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Ibritumomab Tiuxetan

ZEVALIN®

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

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

WARNINGS

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

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

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 IgG_1 kappa monoclonal antibody directed against the CD20 antigen, which is found on the surface of normal and malignant B lymphocytes. Ibritumomab is produced in Chinese hamster ovary cells and is composed of two murine gamma 1 heavy chains of 445 amino acids each and two kappa light chains of 213 amino acids each.

ZEVALIN Therapeutic Regimen

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

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

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

ZEVALIN Kits

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

(1) One (1) ZEVALIN vial containing 3.2 mg of Ibritumomab Tiuxetan in 2 mL of 0.9% sodium chloride solution; a sterile, pyrogen-free, clear, colorless solution that may contain translucent particles; no preservative present.

(2) One (1) 50 mM Sodium Acetate Vial containing 13.6 mg of sodium acetate trihydrate in 2 mL of Water for Injection; a sterile, pyrogen-free, clear, colorless solution; no preservative present.

(3) One (1) Formulation Buffer Vial containing 750 mg of Albumin (Human), 76 mg of sodium chloride, 21 mg of sodium phosphate dibasic heptahydrate, 4 mg of pentetic acid, 2 mg of potassium phosphate monobasic and 2 mg of potassium chloride in 10 mL of Water for Injection adjusted to pH 7.1 with either sodium hydroxide or hydrochloric acid; a sterile, pyrogen-free, clear yellow to amber colored solution; no preservative present.

(4) One (1) empty Reaction Vial, sterile, pyrogen-free.

Physical/Radiochemical Characteristics of In-111

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

Table 1.
Principal In-111 Radiation Emission Data

Radiation	Mean % per Disintegration	Mean Energy (keV)
Gamma-2	90.2	171.3
Gamma-3	94.0	245.4

External Radiation

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

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

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

<u>Physical/Radiochemical Characteristics of Y-90</u>

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

Table 3.
Principal Y-90 Radiation Emission Data

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

External Radiation

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

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

Table 4.
Physical Decay Chart: Y-90
Half-life 2.67 Days (64.1 Hours)

Calibration Time (Hrs.)	Fraction Remaining	Calibration Time (Hrs.)	Fraction Remaining
-36	1.48	0	1.00
-24	1.30	1	0.99
-12	1.14	2	0.98
-8	1.09	3	0.97
-7	1.08	4	0.96
-6	1.07	5	0.95
-5	1.06	6	0.94
-4	1.04	7	0.93
-3	1.03	8	0.92
-2	1.02	12	0.88
-1	1.01	24	0.77
0	1.00	36	0.68

CLINICAL PHARMACOLOGY

General Pharmacology

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

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*.[6] 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.[7]
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^3). 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^3) 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.
169

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.[8, 9] 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.

178 **Table 5.**
179 **Estimated Radiation Absorbed Doses From Y-90 ZEVALIN and In-111 ZEVALIN**
180

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

181 1 Organ region of interest
182 2 Sacrum region of interest [10]
183 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^3).
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[11]. The primary efficacy endpoint of the
196 study was the overall response rate (ORR) using the International Workshop Response
197 Criteria (IWRC).[12] 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^2
209 weekly times 4 doses. The primary efficacy endpoint of the study was to determine the
210 ORR using the IWRC[12] (see Table 6). The ORR was significantly higher (80% vs. 56%,
211 $p = 0.002$)[13] 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.
214

215 **Table 6.**
216 **Summary of Efficacy Data[1]**

	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[5]]	6.4 [0.5-49.9+]	13.9 [1.0-47.6+]	11.8 [1.2-49.7+]
Median TTP[3,6] (Months) [Range[5]]	6.8 [1.1-50.9+]	10.6 [0.8-49.0+]	10.1 [0.7-51.3+]

217 [1]IWRC: International Workshop response criteria
218 [2]CRu and CR: Unconfirmed and confirm complete response
219 [3]Estimated with observed range
220 [4]Duration of response: interval from the onset of response to disease progression
221 [5]"+" indicates an ongoing response
222 [6]Time to Disease Progression: interval from the first infusion to disease progression
223
224
225

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^3). 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^3; or neutrophil count <1,500
234 cells/mm^3. 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%)[14],
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 cells/mm^3) and neutropenia (57% of patients with absolute neutrophil count (ANC)
274 <1,000 cells/mm^3) in patients with ≥150,000 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 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 ≥ 25%
295 lymphoma marrow involvement and/or impaired bone marrow reserve, e.g., prior
296 myeloablative therapies; platelet count <100,000 cells/mm^3; neutrophil count <1,500
297 cells/mm^3; hypocellular bone marrow (≤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 ≥ 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 **Table 7.**
411 **Incidence of Adverse Events in ≥ 5 % of Patients Receiving the ZEVALIN**
412 **therapeutic regimen †**
413 **(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**

414 † Adverse events were followed for a period of 12 weeks following the first
415 Rituximab infusion of the ZEVALIN therapeutic regimen
416 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^3) treated
432 with the ZEVALIN therapeutic regimen and patients with mild thrombocytopenia
433 (platelet count 100,000 to 149,000 cells/mm^3) 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

Table 8.
Severe Hematologic Toxicity

439
440

	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

441 *Median duration of neutropenia for patients with ANC <1000 cells/mm^3 (Date from last laboratory value
442 showing ANC ≥1000 cells/mm^3 to date of first laboratory value following nadir showing ANC ≥1000
443 cells/mm^3, censored at initiation of next treatment or death)
444 # Median duration of thrombocytopenia for patients with platelets <50,000 cells/mm^3 (Date from last
445 laboratory value showing platelet count ≥50,000 cells/mm^3 to date of first laboratory value following nadir
446 showing platelet count ≥50,000 cells/mm^3, 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

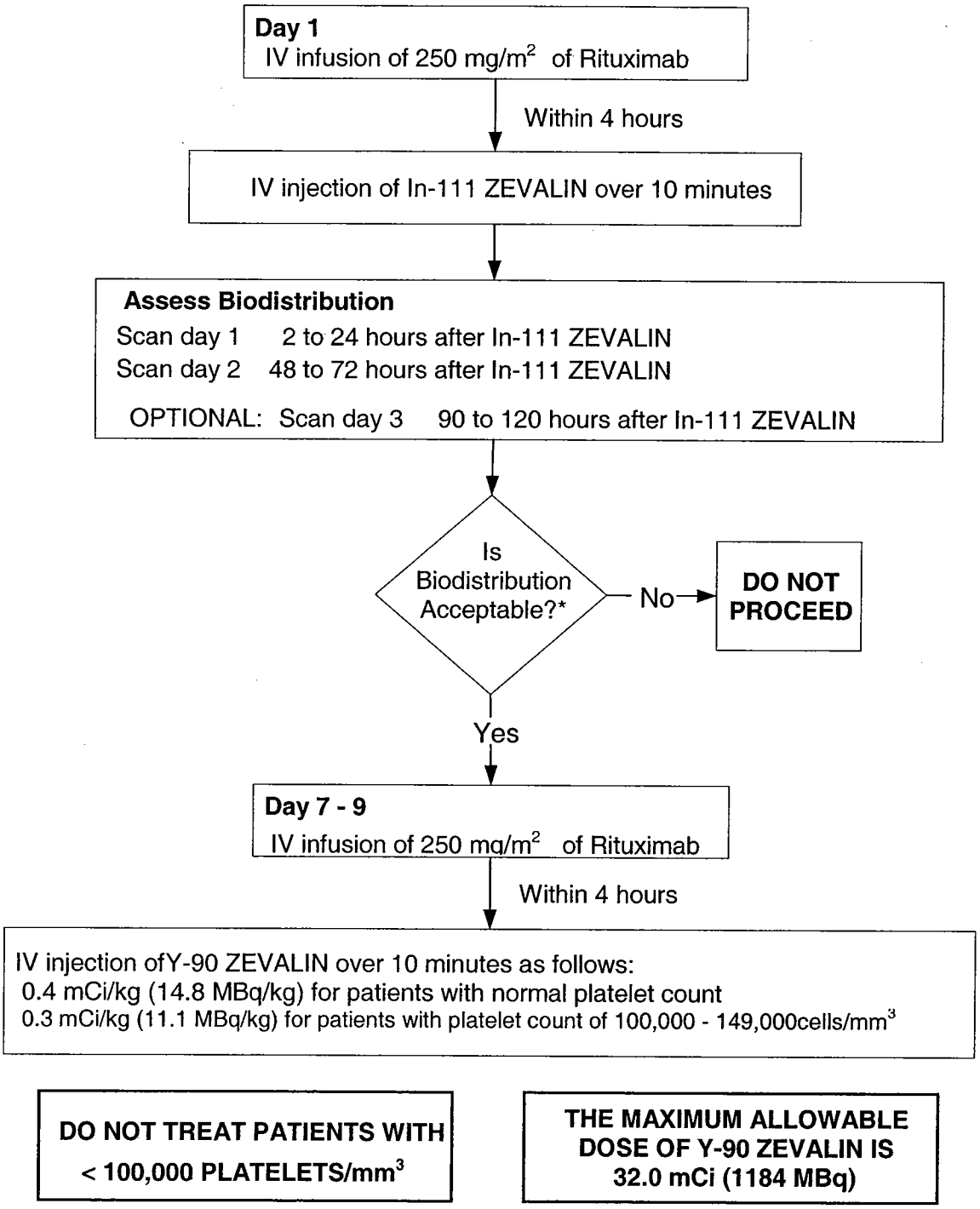
458 infection. Life threatening infections were reported for 2% of patients that included
459 sepsis, empyema, pneumonia, febrile neutropenia, fever, and biliary stent-associated
460 cholangitis. During follow-up from 3 months to 4 years after the start of treatment with
461 ZEVALIN, 6% of patients developed 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^2 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^2 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^3.
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^2 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^2 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 ≥150,000
568 cells/mm^3, 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^3 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^3 (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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

B. PREPARATION OF THE Y-90 ZEVALIN DOSE

GENERAL:

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

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

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

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

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

    a. Calculate the volume of Y-90 chloride that is equivalent to 40 mCi based on the activity concentration of the Y-90 chloride stock.

    b. The volume of 50 mM sodium acetate solution needed is 1.2 times the volume of Y-90 chloride solution determined in step 5.a., above. (The 50 mM sodium acetate is used to adjust the pH for the radiolabeling reaction.)

    c. Calculate the volume of Formulation Buffer needed to bring the Reaction Vial contents to a final volume of 10 mL. This is the volume of Formulation Buffer needed to protect the labeled product from radiolysis and to terminate the labeling reaction. For example if the volumes were 0.5 mL of Y-90 chloride, 0.6 mL of sodium acetate and 1.3 mL of ZEVALIN, then the amount of formulation buffer would be $10-(0.5 + 0.6 + 1.3) = 7.6$ mL.

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

7. Transfer 40 mCi of Y-90 chloride to the Reaction Vial with a sterile 1 mL syringe. Mix the two solutions and coat the entire inner surface of the Reaction Vial by gentle inversion or rolling.

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

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

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

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

12. Calculate the volume required for a Y-90 ZEVALIN dose of 0.4 mCi/kg (14.8 MBq/kg) actual body weight for patients with normal platelet count, and 0.3 mCi/kg (11.1 MBq/kg) actual body weight for patients with platelet count of 100,000 - 149,000 cells/mm^3. **The prescribed, measured, and administered dose of Y-90 ZEVALIN must not exceed the absolute maximum allowable dose of 32.0 mCi (1184 MBq), regardless of the patient's body weight.** Withdraw the required volume from the Reaction Vial contents into a sterile 10 mL syringe with a large bore needle (18 G - 20 G). Assay the syringe and contents in a dose calibrator. The dose calibrator must be operated in accordance with the manufacturer's specifications and quality control for the measurement of

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

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

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

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

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

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

C. PROCEDURE FOR DETERMINING RADIOCHEMICAL PURITY (RCP)

The following procedure should be used for both In-111 ZEVALIN and Y-90 ZEVALIN:

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

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

C. Calculate the percent RCP as follows:

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

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

IMAGE ACQUISITION AND INTERPRETATION

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

EXPECTED BIODISTRIBUTION

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

- On Scan 1 (2-24 hours), activity in the blood pool areas (heart, abdomen, neck, and extremities) is detectable and decreases on Scan 2 (48-72 hours). There is 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 o In less than 0.5% of patients receiving In-111 ZEVALIN, prominent bone
900 marrow uptake was observed, characterized by clear visualization of the
901 long bones and ribs on Scan 1.
902
903 If a visual inspection of the gamma images reveals an altered biodistribution, the patient
904 should not proceed to the Y-90 ZEVALIN dose. The safety and efficacy of the
905 administration of Y-90 ZEVALIN in patients with prominent marrow uptake is not
906 known. Possible causes of prominent bone marrow uptake, such as bone marrow
907 involvement by lymphoma, increased marrow activity due to recent hematopoietic
908 growth factor administration, and increased reticuloendothelial uptake in patients with
909 HAMA and HACA, should be considered. Re-assessment of biodistribution after
910 correction of underlying factors should be performed. Y-90 ZEVALIN should not be

administered to patients with persistently prominent marrow uptake on the repeat biodistribution scans.

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

HOW SUPPLIED

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

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

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

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

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

942 **Storage**

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

944

945 **REFERENCES**

946 1. Kocher DC. Radioactive Decay Data Tables - A Handbook of Decay Data for
947 Application to Radiation Dosimetry and Radiological Assessments: U.S.
948 Department of Energy 1981; DOE/TIC-11026.

949 2. Valentine MA, Meier KE, Rossie S, Clark EA. Phosphorylation of the CD20
950 phosphoprotein in resting B lymphocytes. Regulation by protein kinase C. J Biol
951 Chem 1989;264(19):11282-7.

952 3. Einfeld D, Brown J, Valentine M, Clark E, Ledbetter J. Molecular cloning of the
953 human B cell CD20 receptor predicts a hydrophobic protein with multiple
954 transmembrane domains. EMBO J 1988;7(3):711-7.

955 4. Anderson KC, Bates MP, Slaughenhoupt BL, Pinkus GS, Schlossman SF, Nadler
956 LM. Expression of human B cell-associated antigens on leukemias and
957 lymphomas: a model of human B cell differentiation. Blood 1984;63(6):1424-33.

958 5. Tedder T, Boyd A, Freedman A, Nadler L, Schlossman S. The B cell surface
959 molecule B1 is functionally linked with B cell activation and differentiation. J
960 Immunol 1985;135(2):973-9.

961 6. Press O, Appelbaum F, Ledbetter J, Martin P, Zarling J, Kidd P, et al. Monoclonal
962 antibody 1F5 (anti-CD20) serotherapy of human B-cell lymphomas. Blood
963 1987;69(2):584-91.

964 7. Chakrabarti MC, Le N, Paik CH, De Graff WG, Carrasquillo JA. Prevention of
965 radiolysis of monoclonal antibody during labeling. J Nucl Med
966 1996;37(8):1384-8.

967 8. Wiseman GA, White CA, Stabin M, Dunn WL, Erwin W, Dahlbom M, et al.
968 Phase I/II 90Y ZevalinTM (90yttrium ibritumomab tiuxetan, IDEC-Y2B8)
969 radioimmunotherapy dosimetry results in relapsed or refractory non-Hodgkin's
970 lymphoma. Eur J Nucl Med 2000;27(7):766-77.

9. Wiseman GA, White CA, Sparks RB, Erwin WD, Podoloff DA, Lamonica DA, et al. Biodistribution and dosimetry results from a phase III prospectively randomized controlled trial of Zevalin radioimmunotherapy for low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. Crit Rev Oncol Hematol 2001;39(1-2):181-94.

10. Siegel J, Lee R, Pawlyk D, Horowitz J, Sharkey R, Goldenberg D. Sacral scintigraphy for bone marrow dosimetry in radioimmunotherapy. Int J Appl Radiat Instr 1989;16(Part B):553-9.

11. Witzig TE, Flinn IW, Gordon LI, Emmanouilides C, Czuczman MS,Saleh MN, et al. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's Lymphoma. J. Clin Oncol 2002 in press.

12. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphoma. J Clin Oncol 1999;17(4):1244-53.

13. Witzig TE, Gordon LI, Cabanillas F, Czuczman MS, Emmanouilides C, Joyce R, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-hodgkins lymphoma. J Clin Oncol. 2002;20(10):2453-63.

14. Wiseman GA, Gordon LI, Multani PS, Witzig TE, Spies S, Bartlett NL, et al. Ibritumomab tiuxetan radioimmunotherapy for relapsed or refractory non-hodgkins lymphoma patients with mild thrombocytopenia: a phase II multicenter trial. Blood 2002; 99(12):4336-4342.

Rx Only

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

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

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