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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

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 **Dosing**

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- 28 • The prescribed, measured, and administered dose of Y-90 ZEVALIN should not  
exceed the absolute maximum allowable dose of 32.0 mCi (1184 MBq).
  - 29 • Y-90 ZEVALIN should not be administered to patients with altered  
30 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 IgG<sub>1</sub> 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

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

63

64 **ZEVALIN Kits**

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

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- 68 (1) One (1) ZEVALIN vial containing 3.2 mg of Ibritumomab Tiuxetan in 2 mL of  
69 0.9% sodium chloride solution; a sterile, pyrogen-free, clear, colorless solution  
70 that may contain translucent particles; no preservative present.
- 71 (2) One (1) 50 mM Sodium Acetate Vial containing 13.6 mg of sodium acetate  
72 trihydrate in 2 mL of Water for Injection; a sterile, pyrogen-free, clear, colorless  
73 solution; no preservative present.
- 74 (3) One (1) Formulation Buffer Vial containing 750 mg of Albumin (Human), 76 mg  
75 of sodium chloride, 21 mg of sodium phosphate dibasic heptahydrate, 4 mg of  
76 pentetic acid, 2 mg of potassium phosphate monobasic and 2 mg of potassium  
77 chloride in 10 mL of Water for Injection adjusted to pH 7.1 with either sodium  
78 hydroxide or hydrochloric acid; a sterile, pyrogen-free, clear yellow to amber  
79 colored solution; no preservative present.
- 80 (4) One (1) empty Reaction Vial, sterile, pyrogen-free.

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

83 Indium-111 decays by electron capture, with a physical half-life of 67.3 hours  
84 (2.81 days).<sup>[1]</sup> The product of radioactive decay is nonradioactive cadmium-111.

85 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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90 **External Radiation**

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

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95 To allow correction for physical decay of In-111, the fractions that remain at selected  
96 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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102 **Physical/Radiochemical Characteristics of Y-90**

103 Yttrium-90 decays by emission of beta particles, with a physical half-life of 64.1 hours  
104 (2.67 days).<sup>[1]</sup> The product of radioactive decay is non-radioactive  
105 zirconium-90. The range of beta particles in soft tissue ( $\chi_{90}$ ) is 5 mm. Radiation  
106 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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111 **External Radiation**

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

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116 To allow correction for physical decay of Y-90, the fractions that remain at selected  
117 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

122

123 **CLINICAL PHARMACOLOGY**

124 **General Pharmacology**

125 Ibritumomab Tiuxetan binds specifically to the CD20 antigen (human  
126 B-lymphocyte-restricted differentiation antigen, Bp35).<sup>[2, 3]</sup> The apparent affinity ( $K_D$ ) of  
127 Ibritumomab Tiuxetan for the CD20 antigen ranges between approximately 14 to 18 nM.  
128 The CD20 antigen is expressed on pre-B and mature B lymphocytes and on > 90% of  
129 B-cell non-Hodgkin's lymphomas (NHL).<sup>[4, 5]</sup> The CD20 antigen is not shed from the  
130 cell surface and does not internalize upon antibody binding.<sup>[6]</sup>

131

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

138

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

145

#### 146 **Pharmacokinetics / Pharmacodynamics**

147 Pharmacokinetic and biodistribution studies were performed using In-111 ZEVALIN  
148 (5 mCi [185 MBq] In-111, 1.6 mg Ibritumomab Tiuxetan). In an early study designed to  
149 assess the need for pre-administration of unlabeled antibody, only 18% of known sites of  
150 disease were imaged when In-111 ZEVALIN was administered without unlabeled  
151 Ibritumomab. When preceded by unlabeled Ibritumomab (1.0 mg/kg or 2.5 mg/kg),  
152 In-111 ZEVALIN detected 56% and 92% of known disease sites, respectively. These  
153 studies were conducted with a ZEVALIN therapeutic regimen that included unlabeled  
154 Ibritumomab.

155

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

160

161 In clinical studies, administration of the ZEVALIN therapeutic regimen resulted in  
162 sustained depletion of circulating B cells. At four weeks, the median number of  
163 circulating B cells was zero (range, 0-1084 cell/mm<sup>3</sup>). B-cell recovery began at  
164 approximately 12 weeks following treatment, and the median level of B cells was within  
165 the normal range (32 to 341 cells/mm<sup>3</sup>) by 9 months after treatment. Median serum  
166 levels of IgG and IgA remained within the normal range throughout the period of B-cell  
167 depletion. Median IgM serum levels dropped below normal (median 49 mg/dL, range  
168 13-3990 mg/dL) after treatment and recovered to normal values by 6-month post therapy.

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#### 170 **Radiation Dosimetry**

171 Estimations of radiation-absorbed doses for In-111 ZEVALIN and Y-90 ZEVALIN were  
172 performed using sequential whole body images and the MIRDOSE 3 software  
173 program.<sup>[8, 9]</sup> The estimated radiation absorbed doses to organs and marrow from a  
174 course of the ZEVALIN therapeutic regimen are summarized in Table 5. Absorbed dose  
175 estimates for the lower large intestine, upper large intestine, and small intestine have been  
176 modified from the standard MIRDOSE 3 output to account for the assumption that  
177 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 <sup>1</sup>	9.4	1.8 - 20.0	0.9	0.2 - 1.8
Liver <sup>1</sup>	4.8	2.9 - 8.1	0.7	0.4 - 1.1
Lower Large Intestinal Wall <sup>1</sup>	4.7	3.1 - 8.2	0.4	0.2 - 0.6
Upper Large Intestinal Wall <sup>1</sup>	3.6	2.0 - 6.7	0.3	0.2 - 0.6
Heart Wall <sup>1</sup>	2.9	1.5 - 3.2	0.4	0.2 - 0.5
Lungs <sup>1</sup>	2.0	1.2 - 3.4	0.2	0.2 - 0.4
Testes <sup>1</sup>	1.5	1.0 - 4.3	0.1	0.1 - 0.3
Small Intestine <sup>1</sup>	1.4	0.8 - 2.1	0.2	0.2 - 0.3
Red Marrow <sup>2</sup>	1.3	0.6 - 1.8	0.2	0.1 - 0.2
Urinary Bladder Wall <sup>3</sup>	0.9	0.7 - 1.3	0.2	0.1 - 0.2
Bone Surfaces <sup>2</sup>	0.9	0.5 - 1.2	0.2	0.1 - 0.2
Total Body <sup>3</sup>	0.5	0.4 - 0.7	0.1	0.1 - 0.2
Ovaries <sup>3</sup>	0.4	0.3 - 0.5	0.2	0.2 - 0.2
Uterus <sup>3</sup>	0.4	0.3 - 0.5	0.2	0.1 - 0.2
Adrenals <sup>3</sup>	0.3	0.2 - 0.5	0.2	0.2 - 0.3
Brain <sup>3</sup>	0.3	0.2 - 0.5	0.1	0.0 - 0.1
Breasts <sup>3</sup>	0.3	0.2 - 0.5	0.1	0.1 - 0.1
Gallbladder Wall <sup>3</sup>	0.3	0.2 - 0.5	0.3	0.2 - 0.4
Muscle <sup>3</sup>	0.3	0.2 - 0.5	0.1	0.1 - 0.1
Pancreas <sup>3</sup>	0.3	0.2 - 0.5	0.2	0.2 - 0.3
Skin <sup>3</sup>	0.3	0.2 - 0.5	0.1	0.0 - 0.1
Stomach <sup>3</sup>	0.3	0.2 - 0.5	0.2	0.1 - 0.2
Thymus <sup>3</sup>	0.3	0.2 - 0.5	0.1	0.1 - 0.2
Thyroid <sup>3</sup>	0.3	0.2 - 0.5	0.1	0.0 - 0.1
Kidneys <sup>1</sup>	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 <sup>[10]</sup>  
 3 Whole body region of interest

184 **CLINICAL STUDIES**

185 The safety and efficacy of the ZEVALIN therapeutic regimen were evaluated in two  
186 multi-center trials enrolling a total of 197 subjects. The ZEVALIN therapeutic regimen  
187 was administered in two steps (see DOSAGE AND ADMINISTRATION). The activity  
188 and toxicity of a variation of the ZEVALIN therapeutic regimen employing a reduced  
189 dose of Y-90 ZEVALIN was further defined in a third study enrolling a total of 30  
190 patients who had mild thrombocytopenia (platelet count 100,000 to 149,000 cells/mm<sup>3</sup>).

191

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

203

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

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**Table 6.**  
**Summary of Efficacy Data<sup>1</sup>**

	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 <sup>2</sup> (%)	15	34	20
Median DR <sup>3,4</sup> (Months) [Range <sup>3</sup> ]	6.4 [0.5-49.9+]	13.9 [1.0-47.6+]	11.8 [1.2-49.7+]
Median TTP <sup>3,6</sup> (Months) [Range <sup>5</sup> ]	6.8 [1.1-50.9+]	10.6 [0.8-49.0+]	10.1 [0.7-51.3+]

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<sup>1</sup>IWRC: International Workshop response criteria  
<sup>2</sup>CRu and CR: Unconfirmed and confirm complete response  
<sup>3</sup>Estimated with observed range  
<sup>4</sup>Duration of response: interval from the onset of response to disease progression  
<sup>5</sup>“+” indicates an ongoing response  
<sup>6</sup>Time to Disease Progression: interval from the first infusion to disease progression

226  
227 Study 3 was a single arm study of 30 patients with relapsed or refractory low-grade,  
228 follicular, or transformed B-cell NHL who had mild thrombocytopenia (platelet count  
229 100,000 to 149,000 cells/mm<sup>3</sup>). Excluded from the study were patients with ≥ 25%  
230 lymphoma marrow involvement and/or impaired bone marrow reserve. Patients were  
231 considered to have impaired bone marrow reserve if they had any of the following: prior  
232 myeloablative therapy with stem cell support; prior external beam radiation to > 25% of  
233 active marrow; a platelet count <100,000 cells/mm<sup>3</sup>; or neutrophil count <1,500  
234 cells/mm<sup>3</sup>. In this study, a modification of the ZEVALIN therapeutic regimen with a  
235 lower Y-90 ZEVALIN dose [(Y-90 ZEVALIN at 0.3 mCi/kg (11.1 MBq/kg)] was used.  
236 Objective, durable clinical responses were observed [83% ORR (95% CI: 65-94%)<sup>[14]</sup>,  
237 11.5 months median DR (range: 1-42.4+ months)] and resulted in a greater incidence of  
238 hematologic toxicity (see ADVERSE REACTIONS) than in Studies 1 and 2.

239

#### 240 **INDICATIONS AND USAGE**

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

248

#### 249 **CONTRAINDICATIONS**

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

253

#### 254 **WARNINGS (SEE BOXED WARNING)**

255 **Altered Biodistribution:** Y-90 ZEVALIN should not be administered to patients with  
256 altered biodistribution of In-111 ZEVALIN. For additional information regarding  
257 biodistribution, see IMAGE ACQUISITION AND INTERPRETATION.

258

259 **Severe Infusion Reactions (See PRECAUTIONS, Hypersensitivity):** The ZEVALIN  
260 therapeutic regimen may cause severe, and potentially fatal, infusion reactions. These  
261 severe reactions typically occur during the first Rituximab infusion with time to onset of  
262 30 to 120 minutes. Signs and symptoms of severe infusion reaction may include  
263 hypotension, angioedema, hypoxia, or bronchospasm, and may require interruption of  
264 Rituximab, In-111 ZEVALIN, or Y-90 ZEVALIN administration. The most severe  
265 manifestations and sequelae may include pulmonary infiltrates, acute respiratory distress  
266 syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock.

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

269

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

271 The most common severe adverse events reported with the ZEVALIN therapeutic  
272 regimen were thrombocytopenia (61% of patients with platelet counts  $<50,000$   
273  $\text{cells/mm}^3$ ) and neutropenia (57% of patients with absolute neutrophil count (ANC)  
274  $<1,000 \text{ cells/mm}^3$ ) in patients with  $\geq 150,000 \text{ platelets/mm}^3$  prior to treatment. Both  
275 incidences of severe thrombocytopenia and neutropenia increased to 78% and 74% for  
276 patients with mild thrombocytopenia at baseline (platelet count of 100,000 to 149,000  
277  $\text{cells/mm}^3$ ). For all patients, the median time to nadir was 7-9 weeks and the median  
278 duration of cytopenias was 22-35 days. In  $<5\%$  of cases, patients experienced severe  
279 cytopenia that extended beyond the prospectively defined protocol treatment period of 12  
280 weeks following administration of the ZEVALIN therapeutic regimen. Some of these  
281 patients eventually recovered from cytopenia, while others experienced progressive  
282 disease, received further anti-cancer therapy, or died of their lymphoma without having  
283 recovered from cytopenia. The cytopenias may have influenced subsequent treatment  
284 decisions.

285

286 Hemorrhage, including fatal cerebral hemorrhage, and severe infections have occurred in  
287 a minority of patients in clinical studies. Careful monitoring for and management of  
288 cytopenias and their complications (e.g., febrile neutropenia, hemorrhage) for up to 3

289 months after use of the ZEVALIN therapeutic regimen are necessary. Caution should be  
290 exercised in treating patients with drugs that interfere with platelet function or  
291 coagulation following the ZEVALIN therapeutic regimen and patients receiving such  
292 agents should be closely monitored.

293

294 The ZEVALIN therapeutic regimen should not be administered to patients with  $\geq 25\%$   
295 lymphoma marrow involvement and/or impaired bone marrow reserve, e.g., prior  
296 myeloablative therapies; platelet count  $<100,000$  cells/mm<sup>3</sup>; neutrophil count  $<1,500$   
297 cells/mm<sup>3</sup>; hypocellular bone marrow ( $\leq 15\%$  cellularity or marked reduction in bone  
298 marrow precursors); or to patients with a history of failed stem cell collection.

299

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

304

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

310

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

316

## 317 **PRECAUTIONS**

318 The ZEVALIN therapeutic regimen is intended as a single course treatment. The safety  
319 and toxicity profile from multiple courses of the ZEVALIN therapeutic regimen or of

320 other forms of therapeutic irradiation preceding, following, or in combination with the  
321 ZEVALIN therapeutic regimen have not been established.

322

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

327

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

336

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

341

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

346

347 **Drug Interactions:** No formal drug interaction studies have been performed with  
348 ZEVALIN. Due to the frequent occurrence of severe and prolonged thrombocytopenia,  
349 the potential benefits of medications which interfere with platelet function and/or  
350 anticoagulation should be weighed against the potential increased risks of bleeding and

351 hemorrhage. Patients receiving medications that interfere with platelet function or  
352 coagulation should have more frequent laboratory monitoring for thrombocytopenia. In  
353 addition, the transfusion practices for such patients may need to be modified given the  
354 increased risk of bleeding.

355

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

359

360 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No long-term animal studies  
361 have been performed to establish the carcinogenic or mutagenic potential of the  
362 ZEVALIN therapeutic regimen, or to determine its effects on fertility in males or  
363 females. However, radiation is a potential carcinogen and mutagen. The ZEVALIN  
364 therapeutic regimen results in a significant radiation dose to the testes. The radiation  
365 dose to the ovaries has not been established. There have been no studies to evaluate  
366 whether the ZEVALIN therapeutic regimen causes hypogonadism, premature  
367 menopause, azoospermia and/or mutagenic alterations to germ cells. There is a potential  
368 risk that the ZEVALIN therapeutic regimen could cause toxic effects on the male and  
369 female gonads. Effective contraceptive methods should be used during treatment and for  
370 up to 12 months following the ZEVALIN therapeutic regimen.

371

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

373

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

378

379 **Geriatric Use:** Of 349 patients treated with the ZEVALIN therapeutic regimen in  
380 clinical studies, 38% (132 patients) were age 65 years and over, while 12% (41 patients)  
381 were age 75 years and over. No overall differences in safety or effectiveness were

382 observed between these subjects and younger subjects, but greater sensitivity of some  
383 older individuals cannot be ruled out.

384

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

387

### 388 **ADVERSE REACTIONS**

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

393

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

401

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

410  
 411  
 412  
 413

**Table 7.**  
**Incidence of Adverse Events in ≥ 5 % of Patients Receiving the ZEVALIN**  
**therapeutic regimen<sup>†</sup>**  
**(N = 349)**

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

414  
 415  
 416

<sup>†</sup> 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.

417 The following adverse events (except for those noted in Table 7) occurred in between 1  
418 and 4% of patients during the treatment period: urticaria (4%), anxiety (4%), dyspepsia  
419 (4%), sweats (4%), petechia (3%), epistaxis (3%), allergic reaction (2%), and melena  
420 (2%).

421

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

428

429 **Hematologic Events:** Hematologic toxicity was the most frequently observed adverse  
430 event in clinical trials. Table 8 presents the incidence and duration of severe hematologic  
431 toxicity for patients with normal baseline platelet count ( $\geq 150,000$  cells/mm<sup>3</sup>) treated  
432 with the ZEVALIN therapeutic regimen and patients with mild thrombocytopenia  
433 (platelet count 100,000 to 149,000 cells/mm<sup>3</sup>) at baseline who were treated with a  
434 modified ZEVALIN therapeutic regimen that included a lower Y-90 ZEVALIN dose at  
435 0.3 mCi/kg (11.1 MBq/kg).

436

437  
 438  
 439  
 440

**Table 8.**  
**Severe Hematologic Toxicity**

	<b>ZEVALIN therapeutic regimen using 0.4 mCi/kg Y-90 Dose (14.8 MBq/kg)</b>	<b>Modified ZEVALIN therapeutic regimen using 0.3 mCi/kg Y-90 dose (11.1 MBq/kg)</b>
<b>ANC</b>		
Median nadir (cells/mm <sup>3</sup> )	800	600
Per Patient Incidence ANC <1000 cells/mm <sup>3</sup>	57%	74%
Per Patient Incidence ANC <500 cells/mm <sup>3</sup>	30%	35%
Median Duration (Days)* ANC <1000 cells/mm <sup>3</sup>	22	29
<b>Platelets</b>		
Median nadir (cells/mm <sup>3</sup> )	41,000	24,000
Per Patient Incidence Platelets <50,000 cells/mm <sup>3</sup>	61%	78%
Per Patient Incidence Platelets <10,000 cells/mm <sup>3</sup>	10%	14%
Median Duration (Days)# Platelets <50,000 cells/mm <sup>3</sup>	24	35

441 \*Median duration of neutropenia for patients with ANC <1000 cells/mm<sup>3</sup> (Date from last laboratory value  
 442 showing ANC ≥1000 cells/mm<sup>3</sup> to date of first laboratory value following nadir showing ANC ≥1000  
 443 cells/mm<sup>3</sup>, censored at initiation of next treatment or death)

444 # Median duration of thrombocytopenia for patients with platelets <50,000 cells/mm<sup>3</sup> (Date from last  
 445 laboratory value showing platelet count ≥50,000 cells/mm<sup>3</sup> to date of first laboratory value following nadir  
 446 showing platelet count ≥50,000 cells/mm<sup>3</sup>, censored at initiation of next treatment or death)  
 447

448 Median time to ANC nadir was 62 days, to platelet nadir was 53 days, and to hemoglobin  
 449 nadir was 68 days. Information on growth factor use and platelet transfusions is based on  
 450 211 patients for whom data were collected. Filgrastim was given to 13% of patients and  
 451 erythropoietin to 8%. Platelet transfusions were given to 22% of patients and red blood  
 452 cell transfusions to 20%.

453

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

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

466

467 **Secondary Malignancies:** A total of 2% of patients developed secondary malignancies  
468 following the ZEVALIN therapeutic regimen. One patient developed a Grade 1  
469 meningioma, three developed acute myelogenous leukemia, and two developed a  
470 myelodysplastic syndrome. The onset of a second cancer was 8-34 months following the  
471 ZEVALIN therapeutic regimen and 4 to 14 years following the patients' diagnosis of  
472 NHL.

473

474 **Immunogenicity:** Of 211 patients who received the ZEVALIN therapeutic regimen in  
475 clinical trials and who were followed for 90 days, there were eight (3.8%) patients with  
476 evidence of human anti-mouse antibody (HAMA) (n=5) or human anti-chimeric antibody  
477 (HACA) (n=4) at any time during the course of the study. Two patients had low titers of  
478 HAMA prior to initiation of the ZEVALIN therapeutic regimen; one remained positive  
479 without an increase in titer while the other had a negative titer post-treatment. Three  
480 patients had evidence of HACA responses prior to initiation of the ZEVALIN therapeutic  
481 regimen; one had a marked increase in HACA titer while the other two had negative titers  
482 post-treatment. Of the three patients who had negative HAMA or HACA titers prior to  
483 the ZEVALIN therapeutic regimen, two developed HAMA in absence of HACA titers,  
484 and one had both HAMA and HACA positive titers post-treatment. Evidence of  
485 immunogenicity may be masked in patients who are lymphopenic. There has not been  
486 adequate evaluation of HAMA and HACA at delayed timepoints, concurrent with the  
487 recovery from lymphopenia at 6-12 months, to establish whether masking of the  
488 immunogenicity at early timepoints occurs. The data reflect the percentage of patients

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

496

#### 497 **OVERDOSAGE**

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

505

#### 506 **DOSAGE AND ADMINISTRATION**

507 The ZEVALIN therapeutic regimen is administered in two steps: Step 1 includes a single  
508 infusion of 250 mg/m<sup>2</sup> Rituximab (not included in the ZEVALIN kits) preceding a fixed  
509 dose of 5.0 mCi (1.6 mg total antibody dose) of In-111 ZEVALIN administered as a 10  
510 minute IV push. Step 2 follows step 1 by seven to nine days and consists of a second  
511 infusion of 250 mg/m<sup>2</sup> of Rituximab prior to 0.4 mCi/kg of Y-90 ZEVALIN administered  
512 as a 10 minute IV push.

513

514 **Rituximab Administration: NOTE THAT THE DOSE OF RITUXIMAB IS**  
515 **LOWER WHEN USED AS PART OF THE ZEVALIN THERAPEUTIC**  
516 **REGIMEN, AS COMPARED TO THE DOSE OF RITUXIMAB WHEN USED AS**  
517 **A SINGLE AGENT. DO NOT ADMINISTER RITUXIMAB AS AN**  
518 **INTRAVENOUS PUSH OR BOLUS.** Hypersensitivity reactions may occur (see  
519 **WARNINGS).** Premedication, consisting of acetaminophen and diphenhydramine,  
520 should be considered before each infusion of Rituximab.

521

522 **ZEVALIN Therapeutic Regimen Dose Modification in Patients with Mild**  
523 **Thrombocytopenia:** The Y-90 ZEVALIN dose should be reduced to 0.3 mCi/kg (11.1  
524 MBq/kg) for patients with a baseline platelet count between 100,000 and 149,000  
525 cells/mm<sup>3</sup>.

526

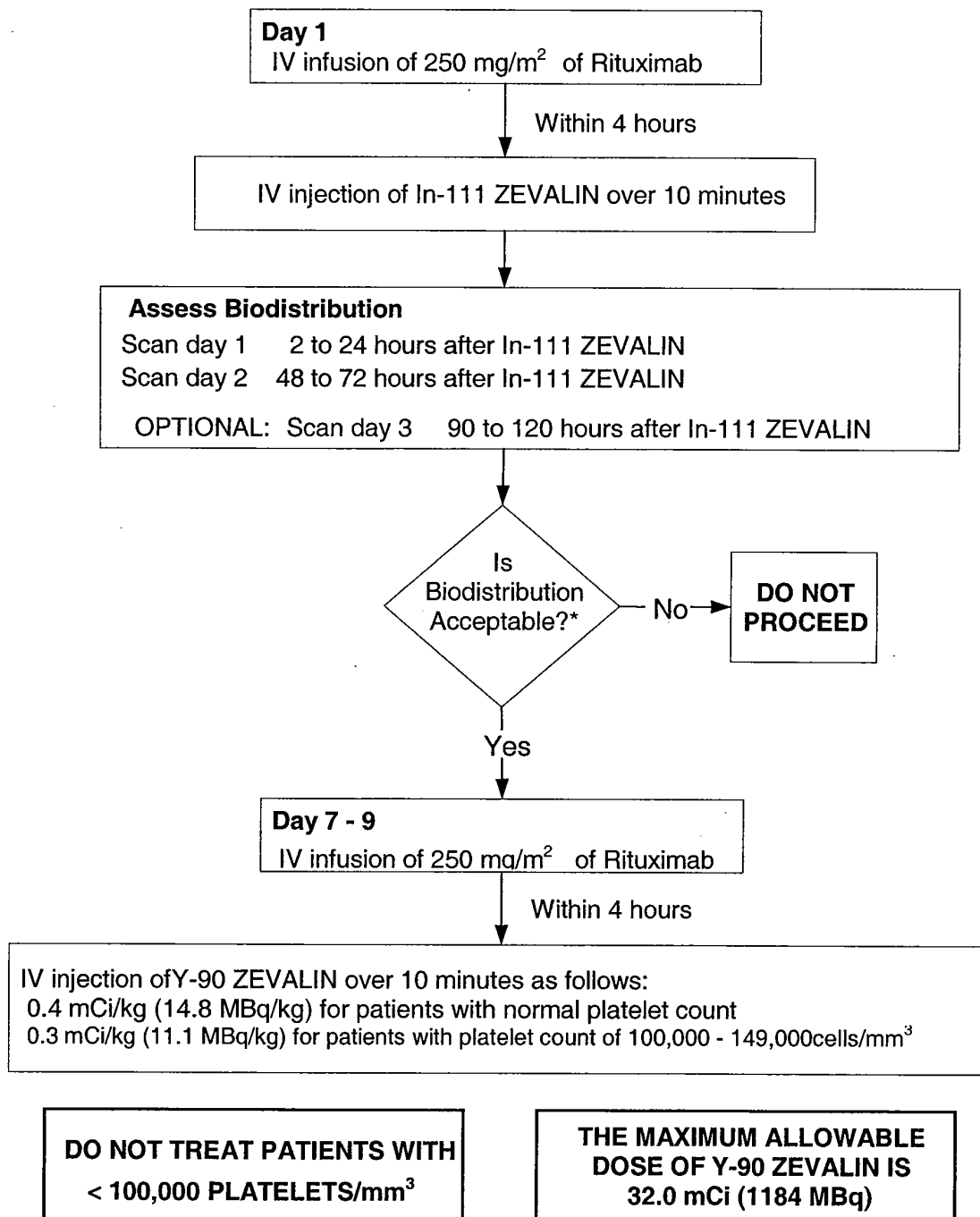
527 Two separate and distinctly-labeled kits are ordered for the preparation of a single dose  
528 each of In-111 ZEVALIN and Y-90 ZEVALIN. In-111 ZEVALIN and Y-90 ZEVALIN  
529 are radiopharmaceuticals and should be used only by physicians and other professionals  
530 qualified by training and experienced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

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

534

535 **Overview of Dosing Schedule:**

536



\*See IMAGE ACQUISITION AND INTERPRETATION

537

538

539 **ZEVALIN Therapeutic Regimen Administration**

540 Step 1:

541 First Rituximab Infusion: Rituximab at a dose of 250 mg/m<sup>2</sup> should be administered  
542 intravenously at an initial rate of 50 mg/hr. Rituximab should not be mixed or diluted  
543 with other drugs. If hypersensitivity or infusion-related events do not occur, escalate the  
544 infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If  
545 hypersensitivity or an infusion-related event develops, the infusion should be temporarily  
546 slowed or interrupted (see WARNINGS). The infusion can continue at one-half the  
547 previous rate upon improvement of patient symptoms.

548

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

555

556 Step 2:

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

559

560 Second Rituximab Infusion: Rituximab at a dose of 250 mg/m<sup>2</sup> is administered I.V. at an  
561 initial rate of 100 mg/hr (50 mg/hr if infusion related events were documented during the  
562 first Rituximab administration) and increased by 100 mg/hr increments at 30 minute  
563 intervals, to a maximum of 400 mg/hr, as tolerated.

564

565 Y-90 ZEVALIN Injection:

566 Within 4 hours following completion of the Rituximab dose, Y-90 ZEVALIN at a dose of  
567 0.4 mCi/kg (14.8 MBq/kg) actual body weight for patients with a platelet count  $\geq 150,000$   
568 cells/mm<sup>3</sup>, and 0.3 mCi/kg (11.1 MBq/kg) actual body weight for patients with a platelet  
569 count of 100,000-149,000 cells/mm<sup>3</sup> is injected intravenously (I.V.) over a period of 10

570 minutes. A 0.22 micrometer low-protein-binding filter should be in-line between the  
571 syringe and the infusion port prior to injection of Y-90 ZEVALIN. After injection, the  
572 line should be flushed with at least 10 mL of normal saline. Precautions should be taken  
573 to avoid extravasation. A free flowing I.V. line should be established prior to Y-90  
574 ZEVALIN injection. Close monitoring for evidence of extravasation during the injection  
575 of Y-90 ZEVALIN is required. If any signs or symptoms of extravasation have occurred,  
576 the infusion should be immediately terminated and restarted in another vein. **The**  
577 **prescribed, measured, and administered dose of Y-90 ZEVALIN must not exceed**  
578 **the absolute maximum allowable dose of 32.0 mCi (1184 MBq), regardless of the**  
579 **patient's body weight. Do not give Y-90 ZEVALIN to patients with a platelet count**  
580 **<100,000/mm<sup>3</sup> (see WARNINGS).**

581

#### 582 **DIRECTIONS FOR PREPARATION OF RADIOLABELED ZEVALIN.**

583

#### 584 **A. PREPARATION OF THE IN-111 ZEVALIN DOSE**

585

##### 586 **GENERAL:**

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

590

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

595

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

600 administration to the patient. The radiolabeling of ZEVALIN shall be done according to  
601 the following directions.

602

603 Required materials not supplied in the kit:

604

- 605 A. Indium-111 Chloride Sterile Solution (In-111 Chloride) from Amersham  
606 Health, Inc. or Mallinckrodt, Inc.
- 607 B. Three sterile 1 mL syringes
- 608 C. One sterile 3 mL syringe
- 609 D. Two sterile 10 mL syringes with 18-20 G needles
- 610 E. Instant thin-layer chromatographic silica gel strips
- 611 F. 0.9% sodium chloride aqueous solution for the chromatography solvent
- 612 G. Developing chamber for chromatography
- 613 H. Suitable radioactivity counting apparatus
- 614 I. Filter, 0.22 micrometer, low-protein-binding (see DOSAGE AND  
615 ADMINISTRATION, Zevalin Therapeutic Regimen Administration)
- 616 J. Vial and syringe shield

617

618 Method:

619

- 620 1. Sterile, pyrogen-free In-111 chloride must be used for the preparation of  
621 In-111 ZEVALIN. The use of high purity In-111 chloride manufactured by  
622 Amersham Health, Inc. or Mallinckrodt, Inc. is required.  
623
- 624 2. Before radiolabeling, allow contents of the refrigerated carton to reach room  
625 temperature. Note: The ZEVALIN vial contains a protein solution that may  
626 develop translucent particulates. These particulates will be removed by filtration  
627 prior to administration.  
628
- 629 3. Clean the rubber stoppers of all of the vials in the kit and the In-111 chloride vial  
630 with a suitable alcohol swab and allow to air dry.

631

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

635

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

638

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

641

642 b. The volume of 50 mM sodium acetate solution needed is 1.2 times the  
643 volume of In-111 chloride solution determined in step 5.a., above. (The  
644 50 mM sodium acetate is used to adjust the pH for the radiolabeling  
645 reaction.)

646

647 c. Calculate the volume of Formulation Buffer needed to bring the Reaction  
648 Vial contents to a final volume of 10 mL. This is the volume of  
649 Formulation Buffer needed to protect the labeled product from radiolysis  
650 and to terminate the labeling reaction. For example, if volumes of 0.5 mL  
651 of In-111 chloride, 0.6 mL of sodium acetate and 1.0 mL of ZEVALIN  
652 were used, then the amount of formulation buffer would be  $10 - (0.5 + 0.6 +$   
653  $1.0) = 7.9$  mL.

654

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

658

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

662

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

667

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

671

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

679

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

683

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

692

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

696

697 14. Indium-111 ZEVALIN should be stored at 2 - 8°C (36-46°F) until use and  
698 administered within 12 hours of radiolabeling.

699

700 15. See DOSAGE AND ADMINISTRATION: ZEVALIN Therapeutic Regimen  
701 Administration: Step 1

702

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

705

## 706 **B. PREPARATION OF THE Y-90 ZEVALIN DOSE**

707

### 708 **GENERAL:**

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

712

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

717

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

724 Required materials not supplied in the kit:

725

- 726 A. Yttrium-90 Chloride Sterile Solution from MDS Nordion (shipped directly
- 727 from MDS Nordion upon placement of an order for the Y-90 ZEVALIN kit)
- 728 B. Three sterile 1 mL syringes
- 729 C. One sterile 3 mL syringe
- 730 D. Two sterile 10 mL syringes with 18-20 G needles
- 731 E. Instant thin-layer chromatographic silica gel strips (ITLC-SG)
- 732 F. 0.9% sodium chloride aqueous solution for the chromatography solvent
- 733 G. Suitable radioactivity counting apparatus
- 734 H. Developing chamber for chromatography
- 735 I. Filter, 0.22 micrometer, low-protein-binding (see DOSAGE AND
- 736 ADMINISTRATION, ZEVALIN Therapeutic Regimen Administration)
- 737 J. Vial and syringe shield

738

739 Method:

740

- 741 1. Sterile, pyrogen-free Y-90 chloride must be used for the preparation of Y-90
- 742 ZEVALIN. The use of high purity Y-90 chloride manufactured by MDS Nordion
- 743 is required.
- 744
- 745 2. Before radiolabeling, allow the contents of the refrigerated carton to reach room
- 746 temperature. Note: The ZEVALIN vial contains a protein solution that may
- 747 develop translucent particulates. These particulates will be removed by filtration
- 748 prior to administration.
- 749
- 750 3. Clean the rubber stoppers of all of the vials in the kit and the Y-90 chloride vial
- 751 with a suitable alcohol swab and allow to air dry.

752

- 753 4. Place the empty Reaction Vial in a suitable dispensing shield (pre-warmed to  
754 room temperature). To avoid the buildup of excessive pressure during the  
755 procedure, use a 10 mL syringe to withdraw 10 mL of air from the Reaction Vial.  
756
- 757 5. Prior to initiating the radiolabeling reaction, determine the amount of each  
758 component needed according to the directions below:  
759
- 760 a. Calculate the volume of Y-90 chloride that is equivalent to 40 mCi based  
761 on the activity concentration of the Y-90 chloride stock.  
762
- 763 b. The volume of 50 mM sodium acetate solution needed is 1.2 times the  
764 volume of Y-90 chloride solution determined in step 5.a., above. (The  
765 50 mM sodium acetate is used to adjust the pH for the radiolabeling  
766 reaction.)  
767
- 768 c. Calculate the volume of Formulation Buffer needed to bring the Reaction  
769 Vial contents to a final volume of 10 mL. This is the volume of  
770 Formulation Buffer needed to protect the labeled product from radiolysis  
771 and to terminate the labeling reaction. For example if the volumes were  
772 0.5 mL of Y-90 chloride, 0.6 mL of sodium acetate and 1.3 mL of  
773 ZEVALIN, then the amount of formulation buffer would be  
774  $10 - (0.5 + 0.6 + 1.3) = 7.6$  mL.  
775
- 776 6. With a sterile 1 mL syringe, transfer the calculated volume of 50 mM sodium  
777 acetate to the empty Reaction Vial. Coat the entire inner surface of the Reaction  
778 Vial by gentle inversion or rolling.  
779
- 780 7. Transfer 40 mCi of Y-90 chloride to the Reaction Vial with a sterile 1 mL  
781 syringe. Mix the two solutions and coat the entire inner surface of the Reaction  
782 Vial by gentle inversion or rolling.  
783

- 784 8. With a sterile 3 mL syringe, transfer 1.3 mL of ZEVALIN (Ibritumomab  
785 Tiuxetan) to the Reaction Vial. Coat the entire surface of the Reaction Vial by  
786 gentle inversion or rolling. **Do not shake or agitate the vial contents, since this**  
787 **will cause foaming and denaturation of the protein.**  
788
- 789 9. Allow the labeling reaction to proceed at room temperature for 5 minutes.  
790 Allowing the labeling reaction to proceed for a longer or shorter time may result  
791 in inadequate labeling.  
792
- 793 10. **Immediately** after the 5-minute incubation period, using a sterile 10 mL syringe  
794 with a large bore needle (18 G - 20 G), transfer the calculated volume of  
795 Formulation Buffer from step 5.c. to the Reaction Vial, terminating incubation.  
796 Gently add the Formulation Buffer down the side of the Reaction Vial. If  
797 necessary to normalize air pressure, withdraw an equal volume of air. Coat the  
798 entire inner surface of the Reaction Vial by gentle inversion or rolling. Do not  
799 shake or agitate the vial contents. Avoid foaming.  
800
- 801 11. Using the supplied labels, record the patient identification, the date and time of  
802 preparation, the total activity and volume, and the date and time of expiration and  
803 affix these labels to the reaction vial and shielded reaction vial container.  
804
- 805 12. Calculate the volume required for a Y-90 ZEVALIN dose of 0.4 mCi/kg  
806 (14.8 MBq/kg) actual body weight for patients with normal platelet count, and  
807 0.3 mCi/kg (11.1 MBq/kg) actual body weight for patients with platelet count of  
808 100,000 - 149,000 cells/mm<sup>3</sup>. **The prescribed, measured, and administered**  
809 **dose of Y-90 ZEVALIN must not exceed the absolute maximum allowable**  
810 **dose of 32.0 mCi (1184 MBq), regardless of the patient's body weight.**  
811 Withdraw the required volume from the Reaction Vial contents into a sterile  
812 10 mL syringe with a large bore needle (18 G - 20 G). Assay the syringe and  
813 contents in a dose calibrator. The dose calibrator must be operated in accordance  
814 with the manufacturer's specifications and quality control for the measurement of

815 Y-90. The syringe should contain the dose of Y-90 ZEVALIN to be administered  
816 to the patient, and should be within 10% of the actual prescribed dose of Y-90  
817 ZEVALIN, not to exceed a maximum dose of 32.0 mCi. Do not exceed  $\pm 10\%$  of  
818 the prescribed dose. Using the supplied labels, record the patient identification,  
819 the date and time of preparation, the total activity and volume added, and the date  
820 and time of expiration and affix these labels to the syringe and shielded unit dose  
821 container.

822

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

826

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

829

830 15. See DOSAGE AND ADMINISTRATION: ZEVALIN Therapeutic Regimen  
831 Administration: Step 2.

832

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

835

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

839

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

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

842 **Y-90 ZEVALIN:**

843

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

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

851 C. Calculate the percent RCP as follows:

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

852

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

856

#### 857 **IMAGE ACQUISITION AND INTERPRETATION**

858 The biodistribution of In-111 ZEVALIN should be assessed by a visual evaluation of  
859 whole body planar view anterior and posterior gamma images at 2 - 24 hours and 48 - 72  
860 hours after injection. To resolve ambiguities, a third image at 90 - 120 hours may be  
861 necessary. Images should be acquired using a large field of view gamma camera  
862 equipped with a medium energy collimator. Whole body anterior/posterior planar images  
863 should be acquired using a large field-of-view gamma camera and medium energy  
864 collimators. Suggested gamma camera settings: 256 x 1024 matrix; dual energy  
865 photopeaks set at 172 and 247 keV; 15% symmetric window; scan speed of 10 cm/min  
866 for the 2-24 hour scan, 7-10 cm/min for the 48-72 hour scan and 5 cm/min for the  
867 optional 90-120 hour scan.

868

#### 869 **EXPECTED BIODISTRIBUTION**

870 Visual inspection of gamma images of expected biodistribution reveal the following:

871

- 872 • On Scan 1 (2-24 hours), activity in the blood pool areas (heart, abdomen, neck,  
873 and extremities) is detectable and decreases on Scan 2 (48-72 hours). There is  
874 variability within patients in the visualization of the blood pool especially when

- 875 images are performed late in the time window of Scan 1 and in an occasional  
876 patient, blood pool may not be visible late in the time window of Scan 1.
- 877 • Moderately high to high uptake in normal liver and spleen on Scans 1 and 2.
  - 878 • Moderately low or very low uptake in normal kidneys, urinary bladder, and  
879 normal (uninvolved) bowel on Scans 1 and 2.
  - 880 • Localization to lymphoid aggregates in the bowel wall has been reported.

881

882 Tumor uptake may be visualized in soft tissue as areas of increased intensity, and tumor-  
883 bearing areas in normal organs may be seen as areas of increased or decreased intensity.  
884 Tumor visualization on the In-111 Zevalin scan is not required for Y-90 Zevalin therapy.

885

#### 886 **ALTERED BIODISTRIBUTION**

887 The criteria for altered biodistribution is met if any one of the following is detected on  
888 visual inspection of gamma images:

889

- 890 • Rapid clearance of the radioimmunoconjugate from the blood pool with liver,  
891 spleen, and/ or bone marrow uptake in Scan 1.
- 892 • Increased uptake in normal organs (not involved by tumor) such as:
  - 893 o Diffuse uptake in normal lung more intense than the cardiac blood pool on  
894 Scan 1, or more intense than the liver Scan 2.
  - 895 o Kidneys with greater intensity than the liver on the posterior view on Scan 2 .  
896 Fixed areas (unchanged with time) of uptake in the normal bowel greater  
897 than uptake in the liver on Scan 2.

898

899 If a visual inspection of the gamma images reveals an altered biodistribution, the patient  
900 should not proceed to the Y-90 ZEVALIN dose.

901

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

907

908 **HOW SUPPLIED**

909 The In-111 ZEVALIN kit provides for the radiolabeling of Ibritumomab Tiuxetan with  
910 In-111. The Y-90 ZEVALIN kit provides for the radiolabeling of Ibritumomab Tiuxetan  
911 with Y-90.

912

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

917

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

922

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

924

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

929

930 **Storage**

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

932

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983

984 **Rx Only**

985 In-111 ZEVALIN kit, NDC 64406-104-04

986 Y-90 ZEVALIN kit, NDC 64406-103-03

987

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