

1 **Ibritumomab Tiuxetan**

2 **ZEVALIN®**

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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).

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10 **WARNINGS**

11 **Fatal Infusion Reactions:** Deaths have occurred within 24 hours of Rituximab infusion,
12 an essential component of the ZEVALIN therapeutic regimen. These fatalities were
13 associated with an infusion reaction symptom complex that included hypoxia, pulmonary
14 infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular
15 fibrillation, or cardiogenic shock. Approximately 80% of fatal infusion reactions occurred
16 in association with the first Rituximab infusion (see WARNINGS and ADVERSE
17 REACTIONS). Patients who develop severe infusion reactions should have Rituximab,
18 In-111 ZEVALIN, and Y-90 ZEVALIN infusions discontinued and receive medical
19 treatment.

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

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26 **Severe Cutaneous and Mucocutaneous Reactions:** Severe cutaneous and
27 mucocutaneous reactions, some with fatal outcome, have been reported in association
28 with the ZEVALIN therapeutic regimen. Patients experiencing a severe cutaneous or
29 mucocutaneous reaction should not receive any further component of the Zevalin
30 therapeutic regimen and should seek prompt medical evaluation. (see WARNINGS and
31 ADVERSE REACTIONS).

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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.

DESCRIPTION

ZEVALIN®

ZEVALIN (Ibritumomab Tiuxetan) is the immunoconjugate resulting from a stable thiourea covalent bond between the monoclonal antibody Ibritumomab and the linker-chelator tiuxetan [N-[2-bis(carboxymethyl)amino]-3-(p-isothiocyanatophenyl)-propyl]-[N-[2-bis(carboxymethyl)amino]-2-(methyl)-ethyl]glycine. This linker-chelator provides a high affinity, conformationally restricted chelation site for Indium-111 or Yttrium-90. The approximate molecular weight of Ibritumomab Tiuxetan is 148 kD.

The antibody moiety of ZEVALIN is Ibritumomab, a murine 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.

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64 ZEVALIN is supplied as two separate and distinctly labeled kits that contain all of the
65 non-radioactive ingredients necessary to produce a single dose of In-111 ZEVALIN and a
66 single dose of Y-90 ZEVALIN, both essential components of the ZEVALIN therapeutic
67 regimen. Indium-111 chloride and Rituximab must be ordered separately from the

68 ZEVALIN kit. Yttrium-90 Chloride Sterile Solution is supplied by MDS Nordion when
69 the Y-90 ZEVALIN kit is ordered.

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71 **ZEVALIN Kits**

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

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- 75 (1) One (1) ZEVALIN vial containing 3.2 mg of Ibritumomab Tiuxetan in 2 mL of
76 0.9% sodium chloride solution; a sterile, pyrogen-free, clear, colorless solution
77 that may contain translucent particles; no preservative present.
- 78 (2) One (1) 50 mM Sodium Acetate Vial containing 13.6 mg of sodium acetate
79 trihydrate in 2 mL of Water for Injection; a sterile, pyrogen-free, clear, colorless
80 solution; no preservative present.
- 81 (3) One (1) Formulation Buffer Vial containing 750 mg of Albumin (Human), 76 mg
82 of sodium chloride, 28 mg of sodium phosphate dibasic dodecahydrate, 4 mg of
83 pentetic acid, 2 mg of potassium phosphate monobasic and 2 mg of potassium
84 chloride in 10 mL of Water for Injection adjusted to pH 7.1 with either sodium
85 hydroxide or hydrochloric acid; a sterile, pyrogen-free, clear yellow to amber
86 colored solution; no preservative present.
- 87 (4) One (1) empty Reaction Vial, sterile, pyrogen-free.

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89 **Physical/Radiochemical Characteristics of In-111**

90 Indium-111 decays by electron capture, with a physical half-life of 67.3 hours

91 (2.81 days).^[1] The product of radioactive decay is nonradioactive cadmium-111.

92 Radiation emission data for In-111 are summarized in Table 1.

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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

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97 **External Radiation**

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

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102 To allow correction for physical decay of In-111, the fractions that remain at selected
103 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

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

110 Yttrium-90 decays by emission of beta particles, with a physical half-life of 64.1 hours
111 (2.67 days).^[1] The product of radioactive decay is non-radioactive

112 zirconium-90. The range of beta particles in soft tissue (χ_{90}) is 5 mm. Radiation
113 emission data for Y-90 are summarized in Table 3.

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Table 3.
Principal Y-90 Radiation Emission Data

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

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118 **External Radiation**

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

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

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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

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130 **CLINICAL PHARMACOLOGY**

131 **General Pharmacology**

132 Ibritumomab Tiuxetan binds specifically to the CD20 antigen (human
133 B-lymphocyte-restricted differentiation antigen, Bp35).^[2, 3] The apparent affinity (K_D) of
134 Ibritumomab Tiuxetan for the CD20 antigen ranges between approximately 14 to 18 nM.
135 The CD20 antigen is expressed on pre-B and mature B lymphocytes and on > 90% of
136 B-cell non-Hodgkin's lymphomas (NHL).^[4, 5] The CD20 antigen is not shed from the
137 cell surface and does not internalize upon antibody binding.^[6]

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139 Mechanism of Action: The complementarity-determining regions of Ibritumomab bind
140 to the CD20 antigen on B lymphocytes. Ibritumomab, like Rituximab, induces apoptosis
141 in CD20+ B-cell lines *in vitro*.^[6] The chelate tiuxetan, which tightly binds In-111 or
142 Y-90, is covalently linked to the amino groups of exposed lysines and arginines contained
143 within the antibody. The beta emission from Y-90 induces cellular damage by the
144 formation of free radicals in the target and neighboring cells.^[7]

145

146 Normal Human Tissue Cross-Reactivity: Ibritumomab Tiuxetan binding was observed *in*
147 *vitro* on lymphoid cells of the bone marrow, lymph node, thymus, red and white pulp of
148 the spleen, and lymphoid follicles of the tonsil, as well as lymphoid nodules of other
149 organs such as the large and small intestines. Binding was not observed on the
150 nonlymphoid tissues or gonadal tissues (see **CLINICAL PHARMACOLOGY,**
151 **Radiation Dosimetry**).

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153 **Pharmacokinetics / Pharmacodynamics**

154 Pharmacokinetic and biodistribution studies were performed using In-111 ZEVALIN
155 (5 mCi [185 MBq] In-111, 1.6 mg Ibritumomab Tiuxetan). In an early study designed to
156 assess the need for pre-administration of unlabeled antibody, only 18% of known sites of
157 disease were imaged when In-111 ZEVALIN was administered without unlabeled
158 Ibritumomab. When preceded by unlabeled Ibritumomab (1.0 mg/kg or 2.5 mg/kg),

159 In-111 ZEVALIN detected 56% and 92% of known disease sites, respectively. These
160 studies were conducted with a ZEVALIN therapeutic regimen that included unlabeled
161 Ibritumomab.

162

163 In pharmacokinetic studies of patients receiving the ZEVALIN therapeutic regimen, the
164 mean effective half-life for Y-90 activity in blood was 30 hours, and the mean area under
165 the fraction of injected activity (FIA) vs. time curve in blood was 39 hours. Over 7 days,
166 a median of 7.2% of the injected activity was excreted in urine.

167

168 In clinical studies, administration of the ZEVALIN therapeutic regimen resulted in
169 sustained depletion of circulating B cells. At four weeks, the median number of
170 circulating B cells was zero (range, 0-1084 cell/mm³). B-cell recovery began at
171 approximately 12 weeks following treatment, and the median level of B cells was within
172 the normal range (32 to 341 cells/mm³) by 9 months after treatment. Median serum
173 levels of IgG and IgA remained within the normal range throughout the period of B-cell
174 depletion. Median IgM serum levels dropped below normal (median 49 mg/dL, range
175 13-3990 mg/dL) after treatment and recovered to normal values by 6-month post therapy.

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177 **Radiation Dosimetry**

178 Estimations of radiation-absorbed doses for In-111 ZEVALIN and Y-90 ZEVALIN were
179 performed using sequential whole body images and the MIRDOSE 3 software
180 program.^[8, 9] The estimated radiation absorbed doses to organs and marrow from a
181 course of the ZEVALIN therapeutic regimen are summarized in Table 5. Absorbed dose
182 estimates for the lower large intestine, upper large intestine, and small intestine have been
183 modified from the standard MIRDOSE 3 output to account for the assumption that
184 activity is within the intestine wall rather than the intestine contents.

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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 – 20.0	0.9	0.2 - 1.8
Liver ¹	4.8	2.9 - 8.1	0.7	0.4 - 1.1
Lower Large Intestinal Wall ¹	4.7	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	2.9	1.5 - 3.2	0.4	0.2 - 0.5
Lungs ¹	2.0	1.2 - 3.4	0.2	0.2 - 0.4
Testes ¹	1.5	1.0 – 4.3	0.1	0.1 - 0.3
Small Intestine ¹	1.4	0.8 – 2.1	0.2	0.2 - 0.3
Red Marrow ²	1.3	0.6 - 1.8	0.2	0.1 - 0.2
Urinary Bladder Wall ³	0.9	0.7 – 1.3	0.2	0.1 - 0.2
Bone Surfaces ²	0.9	0.5 - 1.2	0.2	0.1 - 0.2
Total Body ³	0.5	0.4 - 0.7	0.1	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
Adrenals ³	0.3	0.2 - 0.5	0.2	0.2 - 0.3
Brain ³	0.3	0.2 - 0.5	0.1	0.0 - 0.1
Breasts ³	0.3	0.2 - 0.5	0.1	0.1 - 0.1
Gallbladder Wall ³	0.3	0.2 - 0.5	0.3	0.2 - 0.4
Muscle ³	0.3	0.2 - 0.5	0.1	0.1 - 0.1
Pancreas ³	0.3	0.2 - 0.5	0.2	0.2 - 0.3
Skin ³	0.3	0.2 - 0.5	0.1	0.0 - 0.1
Stomach ³	0.3	0.2 - 0.5	0.2	0.1 - 0.2
Thymus ³	0.3	0.2 - 0.5	0.1	0.1 - 0.2
Thyroid ³	0.3	0.2 - 0.5	0.1	0.0 - 0.1
Kidneys ¹	0.1	0.0 - 0.3	0.2	0.1 - 0.2

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- 1 Organ region of interest
- 2 Sacrum region of interest ^[10]
- 3 Whole body region of interest

191 **CLINICAL STUDIES**

192 The safety and efficacy of the ZEVALIN therapeutic regimen were evaluated in two
193 multi-center trials enrolling a total of 197 subjects. The ZEVALIN therapeutic regimen
194 was administered in two steps (see DOSAGE AND ADMINISTRATION). The activity
195 and toxicity of a variation of the ZEVALIN therapeutic regimen employing a reduced

196 dose of Y-90 ZEVALIN was further defined in a third study enrolling a total of 30
197 patients who had mild thrombocytopenia (platelet count 100,000 to 149,000 cells/mm³).
198

199 Study 1 was a single arm study of 54 patients with relapsed follicular lymphoma
200 refractory to Rituximab treatment. Patients were considered refractory if their last prior
201 treatment with Rituximab did not result in a complete or partial response, or if time to
202 disease progression (TTP) was < 6 months^[11]. The primary efficacy endpoint of the
203 study was the overall response rate (ORR) using the International Workshop Response
204 Criteria (IWRC).^[12] Secondary efficacy endpoints included time to disease progression
205 (TTP) and duration of response (DR). In a secondary analysis comparing objective
206 response to the ZEVALIN therapeutic regimen with that observed with the most recent
207 treatment with Rituximab, the median duration of response following the ZEVALIN
208 therapeutic regimen was 6 vs. 4 months. Table 6 summarizes efficacy data from this
209 study.

210

211 Study 2 was a randomized, controlled, multicenter study comparing the ZEVALIN
212 therapeutic regimen to treatment with Rituximab. The trial was conducted in 143 patients
213 with relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma (NHL), or
214 transformed B-cell NHL. A total of 73 patients received the ZEVALIN therapeutic
215 regimen, and 70 patients received Rituximab given as an IV infusion at 375 mg/m²
216 weekly times 4 doses. The primary efficacy endpoint of the study was to determine the
217 ORR using the IWRC^[12] (see Table 6). The ORR was significantly higher (80% vs. 56%,
218 $p = 0.002$)^[13] for patients treated with the ZEVALIN therapeutic regimen. The secondary
219 endpoints, duration of response and time to progression, were not significantly different
220 between the two treatment arms.

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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 ² (%)	15	34	20
Median DR ^{3,4} (Months) [Range ³]	6.4 [0.5-49.9+]	13.9 [1.0-47.6+]	11.8 [1.2-49.7+]
Median TTP ^{3,6} (Months) [Range ³]	6.8 [1.1-50.9+]	10.6 [0.8-49.0+]	10.1 [0.7-51.3+]

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¹IWRC: International Workshop response criteria

²CRu and CR: Unconfirmed and confirm complete response

³Estimated with observed range

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

⁵“+” indicates an ongoing response

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

231 Study 3 was a single arm study of 30 patients with relapsed or refractory low-grade,
232 follicular, or transformed B-cell NHL who had mild thrombocytopenia (platelet count
233 100,000 to 149,000 cells/mm³). Excluded from the study were patients with ≥ 25%
234 lymphoma marrow involvement and/or impaired bone marrow reserve. Patients were
235 considered to have impaired bone marrow reserve if they had any of the following: prior
236 myeloablative therapy with stem cell support; prior external beam radiation to > 25% of
237 active marrow; a platelet count <100,000 cells/mm³; or neutrophil count <1,500
238 cells/mm³. In this study, a modification of the ZEVALIN therapeutic regimen with a
239 lower Y-90 ZEVALIN dose [(Y-90 ZEVALIN at 0.3 mCi/kg (11.1 MBq/kg)] was used.
240 Objective, durable clinical responses were observed [83% ORR (95% CI: 65-94%)^[14],
241 11.5 months median DR (range: 1-42.4+ months)] and resulted in a greater incidence of
242 hematologic toxicity (see ADVERSE REACTIONS) than in Studies 1 and 2.

243

244 **INDICATIONS AND USAGE**

245 ZEVALIN, as part of the ZEVALIN therapeutic regimen (see DOSAGE AND
246 ADMINISTRATION), is indicated for the treatment of patients with relapsed or
247 refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma,
248 including patients with Rituximab refractory follicular non-Hodgkin's lymphoma.

249 Determination of the effectiveness of the ZEVALIN therapeutic regimen in a relapsed or
250 refractory patient population is based on overall response rates (see CLINICAL
251 STUDIES). The effects of the ZEVALIN therapeutic regimen on survival are not known.
252

253 **CONTRAINDICATIONS**

254 The ZEVALIN therapeutic regimen is contraindicated in patients with known Type I
255 hypersensitivity or anaphylactic reactions to murine proteins or to any component of this
256 product, including Rituximab, yttrium chloride, and indium chloride.
257

258 **WARNINGS (See BOXED WARNING)**

259 **Altered Biodistribution:** Y-90 ZEVALIN should not be administered to patients with
260 altered biodistribution of In-111 ZEVALIN. In a post-marketing registry designed to
261 collect biodistribution images and other information in reported cases of altered
262 biodistribution, there were 12 (1.3%) patients reported to have altered biodistribution
263 among 953 patients registered. For descriptions of expected and altered biodistribution
264 image characteristics, see DOSAGE AND ADMINISTRATION, IMAGE
265 ACQUISITION AND INTERPRETATION.
266

267 **Severe Infusion Reactions (See PRECAUTIONS, Hypersensitivity):** The ZEVALIN
268 therapeutic regimen may cause severe, and potentially fatal, infusion reactions. These
269 severe reactions typically occur during the first Rituximab infusion with time to onset of
270 30 to 120 minutes. Signs and symptoms of severe infusion reaction may include
271 hypotension, angioedema, hypoxia, or bronchospasm, and may require interruption of
272 Rituximab, In-111 ZEVALIN, or Y-90 ZEVALIN administration. The most severe
273 manifestations and sequelae may include pulmonary infiltrates, acute respiratory distress
274 syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock.

275 **Because the ZEVALIN therapeutic regimen includes the use of Rituximab, see also**
276 **prescribing information for RITUXAN (Rituximab).**
277

278 **Cytopenias (See ADVERSE REACTIONS, Hematologic Events):**

279 The most common severe adverse events reported with the ZEVALIN therapeutic
280 regimen were thrombocytopenia (61% of patients with platelet counts <50,000
281 cells/mm³) and neutropenia (57% of patients with absolute neutrophil count (ANC)
282 <1,000 cells/mm³) in patients with $\geq 150,000$ platelets/mm³ prior to treatment. Both
283 incidences of severe thrombocytopenia and neutropenia increased to 78% and 74% for
284 patients with mild thrombocytopenia at baseline (platelet count of 100,000 to 149,000
285 cells/mm³). For all patients, the median time to nadir was 7-9 weeks and the median
286 duration of cytopenias was 22-35 days. In <5% of cases, patients experienced severe
287 cytopenia that extended beyond the prospectively defined protocol treatment period of 12
288 weeks following administration of the ZEVALIN therapeutic regimen. Some of these
289 patients eventually recovered from cytopenia, while others experienced progressive
290 disease, received further anti-cancer therapy, or died of their lymphoma without having
291 recovered from cytopenia. The cytopenias may have influenced subsequent treatment
292 decisions.

293

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

301

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

307

308 **Severe Cutaneous and Mucocutaneous Reactions (See BOXED WARNINGS and**
309 **ADVERSE REACTIONS):** There have been postmarketing reports of erythema
310 multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous dermatitis,
311 and exfoliative dermatitis in patients who received the ZEVALIN therapeutic regimen.
312 ~~Some of these events were fatal. The onset of the reactions was variable; in some cases,~~
313 acute, (days) and in others, delayed (3-4 months). Patients experiencing a severe
314 cutaneous or mucocutaneous reaction should not receive any further components of the
315 ZEVALIN therapeutic regimen and should seek prompt medical evaluation.

316

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

321

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

327

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

333

334 **PRECAUTIONS**

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

339

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

344

345 **Hypersensitivity:** Anaphylactic and other hypersensitivity reactions have been reported
346 following the intravenous administration of proteins to patients. Medications for the
347 treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines and
348 corticosteroids, should be available for immediate use in the event of an allergic reaction
349 during administration of ZEVALIN. Patients who have received murine proteins should
350 be screened for human anti-mouse antibodies (HAMA). Patients with evidence of
351 HAMA have not been studied and may be at increased risk of allergic or serious
352 hypersensitivity reactions during ZEVALIN therapeutic regimen administrations.

353

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

358

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

363

364 **Drug Interactions:** No formal drug interaction studies have been performed with
365 ZEVALIN. Due to the frequent occurrence of severe and prolonged thrombocytopenia,
366 the potential benefits of medications which interfere with platelet function and/or
367 anticoagulation should be weighed against the potential increased risks of bleeding and
368 hemorrhage. Patients receiving medications that interfere with platelet function or
369 coagulation should have more frequent laboratory monitoring for thrombocytopenia. In

370 addition, the transfusion practices for such patients may need to be modified given the
371 increased risk of bleeding.

372

373 Patients in clinical studies were prohibited from receiving growth factor treatment for 2
374 weeks prior to the ZEVALIN therapeutic regimen as well as for 2 weeks following
375 completion of the regimen.

376

377 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No long-term animal studies
378 have been performed to establish the carcinogenic or mutagenic potential of the
379 ZEVALIN therapeutic regimen, or to determine its effects on fertility in males or
380 females. However, radiation is a potential carcinogen and mutagen. The ZEVALIN
381 therapeutic regimen results in a significant radiation dose to the testes. The radiation
382 dose to the ovaries has not been established. There have been no studies to evaluate
383 whether the ZEVALIN therapeutic regimen causes hypogonadism, premature
384 menopause, azoospermia and/or mutagenic alterations to germ cells. There is a potential
385 risk that the ZEVALIN therapeutic regimen could cause toxic effects on the male and
386 female gonads. Effective contraceptive methods should be used during treatment and for
387 up to 12 months following the ZEVALIN therapeutic regimen.

388

389 **Pregnancy Category D: See WARNINGS.**

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391 **Nursing Mothers:** It is not known whether ZEVALIN is excreted in human milk.
392 Because human IgG is excreted in human milk and the potential for ZEVALIN exposure
393 in the infant is unknown, women should be advised to discontinue nursing and formula
394 feeding should be substituted for breast feedings (see CLINICAL PHARMACOLOGY).

395

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

401

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

404

405 **ADVERSE REACTIONS**

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

410

411 The most serious adverse reactions caused by the ZEVALIN therapeutic regimen include
412 prolonged and severe cytopenias, infections (predominantly bacterial in origin),
413 hemorrhage while thrombocytopenic (resulting in deaths), and allergic reactions
414 (bronchospasm and angioedema). In addition, patients who have received the ZEVALIN
415 therapeutic regimen have developed myeloid malignancies and dysplasias. Fatal infusion
416 reactions have occurred following the infusion of Rituximab.

417

418 In postmarketing reports, cutaneous and mucocutaneous reactions have been associated
419 with the ZEVALIN therapeutic regimen. Please refer to the BOXED WARNINGS and
420 WARNINGS sections for detailed descriptions of these reactions.

421

422 The most common toxicities reported were neutropenia, thrombocytopenia, anemia,
423 gastrointestinal symptoms (nausea, vomiting, abdominal pain, and diarrhea), increased
424 cough, dyspnea, dizziness, arthralgia, anorexia, anxiety, and ecchymosis. Hematologic
425 toxicity was often severe and prolonged, whereas most non-hematologic toxicity was
426 mild in severity. Table 7 lists adverse events that occurred in $\geq 5\%$ of patients. A more
427 detailed description of the incidence and duration of hematologic toxicities, according to
428 baseline platelet count (as an indicator of bone marrow reserve) is provided in Table 8,
429 Hematologic Toxicity.

430
431
432
433

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

434
435
436

[†] 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

437 The following adverse events (except for those noted in Table 7) occurred in between 1
438 and 4% of patients during the treatment period: urticaria (4%), anxiety (4%), dyspepsia
439 (4%), sweats (4%), petechia (3%), epistaxis (3%), allergic reaction (2%), and melena
440 (2%).

441

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

448

449 **Hematologic Events:** Hematologic toxicity was the most frequently observed adverse
450 event in clinical trials. Table 8 presents the incidence and duration of severe hematologic
451 toxicity for patients with normal baseline platelet count ($\geq 150,000$ cells/mm³) treated
452 with the ZEVALIN therapeutic regimen and patients with mild thrombocytopenia
453 (platelet count 100,000 to 149,000 cells/mm³) at baseline who were treated with a
454 modified ZEVALIN therapeutic regimen that included a lower Y-90 ZEVALIN dose at
455 0.3 mCi/kg (11.1 MBq/kg).

456

457
458
459
460

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

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

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

467

468 Median time to ANC nadir was 62 days, to platelet nadir was 53 days, and to hemoglobin
469 nadir was 68 days. Information on growth factor use and platelet transfusions is based on
470 211 patients for whom data were collected. Filgrastim was given to 13% of patients and
471 erythropoietin to 8%. Platelet transfusions were given to 22% of patients and red blood
472 cell transfusions to 20%.

473

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

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

486
487 **Secondary Malignancies:** A total of 2% of patients developed secondary malignancies
488 following the ZEVALIN therapeutic regimen. One patient developed a Grade 1
489 meningioma, three developed acute myelogenous leukemia, and two developed a
490 myelodysplastic syndrome. The onset of a second cancer was 8-34 months following the
491 ZEVALIN therapeutic regimen and 4 to 14 years following the patients' diagnosis of
492 NHL.

493
494 **Immunogenicity:** Of 211 patients who received the ZEVALIN therapeutic regimen in
495 clinical trials and who were followed for 90 days, there were eight (3.8%) patients with
496 evidence of human anti-mouse antibody (HAMA) (n=5) or human anti-chimeric antibody
497 (HACA) (n=4) at any time during the course of the study. Two patients had low titers of
498 HAMA prior to initiation of the ZEVALIN therapeutic regimen; one remained positive
499 without an increase in titer while the other had a negative titer post-treatment. Three
500 patients had evidence of HACA responses prior to initiation of the ZEVALIN therapeutic
501 regimen; one had a marked increase in HACA titer while the other two had negative titers
502 post-treatment. Of the three patients who had negative HAMA or HACA titers prior to
503 the ZEVALIN therapeutic regimen, two developed HAMA in absence of HACA titers,
504 and one had both HAMA and HACA positive titers post-treatment. Evidence of
505 immunogenicity may be masked in patients who are lymphopenic. There has not been
506 adequate evaluation of HAMA and HACA at delayed timepoints, concurrent with the
507 recovery from lymphopenia at 6-12 months, to establish whether masking of the
508 immunogenicity at early timepoints occurs. The data reflect the percentage of patients

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

516

517 **OVERDOSAGE**

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

525

526 **DOSAGE AND ADMINISTRATION**

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

533

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

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

541

542 **ZEVALIN Therapeutic Regimen Dose Modification in Patients with Mild**
543 **Thrombocytopenia:** The Y-90 ZEVALIN dose should be reduced to 0.3 mCi/kg (11.1
544 MBq/kg) for patients with a baseline platelet count between 100,000 and 149,000
545 cells/mm³.

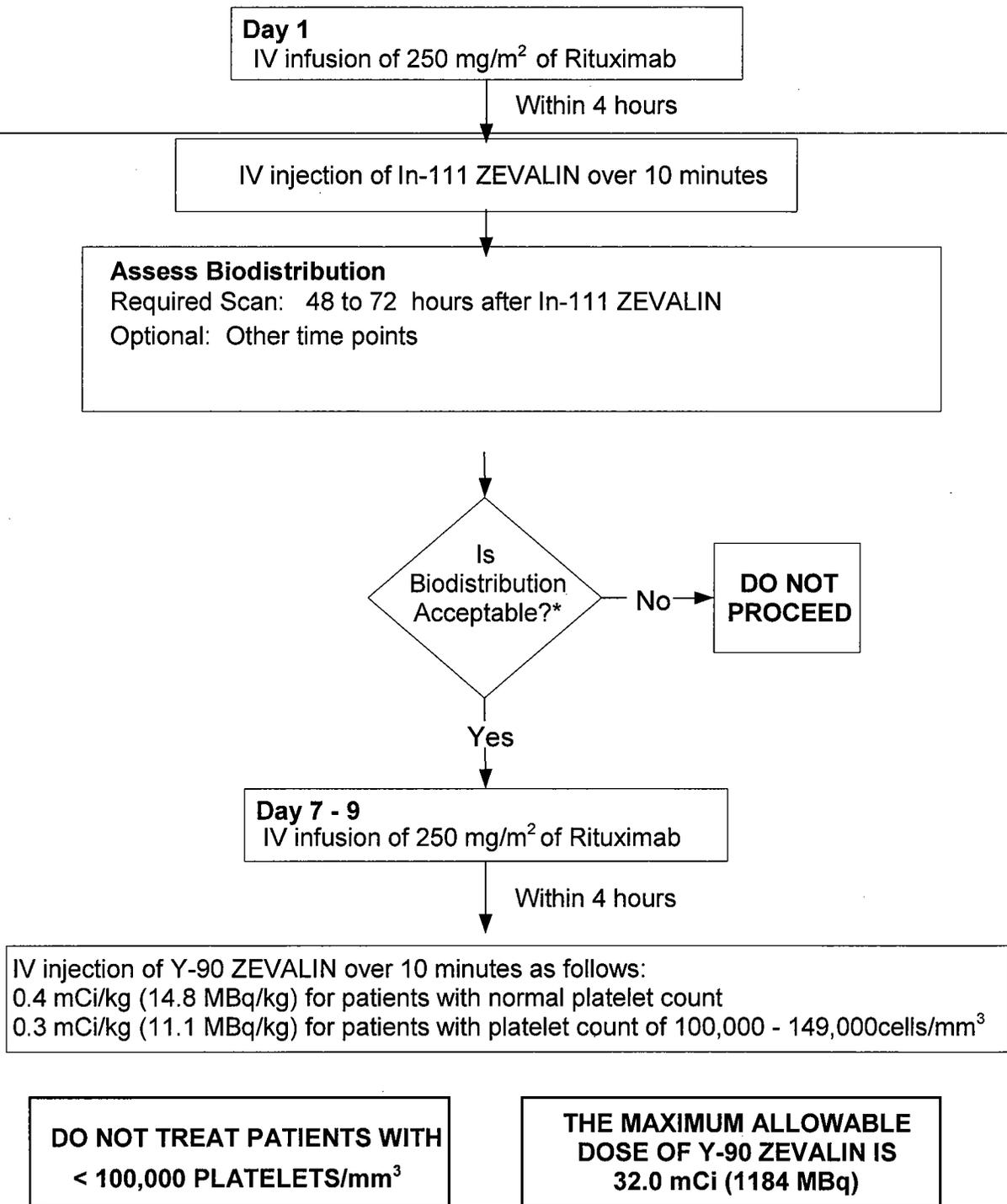
546

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

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

554

555 **Overview of Dosing Schedule:**



*See IMAGE ACQUISITION AND INTERPRETATION

557 **ZEVALIN Therapeutic Regimen Administration**

558 Step 1:

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

566

567 In-111 ZEVALIN Injection: Within 4 hours following completion of the Rituximab
568 dose, 5.0 mCi (1.6 mg total antibody dose) of In-111 ZEVALIN is injected intravenously
569 (I.V.) over a period of 10 minutes. A 0.22 micrometer low-protein-binding filter should
570 be in-line between the syringe and the infusion port prior to injection of In-111
571 ZEVALIN. After injection, the line should be flushed with at least 10 mL of normal
572 saline.

573

574 Step 2:

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

577

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

582

583 Y-90 ZEVALIN Injection:

584 Within 4 hours following completion of the Rituximab dose, Y-90 ZEVALIN at a dose of
585 0.4 mCi/kg (14.8 MBq/kg) actual body weight for patients with a platelet count $\geq 150,000$
586 cells/mm³, and 0.3 mCi/kg (11.1 MBq/kg) actual body weight for patients with a platelet
587 count of 100,000-149,000 cells/mm³ is injected intravenously (I.V.) over a period of 10

588 minutes. A 0.22 micrometer low-protein-binding filter should be in-line between the
589 syringe and the infusion port prior to injection of Y-90 ZEVALIN. After injection, the
590 line should be flushed with at least 10 mL of normal saline. Precautions should be taken
591 to avoid extravasation. A free flowing I.V. line should be established prior to Y-90
592 ZEVALIN injection. Close monitoring for evidence of extravasation during the injection
593 of Y-90 ZEVALIN is required. If any signs or symptoms of extravasation have occurred,
594 the infusion should be immediately terminated and restarted in another vein. **The**
595 **prescribed, measured, and administered dose of Y-90 ZEVALIN must not exceed**
596 **the absolute maximum allowable dose of 32.0 mCi (1184 MBq), regardless of the**
597 **patient's body weight. Do not give Y-90 ZEVALIN to patients with a platelet count**
598 **<100,000/mm³ (see WARNINGS).**

599

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

601

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

603

604 **GENERAL:**

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

608

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

613

614 Proper aseptic technique and precautions for handling radioactive materials should be
615 employed. Waterproof gloves should be utilized in the preparation and during the
616 determination of radiochemical purity of In-111 ZEVALIN. Appropriate shielding
617 should be used during radiolabeling, and use of a syringe shield is recommended during

618 administration to the patient. The radiolabeling of ZEVALIN shall be done according to
619 the following directions.

620

621 Required materials not supplied in the kit:

622

623 A. Indium-111 Chloride Sterile Solution (In-111 Chloride) from GE Healthcare,
624 or Mallinckrodt, Inc.

625 B. Three sterile 1 mL plastic syringes

626 C. One sterile 3 mL plastic syringe

627 D. Two sterile 10 mL plastic syringes with 18-20 G needles

628 E. Instant thin-layer chromatographic silica gel strips

629 F. 0.9% sodium chloride aqueous solution for the chromatography solvent

630 G. Developing chamber for chromatography

631 H. Suitable radioactivity counting apparatus

632 I. Filter, 0.22 micrometer, low-protein-binding (see DOSAGE AND
633 ADMINISTRATION, Zevalin Therapeutic Regimen Administration)

634 J. Vial and syringe shield

635

636 Method:

637

638 1. Sterile, pyrogen-free In-111 chloride must be used for the preparation of
639 In-111 ZEVALIN. The use of high purity In-111 chloride manufactured by GE
640 Healthcare, or Mallinckrodt, Inc. is required.

641

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

646

647 3. Clean the rubber stoppers of all of the vials in the kit and the In-111 chloride vial
648 with a suitable alcohol swab and allow to air dry.

649

650 4. Place the empty Reaction Vial in a suitable dispensing shield (pre-warmed to
651 room temperature). To avoid the buildup of excessive pressure during the
652 procedure, use a 10 mL syringe to withdraw 10 mL of air from the Reaction Vial.

653

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

656

657 a. Calculate the volume of In-111 chloride that is equivalent to 5.5 mCi
658 based on the activity concentration of the In-111 chloride stock.

659

660 b. The volume of 50 mM sodium acetate solution needed is 1.2 times the
661 volume of In-111 chloride solution determined in step 5.a., above. (The
662 50 mM sodium acetate is used to adjust the pH for the radiolabeling
663 reaction.)

664

665 c. Calculate the volume of Formulation Buffer needed to bring the Reaction
666 Vial contents to a final volume of 10 mL. This is the volume of
667 Formulation Buffer needed to protect the labeled product from radiolysis
668 and to terminate the labeling reaction. For example, if volumes of 0.5 mL
669 of In-111 chloride, 0.6 mL of sodium acetate and 1.0 mL of ZEVALIN
670 were used, then the amount of formulation buffer would be $10 - (0.5 + 0.6$
671 $+ 1.0) = 7.9$ mL.

672

673 6. With a sterile 1 mL syringe, transfer the calculated volume of 50 mM of sodium
674 acetate to the empty Reaction Vial. Coat the entire inner surface of the Reaction
675 Vial by gentle inversion or rolling.

676

677 7. Transfer 5.5 mCi of In-111 chloride to the Reaction Vial with a sterile 1 mL
678 syringe. Mix the two solutions and coat the entire inner surface of the Reaction
679 Vial by gentle inversion or rolling.

680

681 8. With a sterile 3 mL syringe, transfer 1.0 mL of ZEVALIN (Ibritumomab
682 Tiuxetan) to the Reaction Vial. Coat the entire surface of the Reaction Vial by
683 gentle inversion or rolling. **Do not shake or agitate the vial contents, since this**
684 **will cause foaming and denaturation of the protein.**

685

686 9. Allow the labeling reaction to proceed at room temperature for 30 minutes.
687 Allowing the labeling reaction to proceed for a longer or shorter time may result
688 in inadequate labeling.

689

690 10. **Immediately** after the 30-minute incubation period, using a sterile 10 mL syringe
691 with a large bore needle (18 G - 20 G), transfer the calculated volume of
692 Formulation Buffer from step 5.c. to the Reaction Vial. Gently add the
693 Formulation Buffer down the side of the Reaction Vial. If necessary, to
694 normalize air pressure, withdraw an equal volume of air. Coat the entire inner
695 surface of the Reaction Vial by gentle inversion or rolling. Do not shake or
696 agitate the vial contents. Avoid foaming.

697

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

701

702 12. Calculate the volume required for an In-111 ZEVALIN dose of 5 mCi. Withdraw
703 the required volume from the Reaction Vial contents into a sterile 10 mL syringe
704 with a large bore needle (18 G - 20 G). Assay the syringe and contents in a dose
705 calibrator. The syringe should contain the dose of In-111 ZEVALIN to be
706 administered to the patient. Using the supplied labels, record the patient
707 identification, the date and time of preparation, the total activity and volume
708 added, and the date and time of expiration, and affix these labels to the syringe
709 and shielded unit dose container.

710

711 13. Determine Radiochemical purity. See Section C: Procedure for Determining
712 Radiochemical Purity Section that follows DIRECTIONS FOR PREPARATION
713 OF THE Y-90 ZEVALIN DOSE.

714

715 14. Store Indium-111 ZEVALIN at 2-8°C (36-46°F) until use and administer within
716 12 hours of radiolabeling.

717

718 15. See DOSAGE AND ADMINISTRATION: ZEVALIN Therapeutic Regimen
719 Administration: Step 1

720

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

723

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

725

726 **GENERAL:**

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

730

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

735

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

742 Required materials not supplied in the kit:

743

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

746 B. Three sterile 1 mL plastic syringes

747 C. One sterile 3 mL plastic syringe

748 D. Two sterile 10 mL plastic syringes with 18-20 G needles

749 E. Instant thin-layer chromatographic silica gel strips (ITLC-SG)

750 F. 0.9% sodium chloride aqueous solution for the chromatography solvent

751 G. Suitable radioactivity counting apparatus

752 H. Developing chamber for chromatography

753 I. Filter, 0.22 micrometer, low-protein-binding (see DOSAGE AND
754 ADMINISTRATION, ZEVALIN Therapeutic Regimen Administration)

755 J. Vial and syringe shield

756

757 Method:

758

759 1. Sterile, pyrogen-free Y-90 chloride must be used for the preparation of Y-90
760 ZEVALIN. The use of high purity Y-90 chloride manufactured by MDS Nordion
761 is required.

762

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

767

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

770

- 771 4. Place the empty Reaction Vial in a suitable dispensing shield (pre-warmed to
772 room temperature). To avoid the buildup of excessive pressure during the
773 procedure, use a 10 mL syringe to withdraw 10 mL of air from the Reaction Vial.
774
-
- 775 5. Prior to initiating the radiolabeling reaction, determine the amount of each
776 component needed according to the directions below:
777
- 778 a. Calculate the volume of Y-90 chloride that is equivalent to 40 mCi based
779 on the activity concentration of the Y-90 chloride stock.
780
 - 781 b. The volume of 50 mM sodium acetate solution needed is 1.2 times the
782 volume of Y-90 chloride solution determined in step 5.a., above. (The
783 50 mM sodium acetate is used to adjust the pH for the radiolabeling
784 reaction.)
785
 - 786 c. Calculate the volume of Formulation Buffer needed to bring the Reaction
787 Vial contents to a final volume of 10 mL. This is the volume of
788 Formulation Buffer needed to protect the labeled product from radiolysis
789 and to terminate the labeling reaction. For example if the volumes were
790 0.5 mL of Y-90 chloride, 0.6 mL of sodium acetate and 1.3 mL of
791 ZEVALIN, then the amount of formulation buffer would be
792 $10 - (0.5 + 0.6 + 1.3) = 7.6$ mL.
793
- 794 6. With a sterile 1 mL syringe, transfer the calculated volume of 50 mM sodium
795 acetate to the empty Reaction Vial. Coat the entire inner surface of the Reaction
796 Vial by gentle inversion or rolling.
797
- 798 7. Transfer 40 mCi of Y-90 chloride to the Reaction Vial with a sterile 1 mL
799 syringe. Mix the two solutions and coat the entire inner surface of the Reaction
800 Vial by gentle inversion or rolling.
801

802 8. With a sterile 3 mL syringe, transfer 1.3 mL of ZEVALIN (Ibritumomab
803 Tiuxetan) to the Reaction Vial. Coat the entire surface of the Reaction Vial by
804 gentle inversion or rolling. **Do not shake or agitate the vial contents, since this**
805 **will cause foaming and denaturation of the protein.**
806

807 9. Allow the labeling reaction to proceed at room temperature for 5 minutes.
808 Allowing the labeling reaction to proceed for a longer or shorter time may result
809 in inadequate labeling.
810

811 10. **Immediately** after the 5-minute incubation period, using a sterile 10 mL syringe
812 with a large bore needle (18 G - 20 G), transfer the calculated volume of
813 Formulation Buffer from step 5.c. to the Reaction Vial, terminating incubation.
814 Gently add the Formulation Buffer down the side of the Reaction Vial. If
815 necessary to normalize air pressure, withdraw an equal volume of air. Coat the
816 entire inner surface of the Reaction Vial by gentle inversion or rolling. Do not
817 shake or agitate the vial contents. Avoid foaming.
818

819 11. Using the supplied labels, record the patient identification, the date and time of
820 preparation, the total activity and volume, and the date and time of expiration and
821 affix these labels to the reaction vial and shielded reaction vial container.
822

823 12. Calculate the volume required for a Y-90 ZEVALIN dose of 0.4 mCi/kg
824 (14.8 MBq/kg) actual body weight for patients with normal platelet count, and
825 0.3 mCi/kg (11.1 MBq/kg) actual body weight for patients with platelet count of
826 100,000 - 149,000 cells/mm³. **The prescribed, measured, and administered**
827 **dose of Y-90 ZEVALIN must not exceed the absolute maximum allowable**
828 **dose of 32.0 mCi (1184 MBq), regardless of the patient's body weight.**
829 Withdraw the required volume from the Reaction Vial contents into a sterile
830 10 mL syringe with a large bore needle (18 G - 20 G). Assay the syringe and
831 contents in a dose calibrator. The dose calibrator must be operated in accordance
832 with the manufacturer's specifications and quality control for the measurement of

833 Y-90. The syringe should contain the dose of Y-90 ZEVALIN to be administered
834 to the patient, and should be within 10% of the actual prescribed dose of Y-90
835 ZEVALIN, not to exceed a maximum dose of 32.0 mCi. Do not exceed $\pm 10\%$ of
836 the prescribed dose. Using the supplied labels, record the patient identification,
837 the date and time of preparation, the total activity and volume added, and the date
838 and time of expiration and affix these labels to the syringe and shielded unit dose
839 container.

840

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

844

845 14. Store Yttrium-90 ZEVALIN at 2-8°C (36-46°F) until use and administer within 8
846 hours of radiolabeling.

847

848 15. See DOSAGE AND ADMINISTRATION: ZEVALIN Therapeutic Regimen
849 Administration: Step 2.

850

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

853

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

857

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

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

860 **Y-90 ZEVALIN:**

861

862 A. At room temperature, place a small drop of either In-111 ZEVALIN or
863 Y-90 ZEVALIN at the origin of an ITLC-SG strip.

864

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

870

871 C. Calculate the percent RCP as follows:

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

872

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

876

877 **IMAGE ACQUISITION AND INTERPRETATION**

878 The biodistribution of In-111 ZEVALIN should be assessed by a visual evaluation of
879 whole body planar view anterior and posterior gamma images. A set of images at 48 - 72
880 hours after injection is required. To resolve ambiguities, optional images at other
881 timepoints may be necessary. Images should be acquired using a large field of view
882 gamma camera equipped with a medium energy collimator. Whole body
883 anterior/posterior planar images should be acquired using a large field-of-view gamma
884 camera and medium energy collimators. Suggested gamma camera settings: 256 x 1024
885 matrix; dual energy photopeaks set at 172 and 247 keV; 15% symmetric window; scan
886 speed of 10 cm/min for the 48-72 hour scan, and 7-10 cm/min for subsequent scans.

887 **EXPECTED BIODISTRIBUTION**

888 Visual inspection of the required gamma images of expected biodistribution reveal the
889 following:

890

- 891 • Activity in the blood pool areas (heart, abdomen, neck, and extremities) may be
892 faintly visible.
- 893 • Moderately high to high uptake in normal liver and spleen.

- 894 • Moderately low or very low uptake in normal kidneys, urinary bladder, and
895 normal (uninvolved) bowel.
- 896 • Non-fixed areas within the bowel lumen that change position with time; delayed
897 imaging as described above may be necessary to confirm gastrointestinal
898 clearance.
-

- 899 • Focal fixed areas of uptake in the bowel wall (localization to lymphoid
900 aggregates in bowel wall).

901

902 Tumor uptake may be visualized in soft tissue as areas of increased intensity, and tumor-
903 bearing areas in normal organs may be seen as areas of increased or decreased intensity.

904 Tumor visualization on the In-111 Zevalin scan is not required for Y-90 Zevalin therapy.
905

906 **ALTERED BIODISTRIBUTION**

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

909

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

920

921 If a visual inspection of the gamma images reveals an altered biodistribution, the patient
922 should not proceed to the Y-90 ZEVALIN dose. The safety and efficacy of the
923 administration of Y-90 ZEVALIN in patients with prominent marrow uptake is not
924 known. Possible causes of prominent bone marrow uptake, such as bone marrow

925 involvement by lymphoma, increased marrow activity due to recent hematopoietic
926 growth factor administration, and increased reticuloendothelial uptake in patients with
927 HAMA and HACA, should be considered. Re-assessment of biodistribution after
928 correction of underlying factors should be performed. Y-90 ZEVALIN should not be
929 administered to patients with persistently prominent marrow uptake on the repeat
930 biodistribution scans.

931
932 During ZEVALIN clinical development, individual tumor radiation absorbed dose
933 estimates as high as 778 cGy/mCi have been reported. Although solid organ toxicity has
934 not been directly attributed to radiation from adjacent tumors, careful consideration
935 should be applied before proceeding with treatment in patients with very high tumor
936 uptake next to critical organs or structures.

937

938 **HOW SUPPLIED**

939 The In-111 ZEVALIN kit provides for the radiolabeling of Ibritumomab Tiuxetan with
940 In-111. The Y-90 ZEVALIN kit provides for the radiolabeling of Ibritumomab Tiuxetan
941 with Y-90.

942

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

947

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

952

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

954

955 The Indium-111 Chloride Sterile Solution (In-111 Chloride) must be ordered separately
956 from either GE Healthcare, or Mallinckrodt, Inc. at the time the In-111 ZEVALIN kit is
957 ordered. The Yttrium-90 Chloride Sterile Solution will be shipped directly from MDS
958 Nordion upon placement of an order for the Y-90 ZEVALIN kit.
959

960 **Storage**

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

962

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1013 Rx Only
1014 In-111 ZEVALIN kit, NDC 64406-104-04
1015 Y-90 ZEVALIN kit, NDC 64406-103-03
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