

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125019/0

APPROVED LABELING

1 **Ibritumomab Tiuxetan**

2 **ZEVALIN™**

3

4 Kits for the Preparation of Indium-111 (In-111) Ibritumomab Tiuxetan (In-111
5 ZEVALIN) and Yttrium-90 (Y-90) Ibritumomab Tiuxetan (Y-90 ZEVALIN)

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7 In-111 Ibritumomab Tiuxetan and Y-90 Ibritumomab Tiuxetan are components of the
8 ZEVALIN therapeutic regimen (See Description).

9

WARNINGS

Fatal Infusion Reactions : Deaths have occurred within 24 hours of Rituximab infusion, an essential component of the ZEVALIN therapeutic regimen. 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. Approximately 80% of fatal infusion reactions occurred in association with the first Rituximab infusion (See WARNINGS and ADVERSE REACTIONS).

Patients who develop severe infusion reactions should have Rituximab, In-111 ZEVALIN, and Y-90 ZEVALIN infusions discontinued and receive medical treatment.

Prolonged and Severe Cytopenias: Y-90 ZEVALIN administration results in severe and prolonged cytopenias in most patients. The ZEVALIN therapeutic regimen should not be administered to patients with $\geq 25\%$ lymphoma marrow involvement and/or impaired bone marrow reserve (See ADVERSE REACTIONS and CLINICAL STUDIES).

Dosing

- The prescribed, measured, and administered dose of Y-90 ZEVALIN should not exceed the absolute maximum allowable dose of 32.0 mCi (1184 MBq).
- Y-90 ZEVALIN should not be administered to patients with altered biodistribution as determined by imaging with In-111 ZEVALIN.

In-111 ZEVALIN and Y-90 ZEVALIN are radiopharmaceuticals and should be used only by physicians and other professionals qualified by training and experienced in the safe use and handling of radionuclides.

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DESCRIPTION

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ZEVALIN

14 ZEVALIN™ (Ibritumomab Tiuxetan) is the immunoconjugate resulting from a stable
15 thiourea covalent bond between the monoclonal antibody Ibritumomab and the
16 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 IgG₁ kappa monoclonal antibody directed against the CD20 antigen, which is found on the surface of normal and malignant B lymphocytes. Ibritumomab is produced in Chinese hamster ovary cells and is composed of two murine gamma 1 heavy chains of 445 amino acids each and two kappa light chains of 213 amino acids each.

ZEVALIN Therapeutic Regimen

The ZEVALIN therapeutic regimen is administered in two steps: Step 1 includes one infusion of Rituximab preceding In-111 ZEVALIN. Step 2 follows Step 1 by seven to nine days and consists of a second infusion of Rituximab followed by Y-90 ZEVALIN.

ZEVALIN™ is supplied as two separate and distinctly labeled kits that contain all of the non-radioactive ingredients necessary to produce a single dose of In-111 ZEVALIN and a single dose of Y-90 ZEVALIN, both essential components of the ZEVALIN therapeutic regimen. Indium-111 chloride and Rituximab must be ordered separately from the ZEVALIN kit. Yttrium-90 Chloride Sterile Solution is supplied by MDS Nordion when the Y-90 ZEVALIN kit is ordered.

ZEVALIN Kits

Each of the two ZEVALIN kits contains four vials that are used to produce a single dose of either In-111 ZEVALIN or Y-90 ZEVALIN, as indicated on the outer container label:

- (1) One (1) ZEVALIN vial containing 3.2 mg of Ibritumomab Tiuxetan in 2 mL of 0.9% sodium chloride solution; a sterile, pyrogen-free, clear, colorless solution that may contain translucent particles; no preservative present.
- (2) One (1) 50 mM Sodium Acetate Vial containing 13.6 mg of sodium acetate trihydrate in 2 mL of Water for Injection; a sterile, pyrogen-free, clear, colorless

solution; no preservative present.

- (3) One (1) Formulation Buffer Vial containing 750 mg of Albumin (Human), 76 mg of sodium chloride, 21 mg of sodium phosphate dibasic heptahydrate, 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; a sterile, pyrogen-free, clear yellow to amber colored solution; no preservative present.
- (4) One (1) empty Reaction Vial, sterile, pyrogen-free.

Physical/Radiochemical Characteristics of In-111

Indium-111 decays by electron capture, with a physical half-life of 67.3 hours (2.81 days).^[1] The product of radioactive decay is nonradioactive cadmium-111. Radiation emission data for In-111 are summarized in Table 1.

Table 1.
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 37 MBq (1 mCi) of In-111 is 8.3×10^{-4} C/kg/hr (3.2 R/hr) at 1 cm. Adequate shielding should be used with this gamma-emitter, in accordance with institutional good radiation safety practices.

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57 To allow correction for physical decay of In-111, the fractions that remain at selected
58 intervals before and after the time of calibration are shown in Table 2.

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Table 2.
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

62

63 **Physical/Radiochemical Characteristics of Y-90**

64 Yttrium-90 decays by emission of beta particles, with a physical half-life of 64.1 hours
65 (2.67 days).^[1] The product of radioactive decay is non-radioactive
66 zirconium-90. The range of beta particles in soft tissue (λ_{90}) is 5 mm. Radiation
67 emission data for Y-90 are summarized in Table 3.

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69

70

Table 3.
Principal Y-90 Radiation Emission Data

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

71

72 **External Radiation**

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

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 4.

Table 4.
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

CLINICAL PHARMACOLOGY

General Pharmacology

Ibritumomab Tiuxetan binds specifically to the CD20 antigen (human B-lymphocyte-restricted differentiation antigen, Bp35).^[2, 3] 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).^[4, 5] The CD20 antigen is not shed from the cell surface and does not internalize upon antibody binding.^[6]

Mechanism of Action: The complementarity-determining regions of Ibritumomab bind to the CD20 antigen on B lymphocytes. Ibritumomab, like Rituximab, induces apoptosis in CD20+ B-cell lines *in vitro*.^[6] The chelate tiuxetan, which tightly binds In-111 or

Y-90, is covalently linked to the amino groups of exposed lysines and arginines contained within the antibody. The beta emission from Y-90 induces cellular damage by the formation of free radicals in the target and neighboring cells.^[7]

Normal Human Tissue Cross-Reactivity: 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. Binding was not observed on the nonlymphoid tissues or gonadal tissues (see **CLINICAL PHARMACOLOGY, Radiation Dosimetry**)

Pharmacokinetics / Pharmacodynamics

Pharmacokinetic and biodistribution studies were performed using In-111 ZEVALIN (5 mCi [185 MBq] In-111, 1.6 mg Ibritumomab Tiuxetan). In a 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.

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.

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 cell/mm³). 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/mm³) by 9 months after treatment. Median serum levels of IgG and IgA remained within the normal range throughout the period of B-cell

depletion. Median IgM serum levels dropped below normal (median 49 mg/dL, range 13-3990 mg/dL) after treatment and recovered to normal values by 6-month post therapy.

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.^{[8,}

^{9]} The estimated radiation absorbed doses to organs and marrow from a course of the ZEVALIN therapeutic regimen are summarized in Table 5. 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 5.
Estimated Radiation Absorbed Doses From Y-90 ZEVALIN and In-111 ZEVALIN

Organ	Y-90 ZEVALIN mGy/MBq		In-111 ZEVALIN mGy/MBq	
	Median	Range	Median	Range
Spleen ¹	9.4	1.8 - 14.4	0.9	0.2 - 1.2
Testes ¹	9.1	5.4 - 11.4	0.6	0.4 - 0.8
Liver ¹	4.8	2.3 - 8.1	0.7	0.3 - 1.1
Lower Large Intestinal Wall ¹	4.8	3.1 - 8.2	0.4	0.2 - 0.6
Upper Large Intestinal Wall ¹	3.6	2.0 - 6.7	0.3	0.2 - 0.6
Heart Wall ¹	2.8	1.5 - 3.2	0.4	0.2 - 0.5
Lungs ¹	2.0	1.2 - 3.4	0.2	0.1 - 0.4
Small Intestine ¹	1.4	0.8 - 2.1	0.2	0.1 - 0.3
Red Marrow ²	1.3	0.7 - 1.8	0.2	0.1 - 0.2
Urinary Bladder Wall ³	0.9	0.7 - 2.1	0.2	0.1 - 0.2
Bone Surfaces ²	0.9	0.5 - 1.2	0.2	0.1 - 0.2
Ovaries ³	0.4	0.3 - 0.5	0.2	0.2 - 0.2
Uterus ³	0.4	0.3 - 0.5	0.2	0.1 - 0.2

Adrenals³	0.3	0.0 - 0.5	0.2	0.1 - 0.3
Brain³	0.3	0.0 - 0.5	0.1	0.0 - 0.1
Breasts³	0.3	0.0 - 0.5	0.1	0.0 - 0.1
Gallbladder Wall³	0.3	0.0 - 0.5	0.3	0.1 - 0.4
Muscle³	0.3	0.0 - 0.5	0.1	0.0 - 0.1
Pancreas³	0.3	0.0 - 0.5	0.2	0.1 - 0.3
Skin³	0.3	0.0 - 0.5	0.1	0.0 - 0.1
Stomach³	0.3	0.0 - 0.5	0.1	0.1 - 0.2
Thymus³	0.3	0.0 - 0.5	0.1	0.1 - 0.2
Thyroid²	0.3	0.0 - 0.5	0.1	0.0 - 0.1
Kidneys¹	0.1	0.0 - 0.2	0.2	0.1 - 0.2
Total Body³	0.5	0.2 - 0.7	0.1	0.1 - 0.2

1 Organ region of interest

2 Sacrum region of interest ^[10]

3 Whole body region of interest

CLINICAL STUDIES

The safety and efficacy of the ZEVALIN therapeutic regimen were evaluated in two multi-center trials enrolling a total of 197 subjects. The ZEVALIN therapeutic regimen was administered in two steps (see DOSAGE and ADMINISTRATION). The activity and toxicity of a variation of the ZEVALIN therapeutic regimen employing a reduced dose of Y-90 ZEVALIN was further defined in a third study enrolling a total of 30 patients who had mild thrombocytopenia (platelet count 100,000 to 149,000 cells/mm³).

Study 1 was a single arm study of 54 patients with relapsed follicular lymphoma refractory to Rituximab treatment. Patients were considered refractory if their last prior treatment with Rituximab did not result in a complete or partial response, or if time to disease progression (TTP) was < 6 months. The primary efficacy endpoint of the study was the overall response rate (ORR) using the International Workshop Response Criteria (IWRC).^[11] Secondary efficacy endpoints included time to disease progression (TTP)

and duration of response (DR). In a secondary analysis comparing objective response to the ZEVALIN therapeutic regimen with that observed with the most recent treatment with Rituximab, the median duration of response following the ZEVALIN therapeutic regimen was 6 vs. 4 months. Table 6 summarizes efficacy data from this study.

Study 2 was a randomized, controlled, multicenter study comparing the ZEVALIN therapeutic regimen to treatment with Rituximab. The trial was conducted in 143 patients with relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma (NHL), or transformed B-cell NHL. A total of 73 patients received the ZEVALIN therapeutic regimen, and 70 patients received Rituximab given as an IV infusion at 375 mg/m² weekly times 4 doses. The primary efficacy endpoint of the study was to determine the ORR using the IWRC^[11] (see Table 6). The ORR was significantly higher (80% vs. 56%, p = 0.002) for patients treated with the ZEVALIN therapeutic regimen. The secondary endpoints, duration of response and time to progression, were not significantly different between the two treatment arms.

Table 6.
Summary of Efficacy Data¹

	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 ² (%)	0	4	4
Median DR ^{3,4} (Months) [Range ⁵]	6.4 [0.5-24.9+]	13.9 [1.0-30.1+]	11.8 [1.2-24.5]
Median TTP ^{3,6} (Months) [Range ⁵]	6.8 [1.1-25.9+]	11.2 [0.8-31.5+]	10.1 [0.7-26.1]

¹IWRC: International Workshop response criteria

²CRu: Unconfirmed complete response

³Estimated with observed range.

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

⁵"+" indicates an ongoing response.

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

Study 3 was a single arm study of 30 patients with relapsed or refractory low-grade, follicular, or transformed B-cell NHL who had mild thrombocytopenia (platelet count

187 100,000 to 149,000 cells/mm³). Excluded from the study were patients with ≥ 25%
188 lymphoma marrow involvement and/or impaired bone marrow reserve. Patients were
189 considered to have impaired bone marrow reserve if they had any of the following: prior
190 myeloablative therapy with stem cell support; prior external beam radiation to > 25% of
191 active marrow; a platelet count <100,000 cells/mm³; or neutrophil count <1,500
192 cells/mm³. In this study, a modification of the ZEVALIN therapeutic regimen with a
193 lower specific activity Y-90 ZEVALIN dose [(Y-90 ZEVALIN at 0.3 mCi/kg (11.1
194 MBq/kg)] was used. Objective, durable clinical responses were observed [67% ORR
195 (95% CI: 48-85%), 11.8 months median DR (range: 4-17 months)] and resulted in a
196 greater incidence of hematologic toxicity (see ADVERSE REACTIONS) than in Studies
197 1 and 2.

198

199 **INDICATIONS AND USAGE**

200 ZEVALIN, as part of the ZEVALIN therapeutic regimen (see DOSAGE AND
201 ADMINISTRATION), is indicated for the treatment of patients with relapsed or
202 refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma,
203 including patients with Rituximab refractory follicular non-Hodgkin's lymphoma.
204 Determination of the effectiveness of the ZEVALIN therapeutic regimen in a relapsed or
205 refractory patient population is based on overall response rates (see CLINICAL
206 STUDIES). The effects of the ZEVALIN therapeutic regimen on survival are not known.

207

208 **CONTRAINDICATIONS**

209 The ZEVALIN therapeutic regimen is contraindicated in patients with known Type I
210 hypersensitivity or anaphylactic reactions to murine proteins or to any component of this
211 product, including Rituximab, yttrium chloride, and indium chloride.

212

213 **WARNINGS (SEE BOXED WARNING)**

214 **Altered Biodistribution:** Y-90 ZEVALIN should not be administered to patients with
215 altered biodistribution of In-111 ZEVALIN. The expected biodistribution of In-111
216 ZEVALIN includes easily detectable uptake in the blood pool areas on the first day
217 image, with less activity in the blood pool areas on the second or third day image;

218 moderately high to high uptake in normal liver and spleen during the first day and the
219 second or third day image; and moderately low or very low uptake in normal kidneys,
220 urinary bladder, and normal bowel on the first day image and the second or third day
221 image. Altered biodistribution of In-111 ZEVALIN can be characterized by diffuse
222 uptake in normal lung more intense than the cardiac blood pool on the first day image or
223 more intense than the liver on the second or third day image; kidneys with greater
224 intensity than the liver on the posterior view of the second or third day image; or intense
225 areas of uptake throughout the normal bowel comparable to uptake by the liver on the
226 second or third day images.

227

228 **Severe Infusion Reactions (See PRECAUTIONS, Hypersensitivity):** The ZEVALIN
229 therapeutic regimen may cause severe, and potentially fatal, infusion reactions. These
230 severe reactions typically occur during the first Rituximab infusion with time to onset of
231 30 to 120 minutes. Signs and symptoms of severe infusion reaction may include
232 hypotension, angioedema, hypoxia, or bronchospasm, and may require interruption of
233 Rituximab, In-111 ZEVALIN, or Y-90 ZEVALIN administration. The most severe
234 manifestations and sequelae may include pulmonary infiltrates, acute respiratory distress
235 syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock.
236 **Because the ZEVALIN therapeutic regimen includes the use of Rituximab, see also**
237 **prescribing information for RITUXAN (Rituximab).**

238

239 **Cytopenias (See ADVERSE REACTIONS, Hematologic Events):**
240 The most common severe adverse events reported with the ZEVALIN therapeutic
241 regimen were thrombocytopenia (61% of patients with platelet counts $<50,000$
242 cells/mm^3) and neutropenia (57% of patients with absolute neutrophil count (ANC)
243 $<1,000 \text{ cells/mm}^3$) in patients with $\geq 150,000 \text{ platelets/mm}^3$ prior to treatment. Both
244 incidences of severe thrombocytopenia and neutropenia increased to 78% and 74% for
245 patients with mild thrombocytopenia at baseline (platelet count of 100,000 to 149,000
246 cells/mm^3). For all patients, the median time to nadir was 7-9 weeks and the median
247 duration of cytopenias was 22-35 days. In $<5\%$ of cases, patients experienced severe
248 cytopenia that extended beyond the prospectively defined protocol treatment period of 12

249 weeks following administration of the ZEVALIN therapeutic regimen. Some of these
250 patients eventually recovered from cytopenia, while others experienced progressive
251 disease, received further anti-cancer therapy, or died of their lymphoma without having
252 recovered from cytopenia. The cytopenias may have influenced subsequent treatment
253 decisions.

254

255 Hemorrhage, including fatal cerebral hemorrhage, and severe infections have occurred in
256 a minority of patients in clinical studies. Careful monitoring for and management of
257 cytopenias and their complications (e.g., febrile neutropenia, hemorrhage) for up to 3
258 months after use of the ZEVALIN therapeutic regimen are necessary. Caution should be
259 exercised in treating patients with drugs that interfere with platelet function or
260 coagulation following the ZEVALIN therapeutic regimen and patients receiving such
261 agents should be closely monitored.

262

263 The ZEVALIN therapeutic regimen should not be administered to patients with $\geq 25\%$
264 lymphoma marrow involvement and/or impaired bone marrow reserve, e.g., prior
265 myeloablative therapies; platelet count $<100,000$ cells/mm³; neutrophil count $<1,500$
266 cells/mm³; hypocellular bone marrow ($\leq 15\%$ cellularity or marked reduction in bone
267 marrow precursors); or to patients with a history of failed stem cell collection.

268

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

273

274 **Pregnancy Category D:** Y-90 ZEVALIN can cause fetal harm when administered to a
275 pregnant woman. There are no adequate and well-controlled studies in pregnant women.
276 If this drug is used during pregnancy, or if the patient becomes pregnant while receiving
277 this drug, the patient should be apprised of the potential hazard to the fetus. Women of
278 childbearing potential should be advised to avoid becoming pregnant.

279

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

285 286 **PRECAUTIONS**

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

291
292 **Radionuclide Precautions:** The contents of the ZEVALIN kit are not radioactive.
293 However, during and after radiolabeling ZEVALIN with In-111 or Y-90, care should be
294 taken to minimize radiation exposure to patients and to medical personnel, consistent
295 with institutional good radiation safety practices and patient management procedures.

296
297 **Hypersensitivity:** Anaphylactic and other hypersensitivity reactions have been reported
298 following the intravenous administration of proteins to patients. Medications for the
299 treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines and
300 corticosteroids, should be available for immediate use in the event of an allergic reaction
301 during administration of ZEVALIN. Patients who have received murine proteins should
302 be screened for human anti-mouse antibodies (HAMA). Patients with evidence of
303 HAMA have not been studied and may be at increased risk of allergic or serious
304 hypersensitivity reactions during ZEVALIN therapeutic regimen administrations.

305
306 **Immunization:** The safety of immunization with live viral vaccines following the
307 ZEVALIN therapeutic regimen has not been studied. Also, the ability of patients who
308 received the ZEVALIN therapeutic regimen to generate a primary or anamnestic humoral
309 response to any vaccine has not been studied.

310

311 **Laboratory Monitoring:** Complete blood counts (CBC) and platelet counts should be
312 obtained weekly following the ZEVALIN therapeutic regimen and should continue until
313 levels recover. CBC and platelet counts should be monitored more frequently in patients
314 who develop severe cytopenia, or as clinically indicated.

315

316 **Drug Interactions:** No formal drug interaction studies have been performed with
317 ZEVALIN. Due to the frequent occurrence of severe and prolonged thrombocytopenia,
318 the potential benefits of medications which interfere with platelet function and/or
319 anticoagulation should be weighed against the potential increased risks of bleeding and
320 hemorrhage. Patients receiving medications that interfere with platelet function or
321 coagulation should have more frequent laboratory monitoring for thrombocytopenia. In
322 addition, the transfusion practices for such patients may need to be modified given the
323 increased risk of bleeding.

324

325 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No long-term animal studies
326 have been performed to establish the carcinogenic or mutagenic potential of the
327 ZEVALIN therapeutic regimen, or to determine its effects on fertility in males or
328 females. However, radiation is a potential carcinogen and mutagen. The ZEVALIN
329 therapeutic regimen results in a significant radiation dose to the testes. The radiation
330 dose to the ovaries has not been established. There have been no studies to evaluate
331 whether the ZEVALIN therapeutic regimen causes hypogonadism, premature
332 menopause, azoospermia and/or mutagenic alterations to germ cells. There is a potential
333 risk that the ZEVALIN therapeutic regimen could cause toxic effects on the male and
334 female gonads. Effective contraceptive methods should be used during treatment and for
335 up to 12 months following the ZEVALIN therapeutic regimen.

336

337 **Pregnancy Category D: SEE WARNINGS.**

338

339 **Nursing Mothers:** It is not known whether ZEVALIN is excreted in human milk.
340 Because human IgG is excreted in human milk and the potential for ZEVALIN exposure

341 in the infant is unknown, women should be advised to discontinue nursing and formula
342 feeding should be substituted for breast feedings (see CLINICAL PHARMACOLOGY).

343

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

349

350 **Pediatric Use:** The safety and effectiveness of the ZEVALIN therapeutic regimen in
351 children have not been established.

352

353 **ADVERSE REACTIONS**

354 Safety data, except where indicated, are based upon 349 patients treated in 5 clinical
355 studies with the ZEVALIN therapeutic regimen (see DOSAGE AND
356 ADMINISTRATION). Because the ZEVALIN therapeutic regimen includes the use of
357 Rituximab, also see prescribing information for RITUXAN (Rituximab).

358

359 The most serious adverse reactions caused by the ZEVALIN therapeutic regimen include
360 infections (predominantly bacterial in origin), allergic reactions (bronchospasm and
361 angioedema), and hemorrhage while thrombocytopenic (resulting in deaths). In addition,
362 patients who have received the ZEVALIN therapeutic regimen have developed myeloid
363 malignancies and dysplasias. Fatal infusion reactions have occurred following the
364 infusion of Rituximab. Please refer to the BOXED WARNINGS and WARNINGS
365 sections for detailed descriptions of these reactions.

366

367 The most common toxicities reported were neutropenia, thrombocytopenia, anemia,
368 gastrointestinal symptoms (nausea, vomiting, abdominal pain, and diarrhea), increased
369 cough, dyspnea, dizziness, arthralgia, anorexia, anxiety, and ecchymosis. Hematologic
370 toxicity was often severe and prolonged, whereas most non-hematologic toxicity was
371 mild in severity. Table 7 lists adverse events that occurred in $\geq 5\%$ of patients. A more

372 detailed description of the incidence and duration of hematologic toxicities, according to
373 baseline platelet count (as an indicator of bone marrow reserve) is provided in Table 8,
374 Hematologic Toxicity.

Table 7.
Incidence of Adverse Events in $\geq 5\%$ of Patients Receiving the ZEVALIN
therapeutic regimen [†]
(N = 349)

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

[†] 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 relationship.

382

383 The following adverse events (except for those noted in Table 7) occurred in between 1
384 and 4% of patients during the treatment period: urticaria (4%), anxiety (4%), dyspepsia
385 (4%), sweats (4%), petechia (3%), epistaxis (3%), allergic reaction (2%), and melena
386 (2%).

387

388 Severe or life-threatening adverse events occurred in 1-5% of patients (except for those
389 noted in Table 7) consisted of pancytopenia (2%), allergic reaction (1%), gastrointestinal
390 hemorrhage (1%), melena (1%), tumor pain (1%), and apnea (1%). The following severe
391 or life threatening events occurred in <1% of patients: angioedema, tachycardia, urticaria,
392 arthritis, lung edema, pulmonary embolus, encephalopathy, hematemesis, subdural
393 hematoma, and vaginal hemorrhage.

394

395 **Hematologic Events:** Hematologic toxicity was the most frequently observed adverse
396 event in clinical trials. Table 8 presents the incidence and duration of severe hematologic
397 toxicity for patients with normal baseline platelet count ($= 150,000 \text{ cells/mm}^3$) treated
398 with the ZEVALIN therapeutic regimen and patients with mild thrombocytopenia
399 (platelet count 100,000 to 149,000 cells/mm^3) at baseline who were treated with a
400 modified ZEVALIN therapeutic regimen that included a lower specific activity Y-90
401 ZEVALIN dose at 0.3 mCi/kg (11.1 MBq/kg).

402

Table 8.
Severe Hematologic Toxicity

	ZEVALIN therapeutic regimen using 0.4 mCi/kg Y-90 Dose (14.8 MBq/kg)	Modified ZEVALIN therapeutic regimen using 0.3 mCi/kg Y-90 dose (11.1 MBq/kg)
ANC		
Median nadir (cells/mm ³)	800	600
Per Patient Incidence ANC <1000 cells/mm ³	57%	74%
Per Patient Incidence ANC <500 cells/mm ³	30%	35%
Median Duration (Days)* ANC <1000 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)# Platelets <50,000 cells/mm ³	24	35

*Median duration of neutropenia for patients with ANC <1000 cells/mm³ (Date from last laboratory value showing ANC =1000 cells/mm³ to date of first laboratory value following nadir showing ANC =1000 cells/mm³, censored at initiation of next treatment or death)

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

Median time to ANC nadir was 62 days, to platelet nadir was 53 days, and to hemoglobin nadir was 68 days. Information on growth factor use and platelet transfusions is based on 211 patients for whom data were collected. Filgrastim was given to 13% of patients and erythropoietin to 8%. Platelet transfusions were given to 22% of patients and red blood cell transfusions to 20%.

Infectious Events: During the first 3 months after initiating the ZEVALIN therapeutic regimen, 29% of patients developed infections. Three percent of patients developed serious infections comprising urinary tract infection, febrile neutropenia, sepsis, pneumonia, cellulitis, colitis, diarrhea, osteomyelitis, and upper respiratory tract

infection. Life threatening infections were reported for 2% of patients that included sepsis, empyema, pneumonia, febrile neutropenia, fever, and biliary stent-associated cholangitis. During follow-up from 3 months to 4 years after the start of treatment with ZEVALIN, 6% of patients developed infections. Two percent of patients had serious infections comprising urinary tract infection, bacterial or viral pneumonia, febrile neutropenia, perihilar infiltrate, pericarditis, and intravenous drug-associated viral hepatitis. One percent of patients had life threatening infections that included bacterial pneumonia, respiratory disease, and sepsis.

Secondary 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 to 14 years following the patients' diagnosis of NHL.

Immunogenicity: 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 antibody (HAMA) (n=5) or human anti-chimeric antibody (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

455 whose test results were considered positive for antibodies to Ibritumomab or Rituximab
456 using kinetic enzyme immunoassays to Ibritumomab and Rituximab. The observed
457 incidence of antibody positivity in an assay is highly dependent on the sensitivity and
458 specificity of the assay and may be influenced by several factors including sample
459 handling and concomitant medications. Comparisons of the incidence of HAMA/HACA
460 to the ZEVALIN therapeutic regimen with the incidence of antibodies to other products
461 may be misleading.

462

463 **OVERDOSAGE**

464 Doses as high as 0.52 mCi/kg (19.2 MBq/kg) of Y-90 ZEVALIN were administered in
465 ZEVALIN therapeutic regimen clinical trials and severe hematological toxicities were
466 observed. No fatalities or second organ injury resulting from overdosage administrations
467 were documented. However, single doses up to 50 mCi (1850 MBq) of Y-90 ZEVALIN,
468 and multiple doses of 20 mCi (740 MBq) followed by 40 mCi (1480 MBq) of
469 Y-90 ZEVALIN were studied in a limited number of subjects. In these trials, some
470 patients required autologous stem cell support to manage hematological toxicity.

471

472 **DOSAGE AND ADMINISTRATION**

473 The ZEVALIN therapeutic regimen is administered in two steps: Step 1 includes a single
474 infusion of 250 mg/m² Rituximab (not included in the ZEVALIN kits) preceding a fixed
475 dose of 5.0 mCi (1.6 mg total antibody dose) of In-111 ZEVALIN administered as a 10
476 minute IV push. Step 2 follows step 1 by seven to nine days and consists of a second
477 infusion of 250 mg/m² of Rituximab prior to 0.4 mCi/kg of Y-90 ZEVALIN administered
478 as a 10 minute IV push.

479

480 **Rituximab Administration: NOTE THAT THE DOSE OF RITUXIMAB IS**
481 **LOWER WHEN USED AS PART OF THE ZEVALIN THERAPEUTIC**
482 **REGIMEN, AS COMPARED TO THE DOSE OF RITUXIMAB WHEN USED AS**
483 **A SINGLE AGENT. DO NOT ADMINISTER RITUXIMAB AS AN**
484 **INTRAVENOUS PUSH OR BOLUS.** Hypersensitivity reactions may occur (see

485 WARNINGS). Premedication, consisting of acetaminophen and diphenhydramine,
486 should be considered before each infusion of Rituximab.

487

488 **ZEVALIN Therapeutic Regimen Dose Modification in Patients with Mild**

489 **Thrombocytopenia:** The Y-90 ZEVALIN dose should be reduced to 0.3 mCi/kg (11.1
490 MBq/kg) for patients with a baseline platelet count between 100,000 and 149,000
491 cells/mm³.

492

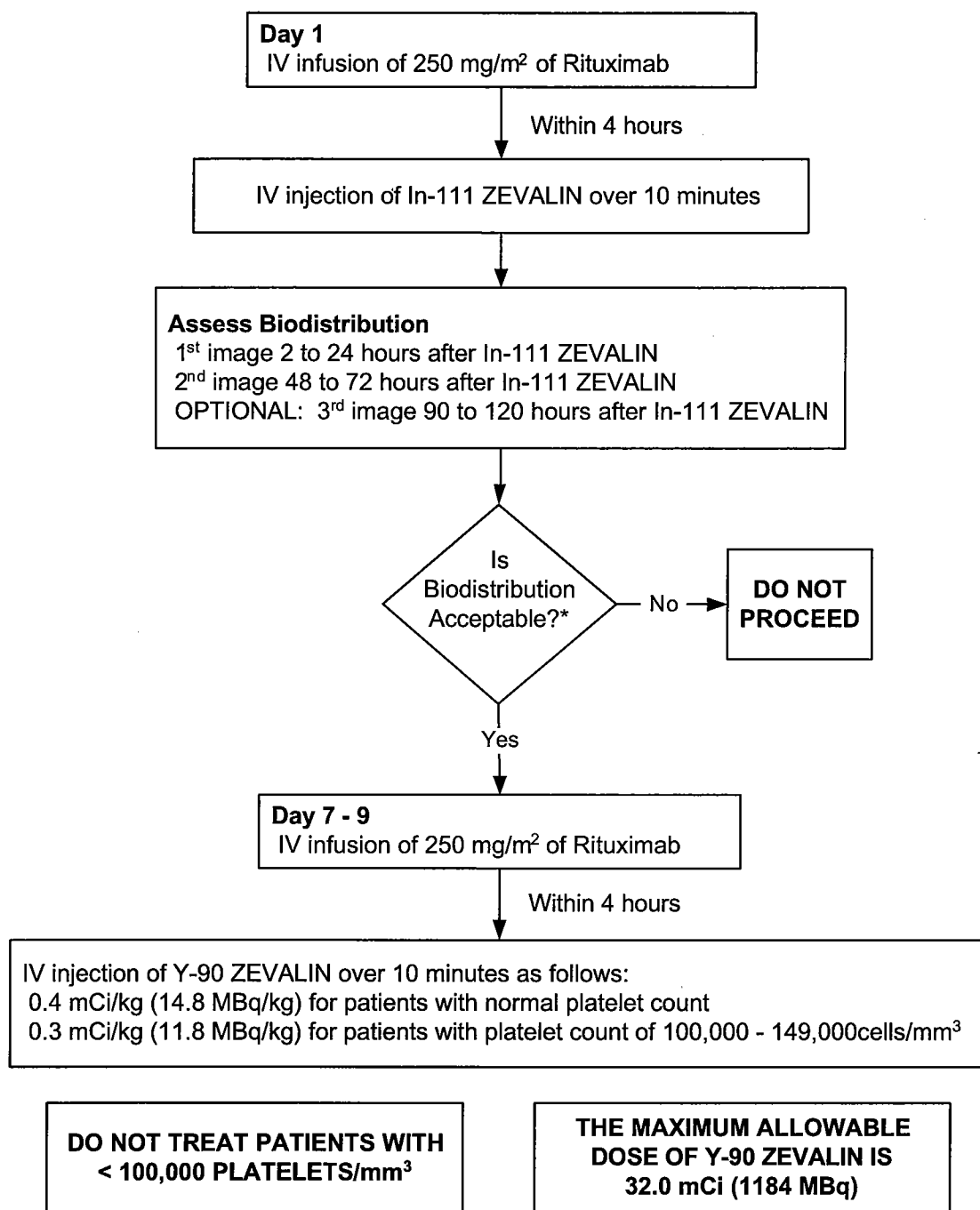
493 Two separate and distinctly-labeled kits are ordered for the preparation of a single dose
494 each of In-111 ZEVALIN and Y-90 ZEVALIN. In-111 ZEVALIN and Y-90 ZEVALIN
495 are radiopharmaceuticals and should be used only by physicians and other professionals
496 qualified by training and experienced in the safe use and handling of radionuclides.

497 **Changing the ratio of any of the reactants in the radiolabeling process may**
498 **adversely impact therapeutic results. In-111 ZEVALIN and Y-90 ZEVALIN should**
499 **not be used in the absence of the Rituximab pre-dose.**

500

501 **Overview of Dosing Schedule:**

502



*See IMAGE ACQUISITION AND INTERPRETATION

503

504

505 **ZEVALIN Therapeutic Regimen Administration**

506 Step 1:

507 First Rituximab Infusion: Rituximab at a dose of 250 mg/m² should be administered
508 intravenously at an initial rate of 50 mg/hr. Rituximab should not be mixed or diluted
509 with other drugs. If hypersensitivity or infusion-related events do not occur, escalate the
510 infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If
511 hypersensitivity or an infusion-related event develops, the infusion should be temporarily
512 slowed or interrupted (see WARNINGS). The infusion can continue at one-half the
513 previous rate upon improvement of patient symptoms.

514

515 In-111 ZEVALIN Injection: Within 4 hours following completion of the Rituximab
516 dose, 5.0 mCi (1.6 mg total antibody dose) of In-111 ZEVALIN is injected intravenously
517 (I.V.) over a period of 10 minutes.

518

519 Step 2:

520 Step 2 of the ZEVALIN therapeutic regimen is initiated seven to nine days following
521 Step 1 administrations.

522

523 Second Rituximab Infusion: Rituximab at a dose of 250 mg/m² is administered I.V. at an
524 initial rate of 100 mg/hr (50 mg/hr if infusion related events were documented during the
525 first Rituximab administration) and increased by 100 mg/hr increments at 30 minute
526 intervals, to a maximum of 400 mg/hr, as tolerated.

527

528 Y-90 ZEVALIN Injection:

529 Within 4 hours following completion of the Rituximab dose, Y-90 ZEVALIN at a dose of
530 0.4 mCi/kg (14.8 MBq/kg) actual body weight for patients with a platelet count >150,000
531 cells/mm³, and 0.3 mCi/kg (11.1 MBq/kg) actual body weight for patients with a platelet
532 count of 100,000-149,000 cells/mm³ is injected intravenously (I.V.) over a period of 10
533 minutes. Precautions should be taken to avoid extravasation. A free flowing I.V. line
534 should be established prior to Y-90 ZEVALIN injection. Close monitoring for evidence
535 of extravasation during the injection of Y-90 ZEVALIN is required. If any signs or

536 symptoms of extravasation have occurred, the infusion should be immediately terminated
537 and restarted in another vein. **The prescribed, measured, and administered dose of**
538 **Y-90 ZEVALIN must not exceed the absolute maximum allowable dose of 32.0 mCi**
539 **(1184 MBq), regardless of the patient's body weight. Do not give Y-90 ZEVALIN to**
540 **patients with a platelet count $<100,000/\text{mm}^3$ (see WARNINGS).**

541

542 **DIRECTIONS FOR PREPARATION OF RADIOLABELED ZEVALIN.**

543

544 **A. PREPARATION OF THE IN-111 ZEVALIN DOSE**

545

546 **GENERAL:**

547 **Read all directions thoroughly and assemble all materials before starting the**
548 **radiolabeling procedure. Important, significant differences exist in the preparation**
549 **of the In-111 ZEVALIN dose and the Y-90 ZEVALIN dose.**

550

551 **The patient dose should be measured by a suitable radioactivity calibration system**
552 **immediately prior to administration. The dose calibrator must be operated in**
553 **accordance with the manufacturer's specifications and quality control for the**
554 **measurement of In-111.**

555

556 **Proper aseptic technique and precautions for handling radioactive materials should be**
557 **employed. Waterproof gloves should be utilized in the preparation and during the**
558 **determination of radiochemical purity of In-111 ZEVALIN. Appropriate shielding**
559 **should be used during radiolabeling, and use of a syringe shield is recommended during**
560 **administration to the patient. The radiolabeling of ZEVALIN shall be done according to**
561 **the following directions.**

562

563 **Required materials not supplied in the kit:**

564

565 **A. Indium-111 Chloride Sterile Solution (In-111 Chloride) from Amersham**
566 **Health, Inc. or Mallinckrodt, Inc.**

- 567 B. Three sterile 1 mL syringes
- 568 C. One sterile 3 mL syringe
- 569 D. Two sterile 10 mL syringes with 18-20 G needles
- 570 E. Instant thin-layer chromatographic silica gel strips
- 571 F. 0.9% sodium chloride aqueous solution for the chromatography solvent
- 572 G. Developing chamber for chromatography
- 573 H. Suitable radioactivity counting apparatus
- 574 I. Filter, 0.22 micrometer, low-protein-binding
- 575 J. Vial and syringe shield

576

577 Method:

578

- 579 1. Sterile, pyrogen-free In-111 chloride must be used for the preparation of
580 In-111 ZEVALIN. The use of high purity In-111 chloride manufactured by
581 Amersham Health, Inc. or Mallinckrodt, Inc. is required.
582
- 583 2. Before radiolabeling, allow contents of the refrigerated carton to reach room
584 temperature. Note: The ZEVALIN vial contains a protein solution that may
585 develop translucent particulates. These particulates will be removed by filtration
586 prior to administration.
587
- 588 3. Clean the rubber stoppers of all of the vials in the kit and the In-111 chloride vial
589 with a suitable alcohol swab and allow to air dry.
590
- 591 4. Place the empty Reaction Vial in a suitable dispensing shield (pre-warmed to
592 room temperature). To avoid the buildup of excessive pressure during the
593 procedure, use a 10 mL syringe to withdraw 10 mL of air from the Reaction Vial.
594
- 595 5. Prior to initiating the radiolabeling reaction, determine the amount of each
596 component needed according to the directions below:
597

- 598 a. Calculate the volume of In-111 chloride that is equivalent to 5.5 mCi
599 based on the activity concentration of the In-111 chloride stock.
600
- 601 b. The volume of 50 mM sodium acetate solution needed is 1.2 times the
602 volume of In-111 chloride solution determined in step 5.a., above. (The
603 50 mM sodium acetate is used to adjust the pH for the radiolabeling
604 reaction.)
605
- 606 c. Calculate the volume of Formulation Buffer needed to bring the Reaction
607 Vial contents to a final volume of 10 mL. This is the volume of
608 Formulation Buffer needed to protect the labeled product from radiolysis
609 and to terminate the labeling reaction. For example, if volumes of 0.5 mL
610 of In-111 chloride, 0.6 mL of sodium acetate and 1.0 mL of ZEVALIN
611 were used, then the amount of formulation buffer would be $10 - (0.5 + 0.6 +$
612 $1.0) = 7.9$ mL.
613
- 614 6. With a sterile 1 mL syringe, transfer the calculated volume of 50 mM of sodium
615 acetate to the empty Reaction Vial. Coat the entire inner surface of the Reaction
616 Vial by gentle inversion or rolling.
617
- 618 7. Transfer 5.5 mCi of In-111 chloride to the Reaction Vial with a sterile 1 mL
619 syringe. Mix the two solutions and coat the entire inner surface of the Reaction
620 Vial by gentle inversion or rolling.
621
- 622 8. With a sterile 3 mL syringe, transfer 1.0 mL of ZEVALIN (Ibritumomab
623 Tiuxetan) to the Reaction Vial. Coat the entire surface of the Reaction Vial by
624 gentle inversion or rolling. **Do not shake or agitate the vial contents, since this**
625 **will cause foaming and denaturation of the protein.**
626

- 627 9. Allow the labeling reaction to proceed at room temperature for 30 minutes.
628 Allowing the labeling reaction to proceed for a longer or shorter time may result
629 in inadequate labeling.
630
- 631 10. **Immediately** after the 30-minute incubation period, using a sterile 10 mL syringe
632 with a large bore needle (18 G - 20 G), transfer the calculated volume of
633 Formulation Buffer from step 5.c. to the Reaction Vial. Gently add the
634 Formulation Buffer down the side of the Reaction Vial. If necessary, to
635 normalize air pressure, withdraw an equal volume of air. Coat the entire inner
636 surface of the Reaction Vial by gentle inversion or rolling. Do not shake or
637 agitate the vial contents. Avoid foaming.
638
- 639 11. Using the supplied labels, record the patient identification, the date and time of
640 preparation, the total activity and volume, and the date and time of expiration, and
641 affix these labels to the reaction vial and shielded reaction vial container.
642
- 643 12. Calculate the volume required for an In-111 ZEVALIN dose of 5 mCi. Withdraw
644 the required volume from the Reaction Vial contents into a sterile 10 mL syringe
645 with a large bore needle (18 G - 20 G). Assay the syringe and contents in a dose
646 calibrator. The syringe should contain the dose of In-111 ZEVALIN to be
647 administered to the patient. Using the supplied labels, record the patient
648 identification, the date and time of preparation, the total activity and volume
649 added, and the date and time of expiration, and affix these labels to the syringe
650 and shielded unit dose container.
651
- 652 13. Determine Radiochemical purity. See Section C: Procedure for Determining
653 Radiochemical Purity Section that follows DIRECTIONS FOR PREPARATION
654 OF THE Y-90 ZEVALIN DOSE.
655
- 656 14. Indium-111 ZEVALIN should be stored at 2 - 8°C (36-46°F) until use and
657 administered within 12 hours of radiolabeling.

658

659 15. See DOSAGE AND ADMINISTRATION: ZEVALIN Therapeutic Regimen
660 Administration: Step 1

661

662 16. Discard vials, needles and syringes in accordance with local, state, and federal
663 regulations governing radioactive and biohazardous waste.

664

665 **B. PREPARATION OF THE Y-90 ZEVALIN DOSE**

666

667 **GENERAL:**

668 **Read all directions thoroughly and assemble all materials before starting the**
669 **radiolabeling procedure. Important, significant differences exist in the preparation**
670 **of the In-111 ZEVALIN dose and the Y-90 ZEVALIN dose.**

671

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

676

677 Proper aseptic technique and precautions for handling radioactive materials should be
678 employed. Waterproof gloves should be utilized in the preparation and during the
679 determination of radiochemical purity of Y-90 ZEVALIN. Appropriate shielding should
680 be used during radiolabeling, and use of a syringe shield is recommended during
681 administration to the patient. The radiolabeling of ZEVALIN shall be done according to
682 the following directions.

683

684 Required materials not supplied in the kit:

685

686 A. Yttrium-90 Chloride Sterile Solution from MDS Nordion (shipped directly
687 from MDS Nordion upon placement of an order for the Y-90 ZEVALIN kit)

688 B. Three sterile 1 mL syringes

- 689 C. One sterile 3 mL syringe
- 690 D. Two sterile 10 mL syringes with 18-20 G needles
- 691 E. Instant thin-layer chromatographic silica gel strips (ITLC-SG)
- 692 F. 0.9% sodium chloride aqueous solution for the chromatography solvent
- 693 G. Suitable radioactivity counting apparatus
- 694 H. Developing chamber for chromatography
- 695 I. Filter, 0.22 micrometer, low-protein-binding
- 696 J. Vial and syringe shield

697

698 Method:

699

- 700 1. Sterile, pyrogen-free Y-90 chloride must be used for the preparation of Y-90
701 ZEVALIN. The use of high purity Y-90 chloride manufactured by MDS Nordion
702 is required.
703
- 704 2. Before radiolabeling, allow the contents of the refrigerated carton to reach room
705 temperature. Note: The ZEVALIN vial contains a protein solution that may
706 develop translucent particulates. These particulates will be removed by filtration
707 prior to administration.
708
- 709 3. Clean the rubber stoppers of all of the vials in the kit and the Y-90 chloride vial
710 with a suitable alcohol swab and allow to air dry.
711
- 712 4. Place the empty Reaction Vial in a suitable dispensing shield (pre-warmed to
713 room temperature). To avoid the buildup of excessive pressure during the
714 procedure, use a 10 mL syringe to withdraw 10 mL of air from the Reaction Vial.
715
- 716 5. Prior to initiating the radiolabeling reaction, determine the amount of each
717 component needed according to the directions below:
718

- 719 a. Calculate the volume of Y-90 chloride that is equivalent to 40 mCi based
720 on the activity concentration of the Y-90 chloride stock.
721
- 722 b. The volume of 50 mM sodium acetate solution needed is 1.2 times the
723 volume of Y-90 chloride solution determined in step 5.a., above. (The
724 50 mM sodium acetate is used to adjust the pH for the radiolabeling
725 reaction.)
726
- 727 c. Calculate the volume of Formulation Buffer needed to bring the Reaction
728 Vial contents to a final volume of 10 mL. This is the volume of
729 Formulation Buffer needed to protect the labeled product from radiolysis
730 and to terminate the labeling reaction. For example if the volumes were
731 0.5 mL of Y-90 chloride, 0.6 mL of sodium acetate and 1.3 mL of
732 ZEVALIN, then the amount of formulation buffer would be
733 $10 - (0.5 + 0.6 + 1.3) = 7.6$ mL.
734
- 735 6. With a sterile 1 mL syringe, transfer the calculated volume 50 mM of sodium
736 acetate to the empty Reaction Vial. Coat the entire inner surface of the Reaction
737 Vial by gentle inversion or rolling.
738
- 739 7. Transfer 40 mCi of Y-90 chloride to the Reaction Vial with a sterile 1 mL
740 syringe. Mix the two solutions and coat the entire inner surface of the Reaction
741 Vial by gentle inversion or rolling.
742
- 743 8. With a sterile 3 mL syringe, transfer 1.3 mL of ZEVALIN (Ibritumomab
744 Tiuxetan) to the Reaction Vial. Coat the entire surface of the Reaction Vial by
745 gentle inversion or rolling. **Do not shake or agitate the vial contents, since this**
746 **will cause foaming and denaturation of the protein.**
747

- 748 9. Allow the labeling reaction to proceed at room temperature for 5 minutes.
749 Allowing the labeling reaction to proceed for a longer or shorter time may result
750 in inadequate labeling.
751
- 752 10. **Immediately** after the 5-minute incubation period, using a sterile 10 mL syringe
753 with a large bore needle (18 G - 20 G), transfer the calculated volume of
754 Formulation Buffer from step 5.c. to the Reaction Vial, terminating incubation.
755 Gently add the Formulation Buffer down the side of the Reaction Vial. If
756 necessary to normalize air pressure, withdraw an equal volume of air. Coat the
757 entire inner surface of the Reaction Vial by gentle inversion or rolling. Do not
758 shake or agitate the vial contents. Avoid foaming.
759
- 760 11. Using the supplied labels, record the patient identification, the date and time of
761 preparation, the total activity and volume, and the date and time of expiration and
762 affix these labels to the reaction vial and shielded reaction vial container.
763
- 764 12. Calculate the volume required for a Y-90 ZEVALIN dose of 0.4 mCi/kg
765 (14.8 MBq/kg) actual body weight for patients with normal platelet count, and
766 0.3 mCi/kg (11.1 MBq/kg) actual body weight for patients with platelet count of
767 100,000 - 149,000 cells/mm³. **The prescribed, measured, and administered**
768 **dose of Y-90 ZEVALIN must not exceed the absolute maximum allowable**
769 **dose of 32.0 mCi (1184 MBq), regardless of the patient's body weight.**
770 Withdraw the required volume from the Reaction Vial contents into a sterile
771 10 mL syringe with a large bore needle (18 G - 20 G). Assay the syringe and
772 contents in a dose calibrator. The dose calibrator must be operated in accordance
773 with the manufacturer's specifications and quality control for the measurement of
774 Y-90. The syringe should contain the dose of Y-90 ZEVALIN to be administered
775 to the patient, and should be within 10% of the actual prescribed dose of Y-90
776 ZEVALIN, not to exceed a maximum dose of 32.0 mCi. Do not exceed $\pm 10\%$ of
777 the prescribed dose. Using the supplied labels, record the patient identification,
778 the date and time of preparation, the total activity and volume added, and the date

779 and time of expiration and affix these labels to the syringe and shielded unit dose
780 container.

781

782 13. Determine Radiochemical Purity. See Section C: Procedure for Determining
783 Radiochemical Purity Section that follows these DIRECTIONS FOR
784 PREPARATION OF THE Y-90 ZEVALIN DOSE.

785

786 14. Yttrium-90 ZEVALIN should be stored at 2 - 8°C (36-46°F) until use and
787 administered within 8 hours of radiolabeling.

788

789 15. See DOSAGE AND ADMINISTRATION: ZEVALIN Therapeutic Regimen
790 Administration: Step 2.

791

792 16. Discard vials, needles and syringes in accordance with local, state, and federal
793 regulations governing radioactive and biohazardous waste.

794

795 Yttrium-90 ZEVALIN is suitable for administration on an outpatient basis. Beyond the
796 use of vial and syringe shields for preparation and injection, no special shielding is
797 necessary.

798

799 **C. PROCEDURE FOR DETERMINING RADIOCHEMICAL PURITY (RCP)**

800 **The following procedure should be used for both In-111 ZEVALIN and**

801 **Y-90 ZEVALIN:**

802

- 803 A. At room temperature, place a small drop of either In-111 ZEVALIN or
804 Y-90 ZEVALIN at the origin of an ITLC-SG strip.
- 805 B. Place the ITLC-SG strip into a chromatography chamber with the origin at the
806 bottom and the solvent front at the top. Allow the solvent (0.9% NaCl) to
807 migrate at least 5 cm from the bottom of the strip. Remove the strip from the
808 chamber and cut the strip in half. Count each half of the ITLC-SG strip for
809 one-minute (CPM) with a suitable counting apparatus.

810 C. Calculate the percent RCP as follows:

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

811

812 D. If the radiochemical purity is <95%, the ITLC procedure should be repeated.

813 If repeat testing confirms that radiochemical purity is <95%, the preparation
814 should not be administered.

815

816 **IMAGE ACQUISITION AND INTERPRETATION**

817 The biodistribution of In-111 ZEVALIN should be assessed by a visual evaluation of
818 whole body planar view anterior and posterior gamma images at 2 - 24 hours and 48 - 72
819 hours after injection. To resolve ambiguities, a third image at 90 - 120 hours may be
820 necessary. Images should be acquired using a large field of view gamma camera
821 equipped with a medium energy collimator. The gamma camera should be calibrated
822 using the 171 and 245 keV photopeaks for In-111 with a 15% - 20% symmetric window.
823 Using a 256 x 1024 computer acquisition matrix, the scan speed should be 10 cm/min for
824 the first scan, 7 cm/min for the second scan, and 5 cm/min for the optional third scan.

825

826 The radiopharmaceutical is expected to be easily detectable in the blood pool areas at the
827 first time point, with less activity in the blood pool on later images. Moderately high to
828 high uptake is seen in the normal liver and spleen, with low uptake in the lungs, kidneys,
829 and urinary bladder. Localization to lymphoid aggregates in the bowel wall has been
830 reported. Tumor uptake may be visualized in soft tissue as areas of increased intensity,
831 and tumor-bearing areas in normal organs may be seen as areas of increased or decreased
832 intensity.

833

834 If a visual inspection of the gamma images reveals an altered biodistribution, the patient
835 should not proceed to the Y-90 ZEVALIN dose. The patient may be considered to have
836 an altered biodistribution if the blood pool is not visualized on the first image indicating
837 rapid clearance of the radiopharmaceutical by the reticuloendothelial system to the liver,
838 spleen, and/or marrow. Other potential examples of altered biodistribution may include

839 diffuse uptake in the normal lungs or kidneys more intense than the liver on the second or
840 third image.

841

842 During ZEVALIN clinical development, individual tumor radiation absorbed dose
843 estimates as high as 778 cGy/mCi have been reported. Although solid organ toxicity has
844 not been directly attributed to radiation from adjacent tumors, careful consideration
845 should be applied before proceeding with treatment in patients with very high tumor
846 uptake next to critical organs or structures.

847

848 **HOW SUPPLIED**

849 The In-111 ZEVALIN kit provides for the radiolabeling of Ibritumomab Tiuxetan with
850 In-111. The Y-90 ZEVALIN kit provides for the radiolabeling of Ibritumomab Tiuxetan
851 with Y-90.

852

853 The kit for the preparation of a single dose of In-111 ZEVALIN includes four vials: one
854 ZEVALIN vial containing 3.2 mg of Ibritumomab Tiuxetan in 2 mL of 0.9% sodium
855 chloride solution; one 50 mM Sodium Acetate vial; one Formulation Buffer vial; one
856 empty Reaction vial and four identification labels.

857

858 The kit for the preparation of a single dose of Y-90 ZEVALIN includes four vials: one
859 ZEVALIN vial containing 3.2 mg of Ibritumomab Tiuxetan in 2 mL of 0.9% sodium
860 chloride solution; one 50 mM Sodium Acetate vial; one Formulation Buffer vial; one
861 empty Reaction vial and four identification labels.

862

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

864

865 The Indium-111 Chloride Sterile Solution (In-111 Chloride) must be ordered separately
866 from either Amersham Health, Inc. or Mallinckrodt, Inc. at the time the In-111
867 ZEVALIN kit is ordered. The Yttrium-90 Chloride Sterile Solution will be shipped
868 directly from MDS Nordion upon placement of an order for the Y-90 ZEVALIN kit.

869

870 **Storage**

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

872

873 **REFERENCES**

- 874 1. Kocher DC. Radioactive Decay Data Tables - A Handbook of Decay Data for
875 Application to Radiation Dosimetry and Radiological Assessments: U.S.
876 Department of Energy 1981; DOE/TIC-11026.
- 877 2. Valentine MA, Meier KE, Rossie S, Clark EA. Phosphorylation of the CD20
878 phosphoprotein in resting B lymphocytes. Regulation by protein kinase C. J Biol
879 Chem 1989;264(19):11282-7.
- 880 3. Einfeld D, Brown J, Valentine M, Clark E, Ledbetter J. Molecular cloning of the
881 human B cell CD20 receptor predicts a hydrophobic protein with multiple
882 transmembrane domains. EMBO J 1988;7(3):711-7.
- 883 4. Anderson KC, Bates MP, Slaughenhaupt BL, Pinkus GS, Schlossman SF, Nadler
884 LM. Expression of human B cell-associated antigens on leukemias and
885 lymphomas: a model of human B cell differentiation. Blood 1984;63(6):1424-33.
- 886 5. Tedder T, Boyd A, Freedman A, Nadler L, Schlossman S. The B cell surface
887 molecule B1 is functionally linked with B cell activation and differentiation. J
888 Immunol 1985;135(2):973-9.
- 889 6. Press O, Appelbaum F, Ledbetter J, Martin P, Zarling J, Kidd P, et al. Monoclonal
890 antibody 1F5 (anti-CD20) serotherapy of human B-cell lymphomas. Blood
891 1987;69(2):584-91.
- 892 7. Chakrabarti MC, Le N, Paik CH, De Graff WG, Carrasquillo JA. Prevention of
893 radiolysis of monoclonal antibody during labeling. J Nucl Med
894 1996;37(8):1384-8.
- 895 8. Wiseman GA, White CA, Stabin M, Raubitschek A, Karvelis K, Schultheiss T, et
896 al. Phase I/II 90Y Zevalin™ (90yttrium ibritumomab tiuxetan, IDEC-Y2B8)
897 radioimmunotherapy dosimetry results in relapsed or refractory non-Hodgkin's
898 lymphoma. Eur J Nucl Med 2000;27(7):766-77.
- 899

- 899 9. Wiseman GA, White CA, Sparks RB, Erwin WD, Podoloff DA, Lamonica DA, et
900 al. Biodistribution and dosimetry results from a phase III prospectively
901 randomized controlled trial of Zevalin radioimmunotherapy for low-grade,
902 follicular, or transformed B-cell non-Hodgkin's lymphoma. Crit Rev Oncol
903 Hematol 2001;39(1-2):181-94.
- 904 10. Siegel J, Lee R, Pawlyk D, Horowitz J, Sharkey R, Goldenberg D. Sacral
905 scintigraphy for bone marrow dosimetry in radioimmunotherapy. Int J Appl
906 Radiat Instr 1989;16(Part B):553-9.
- 907 11. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, et al.
908 Report of an international workshop to standardize response criteria for non-
909 Hodgkin's lymphoma. J Clin Oncol 1999;17(4):1244-53.

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