocutaneous reactions) that maybe sever, life-threatening or that may lead to death. Patients who develop severe mucocutaneous reactions should have rituximab and yttrium (^{90}Y) ibritumomab tiuxetan infusions stopped immediately and should receive appropriate medical treatment.
- Secondary blood cancer (myelodysplastic syndrome or acute leukaemia) can rarely occur after you have completed Zevalin therapeutic regimen.
- To ensure safe administration, the dose of yttrium (^{90}Y) ibritumomab tiuxetan that you receive should not exceed the maximum allowable dose of 32 mCi (1200 MBq).

What is Zevalin used for?
This medicine is a radiopharmaceutical product for therapeutic use.
Zevalin contains ibritumomab tiuxetan. Before use, the solution in the vial is mixed with a radioactive substance/radioisotope called yttrium-90 to make yttrium (^{90}Y) ibritumomab tiuxetan solution (this procedure is called radiolabeling).

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

How does Zevalin work?
Zevalin, after radiolabeling with yttrium-90, contains the active substance yttrium (^{90}Y) ibritumomab tiuxetan. Ibritumomab tiuxetan belongs to a group of medicines called monoclonal antibodies. Yttrium (^{90}Y) ibritumomab tiuxetan attaches to a target protein called CD20 found on the surface of B-cells of non-Hodgkin's lymphoma. Once bound the radiation emitted from yttrium-90 causes the B-cells of non-Hodgkin's lymphoma and adjacent cancer

cells to die. The use of Zevalin involves exposure to amounts of radioactivity. Your doctor and the nuclear medicine doctor have considered that the clinical benefit that you will obtain from the procedure with the radiopharmaceutical outweighs the risk due to radiation. If you have any questions about how Zevalin works or why this medicine has been prescribed for you, ask your nuclear medicine doctor.

What are the ingredients in Zevalin?
Medicinal ingredient: Ibritumomab tiuxetan.

Non-medicinal ingredients: human serum albumin, hydrochloric acid, pentetic acid, potassium chloride, potassium phosphate monobasic, sodium acetate trihydrate, sodium chloride, sodium hydroxide, sodium phosphate dibasic dodecahydrate and water for injection.

Zevalin comes in the following dosage forms:
Kit for radiopharmaceutical preparation of yttrium (^{90}Y) ibritumomab tiuxetan solution for injections, Zevalin contains 3.2 mg ibritumomab tiuxetan in 2 mL 0.9% sodium chloride solution (1.6 mg/mL).

Do not use Zevalin if:

- you have an allergy (hypersensitivity) to the active ingredient (yttrium (^{90}Y) ibritumomab tiuxetan) or to any of the other ingredients of this medicine.
- You have 25% or more of their bone marrow cells affected by lymphoma and/or patients whose bone marrow may have difficulty recovering from therapy.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you receive Zevalin. Talk about any health conditions or problems you may have, including if you:

- Are pregnant or plan to become pregnant. Exposure to radiation during pregnancy may harm unborn infant. Women who are able to become pregnant should use effective contraception and avoid getting pregnant during treatment with Zevalin and for 12 months after treatment.
- Are male with a female partner of childbearing age. Male patients should use effective birth control during treatment and for at least 12 months after completing treatment.
- Are breastfeeding or plan to breastfeed. It is not known if Zevalin passes into your breast milk. Breastfeeding must be stopped.
- Are younger than 18 years of age. it is not known if Zevalin is safe and effective in children.
- Have low level of blood cell counts (absolute neutrophil count, platelet count), bone marrow malignancy, reduction in bone marrow cells, and failed stem cells collection.
- Have symptoms of the severe allergic reaction include low blood oxygen levels, fluid in the lungs, severe difficulty in breathing, disturbances in heart rhythms, heart attack and disruption in bodily functions related to a sudden decline in heart function been developed. Rituximab or Zevalin infusions must be stopped and you should receive appropriate medical treatment.
- Previously received anti-cancer treatment (chemotherapy).
- Notice a skin or mucous membrane reaction during or after Zevalin or rituximab treatment, inform your doctor immediately

Other warnings you should know about

- Check with your healthcare professional before you are given Zevalin if you have had certain other types of antibody treatment before starting Zevalin, you may be more likely to have an allergic reaction (hypersensitivity). You may therefore need to be tested for special antibodies. Your doctor will tell you if this applies to you.
- It is possible that Zevalin will affect your ability to drive and to operate any tools or machines as dizziness is a common side effect. Do not drive or operate machines until you feel better.

- Following treatment with Zevalin, you will likely experience a period of decreased blood cell counts. For some patients, blood cell counts may become very low. Low white blood cell counts can decrease your ability to fight infections. Low red blood cell counts can cause fatigue. Low platelet counts can cause difficulty in forming blood clots, leading to increased bruising or bleeding. Low blood cell counts can occur up to two months following completion of the Zevalin therapeutic regimen and counts may remain low for a few weeks. Your body is usually able to recover normal blood counts within a few weeks after this period of decreased blood cell counts.
- Very low blood counts may lead to serious or life- threatening complications, such as infections. Some patients have needed transfusions or have been given medications to help their blood counts recover faster. Your doctor may provide you with special instructions if your blood counts become very low.

Precautions to be taken after receiving Zevalin:

- Treatment with the Zevalin therapeutic regimen may cause a severe and potentially fatal allergic reaction. This severe reaction typically occurs with the first administration of rituximab. Ask your doctor for rituximab patient information for important information on side effects with rituximab. The amount of radiation that your body will be exposed to during the Zevalin therapeutic regimen is smaller than it would be during radiotherapy. With the type of radioactivity from Zevalin (pure beta emission) there is no direct effect of radiation outside the body. You are not exposing other people to radiation. The effects of Zevalin stay mainly within your body and bodily fluids, such as urine and blood. A small part of the radioactivity will leave your body through your urine. The remainder will break down within the body, leaving no radioactive remains. Observe some safety precautions for the week following treatment with the therapeutic dose of Zevalin, to minimize any potential radiation exposure to other people. If you have any questions concerning the precautions listed below or about participation in a particular activity, be sure to discuss them with your doctor.
- After treatment with Zevalin**,** and if your doctor plans to treat you with some other antibody, please tell your doctor about your treatment with Zevalin. This will help avoid a possible allergic reaction (hypersensitivity).
- After receiving Zevalin, follow your doctor's instructions and the guidelines included in this leaflet regarding going home and back to work.

Safety precautions to be followed for 7 days after receiving Zevalin

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

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Zevalin:

- If you take blood thinners or other medications that interfere with blood clotting, such as warfarin, acetylsalicylic acid, nonsteroidal anti- inflammatory drugs (NSAIDs) like ibuprofen and naproxen, or COX-2 inhibitors like celecoxib, your doctor will need to monitor your blood and platelet counts carefully during and after receiving Zevalin.

How to take Zevalin:

- Zevalin will be administered intravenously (into your vein) under the supervision of a health professional who is experienced in the use safe of radiopharmaceuticals.
- The Zevalin therapeutic regimen is intended as a single course of treatment, consisting of two hospital visits, approximately one week apart.
- In general, you do not need to make any special preparations before you begin treatment with the Zevalin

therapeutic regimen. You can continue with your normal activities and your regular diet. You may also wear your regular clothes to receive your treatments. Your doctor or nurse may have some specific suggestions or recommendations for you to follow.

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

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

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

Usual dose
The doctor will calculate your individual dose. This depends on your body weight and the number of your blood platelets.

Recommended Dose
The Zevalin (ibritumomab tiuxetan) therapeutic regimen is administered in two steps:
Step 1 is a single intravenous infusion of 250 mg/m^2 of rituximab (not included in the Zevalin kit).
Step 2 follows step 1 by 7-9 days and consists of a second infusion of 250 mg/m^2 of rituximab shortly (within 4 hours) prior to 0.4 mCi/kg of yttrium (^{90}Y) ibritumomab tiuxetan administered as a ten- minute intravenous infusion.

The prescribed, measured and administered dose of yttrium (^{90}Y) ibritumomab tiuxetan must not exceed the absolute maximum allowable dose of 32.0 mCi (1,200 MBq), regardless of the patient's body weight.

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

Duration of the procedure
Your nuclear medicine doctor will inform you about the usual duration of the procedure.

Overdose:
Overdose is unlikely. However, in the event of overdose, you will receive the appropriate treatment.

Should you have any further questions on the use of Zevalin, please ask the nuclear medicine doctor who supervises the procedure

What are possible side effects from using Zevalin?
These are not all the possible side affects you may have when taking Zevalin. If you experience any side effects not listed here, tell your healthcare professional.

Very common (may affect more than 1 in 10 people):

- Weakness
- Nausea, vomiting
- Infection
- Chills
- Fever
- Abdominal or general pain

- Shortness of breath
- Headache
- Decrease in blood cell count: red blood cells (anemia), white blood cells (neutropenia), and platelets (thrombocytopenia).

Common side effects (may affect between 1 in 100 and up to 1 in 10 people):

- Sore throat
- Dizziness, trouble sleeping
- Cough, nasal congestion, distressed breathing
- Back pain
- Flushing
- Low blood pressure (hypotension)
- Diarrhea
- Weight loss, loss of appetite (anorexia)
- Abdominal enlargement
- Constipation
- Skin bruising (Ecchymosis)
- Swollen hands, ankles, feet (peripheral edema), lips, tongue, eyelids (angioedema)
- Joints and muscle pain (arthralgia and myalgia)
- Itching, rash

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Common (less than 1 in 10 but more than 1 in 100 patients):			
Allergic reactions		√	
Black tarry stools		√	
High fever		√	
Infections		√	
Prolonged pauses in breathing during sleep		√	
		√	
Uncommon (less than 1 in 100 but more than 1 in 1000 patients):			
Difficulty breathing		√	
Hives or swelling beneath the skin		√	
Rapid heart rate		√	
Unusual vaginal bleeding (hemorrhage)		√	
Vomiting of blood		√	
		√	
Rare (less than 1 in 1000 but more than 1 in 10,000 patients):			
Skin or mucous membrane reactions		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting/drug.html) for

information on how to report online, by mail or by fax; or
Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

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

Keep out of reach and sight of children.

- **If you want more information about Zevalin:** Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug- product-database.html; the manufacturer's website http://www.auropharma.ca, or by calling 1-855-648-6681.

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