

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**125011**

**LABELING**

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Rx Only

**BEXXAR®**

**Tositumomab and Iodine I 131 Tositumomab**

**WARNINGS**

**Hypersensitivity Reactions, including Anaphylaxis:** Medications for the treatment of severe hypersensitivity reactions should be available for immediate use. Patients who develop severe hypersensitivity reactions should have infusions of the BEXXAR therapeutic regimen discontinued and receive medical attention (See **WARNINGS**).

**Prolonged and Severe Cytopenias:** The majority of patients who received the BEXXAR therapeutic regimen experienced severe thrombocytopenia and neutropenia. The BEXXAR therapeutic regimen should not be administered to patients with >25% lymphoma marrow involvement and/or impaired bone marrow reserve (See **WARNINGS** and **ADVERSE REACTIONS**).

**Pregnancy Category X:** The BEXXAR therapeutic regimen can cause fetal harm when administered to a pregnant woman.

**Special requirements:** The BEXXAR therapeutic regimen (Tositumomab and Iodine I 131 Tositumomab) contains a radioactive component and should be administered only by physicians and other health care professionals qualified by training in the safe use and handling of therapeutic radionuclides. The BEXXAR therapeutic regimen should be administered only by physicians who are in the process of being or have been certified by Corixa Corporation in dose calculation and administration of the BEXXAR therapeutic regimen.

**DESCRIPTION**

The BEXXAR therapeutic regimen (Tositumomab and Iodine I 131 Tositumomab) is an anti-neoplastic radioimmunotherapeutic monoclonal

29 antibody-based regimen composed of the monoclonal antibody,  
30 Tositumomab, and the radiolabeled monoclonal antibody, Iodine I 131  
31 Tositumomab.

## 32 **Tositumomab**

33 Tositumomab is a murine IgG<sub>2a</sub> lambda monoclonal antibody directed  
34 against the CD20 antigen, which is found on the surface of normal and  
35 malignant B lymphocytes. Tositumomab is produced in an antibiotic-free  
36 culture of mammalian cells and is composed of two murine gamma 2a  
37 heavy chains of 451 amino acids each and two lambda light chains of 220  
38 amino acids each. The approximate molecular weight of Tositumomab is  
39 150 kD.

40 Tositumomab is supplied as a sterile, pyrogen-free, clear to opalescent,  
41 colorless to slightly yellow, preservative-free liquid concentrate. It is  
42 supplied at a nominal concentration of 14 mg/mL Tositumomab in 35 mg  
43 and 225 mg single-use vials. The formulation contains 10% (w/v) maltose,  
44 145 mM sodium chloride, 10 mM phosphate, and Water for Injection, USP.  
45 The pH is approximately 7.2.

## 46 **Iodine I 131 Tositumomab**

47 Iodine I 131 Tositumomab is a radio-iodinated derivative of Tositumomab  
48 that has been covalently linked to Iodine-131. Unbound radio-iodine and  
49 other reactants have been removed by chromatographic purification steps.  
50 Iodine I 131 Tositumomab is supplied as a sterile, clear, preservative-free  
51 liquid for IV administration. The dosimetric dosage form is supplied at  
52 nominal protein and activity concentrations of 0.1 mg/mL and 0.61 mCi/mL  
53 (at date of calibration), respectively. The therapeutic dosage form is  
54 supplied at nominal protein and activity concentrations of 1.1 mg/mL and  
55 5.6 mCi/mL (at date of calibration), respectively. The formulation for the  
56 dosimetric and the therapeutic dosage forms contains 5.0%–6.0% (w/v)  
57 povidone, 1–2 mg/mL maltose (dosimetric dose) or 9–15 mg/mL maltose  
58 (therapeutic dose), 0.85–0.95 mg/mL sodium chloride, and 0.9–1.3 mg/mL  
59 ascorbic acid. The pH is approximately 7.0.

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61 **BEXXAR Therapeutic Regimen**

62 The BEXXAR therapeutic regimen is administered in two discrete steps:  
63 the dosimetric and therapeutic steps. Each step consists of a sequential  
64 infusion of Tositumomab followed by Iodine I 131 Tositumomab. The  
65 therapeutic step is administered 7-14 days after the dosimetric step. The  
66 Bexxar therapeutic regimen is supplied in two distinct package  
67 configurations as follows:

68 **BEXXAR Dosimetric Packaging**

- 69 • A carton containing two single-use 225 mg vials and one single-use  
70 35 mg vial of Tositumomab supplied by McKesson Biosciences and
- 71 • A package containing a single-use vial of Iodine I 131 Tositumomab  
72 (0.61mCi/mL at calibration), supplied by MDS Nordion.

73 **BEXXAR Therapeutic Packaging**

- 74 • A carton containing two single-use 225 mg vials and one single-use  
75 35 mg vial of Tositumomab, supplied by McKesson Biosciences  
76 and
- 77 • A package containing one or two single-use vials of Iodine I 131  
78 Tositumomab (5.6 mCi/mL at calibration), supplied by MDS  
79 Nordion.

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81 **Physical/Radiochemical Characteristics of Iodine-131**

82 Iodine-131 decays with beta and gamma emissions with a physical  
83 half-life of 8.04 days. The principal beta emission has a mean energy of  
84 191.6 keV and the principal gamma emission has an energy of 364.5 keV  
85 (Ref 1).

86 **External Radiation:** The specific gamma ray constant for Iodine-131 is  
87 2.2 R/millicurie hour at 1 cm. The first half-value layer is 0.24 cm lead.  
88 (Pb) shielding. A range of values is shown in Table 1 for the relative  
89 attenuation of the radiation emitted by this radionuclide that results from  
90 interposition of various thicknesses of Pb. To facilitate control of the

91 radiation exposure from this radionuclide, the use of a 2.55 cm thickness of  
92 Pb will attenuate the radiation emitted by a factor of about 1,000.

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**Table 1**  
**Radiation Attenuation by Lead Shielding**

<b>Shield Thickness (Pb) cm</b>	<b>Attenuation Factor</b>
0.24	0.5
0.89	10 <sup>-1</sup>
1.60	10 <sup>-2</sup>
2.55	10 <sup>-3</sup>
3.7	10 <sup>-4</sup>

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The fraction of Iodine-131 radioactivity that remains in the vial after the date of calibration is calculated as follows:

Fraction of remaining radioactivity of Iodine-131 after x days =  $2^{-(x/8.04)}$   
Physical decay is presented in Table 2.

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**Table 2**  
**Physical Decay Chart: Iodine-131: Half-Life 8.04 Days**

<b>Days</b>	<b>Fraction Remaining</b>
0*	1.000
1	0.917
2	0.842
3	0.772
4	0.708
5	0.650
6	0.596
7	0.547
8	0.502
9	0.460
10	0.422
11	0.387
12	0.355
13	0.326
14	0.299

104 \*(Calibration day)

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## **CLINICAL PHARMACOLOGY**

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### **General Pharmacology**

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108 Tositumomab binds specifically to the CD20 (human B-lymphocyte-  
109 restricted differentiation antigen, Bp 35 or B1) antigen. This antigen is a  
110 transmembrane phosphoprotein expressed on pre-B lymphocytes and at  
111 higher density on mature B lymphocytes (Ref. 2). The antigen is also  
112 expressed on >90% of B-cell non-Hodgkin's lymphomas (NHL) (Ref. 3).  
113 The recognition epitope for Tositumomab is found within the extracellular  
114 domain of the CD20 antigen. CD20 does not shed from the cell surface  
and does not internalize following antibody binding (Ref. 4).

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116 **Mechanism of Action:** Possible mechanisms of action of the BEXXAR  
117 therapeutic regimen include induction of apoptosis (Ref. 5), complement-  
118 dependent cytotoxicity (CDC) (Ref. 6), and antibody-dependent cellular  
119 cytotoxicity (ADCC) (Ref. 5) mediated by the antibody. Additionally, cell  
death is associated with ionizing radiation from the radioisotope.

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121 **Pharmacokinetics/Pharmacodynamics**

122 The phase 1 study of Iodine I 131 Tositumomab determined that a 475 mg  
123 predose of unlabeled antibody decreased splenic targeting and increased  
124 the terminal half-life of the radiolabeled antibody. The median blood  
125 clearance following administration of 485 mg of Tositumomab in  
126 110 patients with NHL was 68.2 mg/hr (range: 30.2–260.8 mg/hr).  
127 Patients with high tumor burden, splenomegaly, or bone marrow  
128 involvement were noted to have a faster clearance, shorter terminal half-  
129 life, and larger volume of distribution. The total body clearance, as  
130 measured by total body gamma camera counts, was dependent on the  
131 same factors noted for blood clearance. Patient-specific dosing, based on  
132 total body clearance, provided a consistent radiation dose, despite  
133 variable pharmacokinetics, by allowing each patient's administered activity  
134 to be adjusted for individual patient variables.

135 Elimination of Iodine-131 occurs by decay (see Table 2) and excretion in  
136 the urine. Urine was collected for 49 dosimetric doses. After 5 days, the  
137 whole body clearance was 67% of the injected dose. Ninety-eight percent  
138 of the clearance was accounted for in the urine.

139 Administration of the BEXXAR therapeutic regimen results in sustained  
140 depletion of circulating CD20 positive cells. The impact of administration  
141 of the BEXXAR therapeutic regimen on circulating CD20 positive cells was  
142 assessed in two clinical studies, one conducted in chemotherapy naïve  
143 patients and one in heavily pretreated patients. The assessment of  
144 circulating lymphocytes did not distinguish normal from malignant cells.  
145 Consequently, assessment of recovery of normal B cell function was not  
146 directly assessed. At seven weeks, the median number of circulating  
147 CD20 positive cells was zero (range: 0 - 490 cells/ mm<sup>3</sup>). Lymphocyte  
148 recovery began at approximately 12 weeks following treatment. Among  
149 patients who had CD20 positive cell counts recorded at baseline and at 6  
150 months, 8 of 58 (14%) chemotherapy naïve patients had CD20 positive  
151 cell counts below normal limits at six months and 6 of 19 (32%) heavily  
152 pretreated patients had CD20 positive cell counts below normal limits at  
153 six months. There was no consistent effect of the BEXXAR therapeutic  
154 regimen on post-treatment serum IgG, IgA, or IgM levels.

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### **Radiation Dosimetry**

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Estimations of radiation-absorbed doses for Iodine I 131 Tositumomab were performed using sequential whole body images and the MIRDOSE 3 software program. Patients with apparent thyroid, stomach, or intestinal imaging were selected for organ dosimetry analyses. The estimated radiation-absorbed doses to organs and marrow from a course of the BEXXAR therapeutic regimen are presented in Table 3.

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Table 3

## Estimated Radiation-Absorbed Organ Doses

		BEXXAR	BEXXAR
		mGy/MBq	mGy/MBq
From Organ ROIs		Median	Range
	Thyroid	2.71	1.4 - 6.2
	Kidneys	1.96	1.5 - 2.5
	ULI Wall	1.34	0.8 - 1.7
	LLI Wall	1.30	0.8 - 1.6
	Heart Wall	1.25	0.5 - 1.8
	Spleen	1.14	0.7 - 5.4
	Testes	0.83	0.3 - 1.3
	Liver	0.82	0.6 - 1.3
	Lungs	0.79	0.5 - 1.1
	Red Marrow	0.65	0.5 - 1.1
	Stomach Wall	0.40	0.2 - 0.8
From Whole Body ROIs			
	Urine Bladder Wall	0.64	0.6 - 0.9
	Bone Surfaces	0.41	0.4 - 0.6
	Pancreas	0.31	0.2 - 0.4
	Gall Bladder Wall	0.29	0.2 - 0.3
	Adrenals	0.28	0.2 - 0.3
	Ovaries	0.25	0.2 - 0.3
	Small Intestine	0.23	0.2 - 0.3
	Thymus	0.22	0.1 - 0.3
	Uterus	0.20	0.2 - 0.2
	Muscle	0.18	0.1 - 0.2
	Breasts	0.16	0.1 - 0.2
	Skin	0.13	0.1 - 0.2
	Brain	0.13	0.1 - 0.2
	Total Body	0.24	0.2 - 0.3

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### CLINICAL STUDIES

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The efficacy of the BEXXAR therapeutic regimen was evaluated in a multi-center, single-arm study in patients with low grade or transformed low-grade or follicular large-cell lymphoma whose disease had not responded to or had progressed after Rituximab therapy. Determination of clinical benefit of the BEXXAR therapeutic regimen was based on evidence of durable responses without evidence of an effect on survival. All patients in the study were required to have received prior treatment with at least four doses of Rituximab without an objective response, or to have progressed following treatment. Patients were also required to have a platelet count  $\geq 100,000/\text{mm}^3$ ; an average of  $\leq 25\%$  of the intratrabecular marrow space involved by lymphoma, and no evidence of progressive disease arising in a field irradiated with  $>3500$  cGy within 1 year of completion of irradiation.

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Forty patients initiated treatment with the BEXXAR therapeutic regimen. The median age was 57 (range: 35–78); the median time from diagnosis to protocol entry was 50 months (range: 11–70); and the median number of prior chemotherapy regimens was 4 (range: 1–11). Twenty-four patients had disease that did not respond to their last treatment with Rituximab, 11 patients had disease that responded to Rituximab for less than 6 months, and five patients had disease that responded to Rituximab, with a duration of response of 6 months or greater. Overall, 35 of the 40 patients met the definition of “Rituximab refractory”, defined as no response or a response of less than 6 months duration. Table 4 summarizes efficacy outcome data from this study, as determined by an independent panel that reviewed patient records and radiologic studies. The median duration of follow-up was 26 months for all patients and 26 months for the Rituximab-refractory subset.

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**Table 4**  
**Efficacy Outcomes Patients**

	Objective Responses to the BEXXAR Therapeutic Regimen in Patients Refractory to Rituximab		Objective Responses to the BEXXAR Therapeutic Regimen in All Patients	
	Response Rate (%) (95% CI <sup>a</sup> ) (n=35)	Median duration of response (Mos) (Range)	Response Rate (%) (95% CI <sup>a</sup> ) (n=40)	Median Duration of Response (Mos) (Range)
Overall Response	63% (45%, 79%)	25 (4+, 35+)	68% (51%, 81%)	16 (1+, 35+)
Complete Response <sup>c</sup>	29% (15%, 46%)	NR <sup>b</sup> (4, 35+)	33% (19%, 49%)	NR (4, 35+)
<sup>a</sup> C.I. = Confidence Interval <sup>b</sup> NR = Not reached <sup>c</sup> Complete response rate = Pathologic and clinical complete responses				

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200 The results of this study were supported by demonstration of durable  
 201 objective responses in four single arm studies enrolling 190 patients  
 202 evaluable for efficacy with Rituximab-naïve, follicular non-Hodgkin's  
 203 lymphoma with or without transformation, who had relapsed following or  
 204 were refractory to chemotherapy. In these studies, the overall response  
 205 rates ranged from 47% to 64% and the median durations of response  
 206 ranged from 12 to 18 months.

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## 208 INDICATIONS AND USAGE

209 The BEXXAR therapeutic regimen (Tositumomab and Iodine I 131  
 210 Tositumomab) is indicated for the treatment of patients with CD20  
 211 positive, follicular, non-Hodgkin's lymphoma, with and without  
 212 transformation, whose disease is refractory to Rituximab and has relapsed  
 213 following chemotherapy. The BEXXAR therapeutic regimen is not  
 214 indicated for the initial treatment of patients with CD20 positive non-  
 215 Hodgkin's lymphoma.

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The BEXXAR therapeutic regimen is intended as a single course of  
 treatment. The safety of multiple courses of the BEXXAR therapeutic

218 regimen, or combination of this regimen with other forms of irradiation or  
219 chemotherapy, has not been evaluated.

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## 221 CONTRAINDICATIONS

222 The BEXXAR therapeutic regimen is contraindicated in patients with  
223 known hypersensitivity to murine proteins or any other component of the  
224 BEXXAR therapeutic regimen.

## 225 PREGNANCY CATEGORY X

226 Iodine I 131 Tositumomab (a component of the BEXXAR therapeutic  
227 regimen) is contraindicated for use in women who are pregnant. Iodine-  
228 131 may cause harm to the fetal thyroid gland when administered to  
229 pregnant women. Review of the literature has shown that transplacental  
230 passage of radioiodide may cause severe, and possibly irreversible,  
231 hypothyroidism in neonates. While there are no adequate and well-  
232 controlled studies of the BEXXAR therapeutic regimen in pregnant  
233 animals or humans, use of the BEXXAR therapeutic regimen in women of  
234 childbearing age should be deferred until the possibility of pregnancy has  
235 been ruled out. If the patient becomes pregnant while being treated with  
236 the BEXXAR therapeutic regimen, the patient should be apprised of the  
237 potential hazard to the fetus. (See **BOXED WARNING, Pregnancy**  
238 **Category X**).

## 239 WARNINGS

240 **Prolonged and Severe Cytopenias (See BOXED WARNINGS;**  
241 **ADVERSE REACTIONS, Hematologic Events):**

242 The most common adverse reactions associated with the BEXXAR  
243 therapeutic regimen were severe or life-threatening cytopenias (NCI CTC  
244 grade 3 or 4) with 71% of the 230 patients enrolled in clinical studies  
245 experiencing grade 3 or 4 cytopenias. These consisted primarily of grade  
246 3 or 4 thrombocytopenia (53%) and grade 3 or 4 neutropenia (63%). The  
247 time to nadir was 4 to 7 weeks and the duration of cytopenias was  
248 approximately 30 days. Thrombocytopenia, neutropenia, and anemia  
249 persisted for more than 90 days following administration of the BEXXAR

250 therapeutic regimen in 16 (7%), 15 (7%), and 12 (5%) patients  
251 respectively (this includes patients with transient recovery followed by  
252 recurrent cytopenia). Due to the variable nature in the onset of cytopenias,  
253 complete blood counts should be obtained weekly for 10-12 weeks. The  
254 sequelae of severe cytopenias were commonly observed in the clinical  
255 studies and included infections (45% of patients), hemorrhage (12%), a  
256 requirement for growth factors (12% G- or GM-CSF; 7% Epoetin alfa) and  
257 blood product support (15% platelet transfusions; 16% red blood cell  
258 transfusions). Prolonged cytopenias may also influence subsequent  
259 treatment decisions.

260 The safety of the BEXXAR therapeutic regimen has not been established  
261 in patients with >25% lymphoma marrow involvement, platelet count  
262 <100,000 cells/mm<sup>3</sup> or neutrophil count <1,500 cells/mm<sup>3</sup>.

263 **Hypersensitivity Reactions Including Anaphylaxis (See BOXED**  
264 **WARNINGS; ADVERSE REACTIONS, Immunogenicity):**

265 Hypersensitivity reactions, including anaphylaxis, were reported during  
266 and following administration of the BEXXAR therapeutic regimen.  
267 Emergency supplies including medications for the treatment of  
268 hypersensitivity reactions, e.g., epinephrine, antihistamines and  
269 corticosteroids, should be available for immediate use in the event of an  
270 allergic reaction during administration of the BEXXAR therapeutic  
271 regimen. Patients who have received murine proteins should be screened  
272 for human anti-mouse antibodies (HAMA). Patients who are positive for  
273 HAMA may be at increased risk of anaphylaxis and serious  
274 hypersensitivity reactions during administration of the BEXXAR  
275 therapeutic regimen.

276 **Secondary Malignancies:** Myelodysplastic syndrome (MDS) and/or  
277 acute leukemia were reported in 8% (19/230) of patients enrolled in the  
278 clinical studies and 2% (13/765) of patients included in expanded access  
279 programs, with median follow-up of 35 and 20 months, respectively.  
280 Among the 32 reported new cases, the median time to development of  
281 MDS/leukemia was 27 months following treatment; however, the  
282 cumulative rate continues to increase. The pretreatment characteristics  
283 (e.g., median age, number of prior chemotherapy regimens) were similar

284 in patients developing MDS/secondary leukemias as compared with those  
285 who did not. Additional malignancies were also reported in 52 of the 995  
286 patients enrolled in clinical studies or included in the expanded access  
287 program. Approximately half of these were non-melanomatous skin  
288 cancers. The remainder which occurred in 2 or more patients included  
289 breast cancer, lung cancer, bladder cancer, head and neck cancer, colon  
290 cancer and melanoma, in order of decreasing incidence. The relative risk  
291 of developing secondary malignancies in patients receiving the BEXXAR  
292 therapeutic regimen over the background rate in this population cannot be  
293 determined, due to the absence of controlled studies (See **ADVERSE**  
294 **REACTIONS**).

295 **Pregnancy Category X:** (See **BOXED WARNINGS**;  
296 **CONTRAINDICATIONS**).

297 **Hypothyroidism:** Administration of the BEXXAR therapeutic regimen  
298 may result in hypothyroidism (See **ADVERSE REACTIONS**,  
299 **Hypothyroidism**). Thyroid-blocking medications should be initiated at  
300 least 24 hours before receiving the dosimetric dose and continued until  
301 14 days after the therapeutic dose (see **DOSAGE and**  
302 **ADMINISTRATION**). All patients must receive thyroid blocking agents;  
303 any patient who is unable to tolerate thyroid blocking agents should not  
304 receive the BEXXAR therapeutic regimen. Patients should be evaluated  
305 for signs and symptoms of hypothyroidism and screened for biochemical  
306 evidence of hypothyroidism annually.

## 307 308 **PRECAUTIONS**

309 **Radionuclide Precautions:** Iodine I 131 Tositumomab is radioactive.  
310 Care should be taken, consistent with the institutional radiation safety  
311 practices and applicable federal guidelines, to minimize exposure of  
312 medical personnel and other patients.

313 **Renal Function:** Iodine I 131 Tositumomab and Iodine-131 are excreted  
314 primarily by the kidneys. Impaired renal function may decrease the rate of  
315 excretion of the radiolabeled iodine and increase patient exposure to the  
316 radioactive component of the BEXXAR therapeutic regimen. There are no

317 data regarding the safety of administration of the BEXXAR therapeutic  
318 regimen in patients with impaired renal function.

319 **Immunization:** The safety of immunization with live viral vaccines  
320 following administration of the BEXXAR therapeutic regimen has not been  
321 studied. The ability of patients who have received the BEXXAR  
322 therapeutic regimen to generate a primary or anamnestic humoral  
323 response to any vaccine has not been studied.

324 **Information for Patients:** Prior to administration of the BEXXAR  
325 therapeutic regimen, patients should be advised that they will have a  
326 radioactive material in their body for several days upon their release from  
327 the hospital or clinic. After discharge, patients should be provided with  
328 both oral and written instructions for minimizing exposure of family  
329 members, friends and the general public. Patients should be given a copy  
330 of the written instructions for use as a reference for the recommended  
331 precautionary actions.

332 The pregnancy status of women of childbearing potential should be  
333 assessed and these women should be advised of the potential risks to the  
334 fetus (See **CONTRAINDICATIONS**). Women who are breastfeeding  
335 should be instructed to discontinue breastfeeding and should be apprised  
336 of the resultant potential harmful effects to the infant if these instructions  
337 are not followed.

338 Patients should be advised of the potential risk of toxic effects on the male  
339 and female gonads following the BEXXAR therapeutic regimen, and be  
340 instructed to use effective contraceptive methods during treatment and for  
341 12 months following the administration of the BEXXAR therapeutic  
342 regimen.

343  
344 Patients should be informed of the risks of hypothyroidism and be advised  
345 of the importance of compliance with thyroid blocking agents and need for  
346 life-long monitoring.

347  
348 Patients should be informed of the possibility of developing a HAMA  
349 immune response and that HAMA may affect the results of *in vitro* and

350 *in vivo* diagnostic tests as well as results of therapies that rely on murine  
351 antibody technology.

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353 Patients should be informed of the risks of cytopenias and symptoms  
354 associated with cytopenia, the need for frequent monitoring for up to  
355 12 weeks after treatment, and the potential for persistent cytopenias  
356 beyond 12 weeks.

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358 Patients should be informed that certain anti-neoplastic agents used in the  
359 treatment of malignancy, e.g., alkylating agents, topoisomerase II  
360 inhibitors, and ionizing radiation, have been associated with the  
361 development of MDS, secondary leukemia and solid tumors. Patients  
362 should be informed that MDS, secondary leukemia, and solid tumors have  
363 also been observed in patients receiving the BEXXAR therapeutic  
364 regimen.

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366 **Laboratory Monitoring:** A complete blood count (CBC) with differential  
367 and platelet count should be obtained prior to, and at least weekly  
368 following administration of the BEXXAR therapeutic regimen. Weekly  
369 monitoring of blood counts should continue for a minimum of 10 weeks or,  
370 if persistent, until severe cytopenias have completely resolved. More  
371 frequent monitoring is indicated in patients with evidence of moderate or  
372 more severe cytopenias (see **BOXED WARNINGS** and **WARNINGS**).  
373 Thyroid stimulating hormone (TSH) level should be monitored before  
374 treatment and annually thereafter. Serum creatinine levels should be  
375 measured immediately prior to administration of the BEXXAR therapeutic  
376 regimen.

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378 **Drug Interactions:** No formal drug interaction studies have been  
379 performed. Due to the frequent occurrence of severe and prolonged  
380 thrombocytopenia, the potential benefits of medications that interfere with  
381 platelet function and/or anticoagulation should be weighed against the  
potential increased risk of bleeding and hemorrhage.

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383 **Drug/Laboratory Test Interactions:** Administration of the BEXXAR  
therapeutic regimen may result in the development of human anti-murine



384 antibodies (HAMA). The presence of HAMA may affect the accuracy of the  
385 results of *in vitro* and *in vivo* diagnostic tests and may affect the toxicity  
386 profile and efficacy of therapeutic agents that rely on murine antibody  
387 technology. Patients who are HAMA positive may be at increased risk for  
388 serious allergic reactions and other side effects if they undergo *in vivo*  
389 diagnostic testing or treatment with murine monoclonal antibodies.

390 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No long-term  
391 animal studies have been performed to establish the carcinogenic or  
392 mutagenic potential of the BEXXAR therapeutic regimen or to determine  
393 its effects on fertility in males or females. However, radiation is a potential  
394 carcinogen and mutagen. Administration of the BEXXAR therapeutic  
395 regimen results in delivery of a significant radiation dose to the testes.  
396 The radiation dose to the ovaries has not been established. There have  
397 been no studies to evaluate whether administration of the BEXXAR  
398 therapeutic regimen causes hypogonadism, premature menopause,  
399 azoospermia and/or mutagenic alterations to germ cells. There is a  
400 potential risk that the BEXXAR therapeutic regimen may cause toxic  
401 effects on the male and female gonads. Effective contraceptive methods  
402 should be used during treatment and for 12 months following  
403 administration of the BEXXAR therapeutic regimen.

404 **Pregnancy Category X: See CONTRAINDICATIONS; WARNINGS.**

405 **Nursing Mothers:** Radioiodine is excreted in breast milk and may reach  
406 concentrations equal to or greater than maternal plasma concentrations.  
407 Immunoglobulins are also known to be excreted in breast milk. The  
408 absorption potential and potential for adverse effects of the monoclonal  
409 antibody component (Tositumomab) in the infant are not known.  
410 Therefore, formula feedings should be substituted for breast feedings  
411 before starting treatment. Women should be advised to discontinue  
412 nursing.

413 **Pediatric Use:** The safety and effectiveness of the BEXXAR therapeutic  
414 regimen in children have not been established.

415 **Geriatric Use:** Clinical studies of the BEXXAR therapeutic regimen did  
416 not include sufficient numbers of patients aged 65 and over to determine  
417 whether they respond differently from younger patients. In clinical studies,  
418 230 patients received the BEXXAR therapeutic regimen at the  
419 recommended dose. Of these, 27% (61 patients) were age 65 or older  
420 and 4% (10 patients) were age 75 or older. Across all studies, the overall  
421 response rate was lower in patients age 65 and over (41% vs. 61%) and  
422 the duration of responses were shorter (10 months vs. 16 months),  
423 however these findings are primarily derived from 2 of the 5 studies.  
424 While the incidence of severe hematologic toxicity was lower, the duration  
425 of severe hematologic toxicity was longer in those age 65 or older as  
426 compared to patients less than 65 years of age. Due to the limited  
427 experience greater sensitivity of some older individuals cannot be ruled  
428 out.

429 **ADVERSE REACTIONS**

430 The most serious adverse reactions observed in the clinical trials were  
431 severe and prolonged cytopenias and the sequelae of cytopenias which  
432 included infections (sepsis), and hemorrhage in thrombocytopenic  
433 patients, allergic reactions (bronchospasm and angioedema), secondary  
434 leukemia and myelodysplasia. (See BOXED WARNINGS and  
435 WARNINGS).

436 The most common adverse reactions occurring in the clinical trials  
437 included neutropenia, thrombocytopenia, and anemia that are both  
438 prolonged and severe. Less common but severe adverse reactions  
439 included pneumonia, pleural effusion and dehydration.

440 Data regarding adverse events were primarily obtained in 230 patients  
441 with non-Hodgkin's lymphoma enrolled in five clinical trials using the  
442 recommended dose and schedule. Patients had a median follow-up of 35  
443 months and 79% of the patients were followed at least 12 months for  
444 survival and selected adverse events. Patients had a median of 3 prior  
445 chemotherapy regimens, a median age of 55 years, 60% male, 27% had  
446 transformation to a higher grade histology, 29% were intermediate grade  
447 and 2% high grade histology (IWF) and 68% had Ann Arbor stage IV

448 disease. Patients enrolled in these studies were not permitted to have  
449 prior hematopoietic stem cell transplantation or irradiation to more than  
450 25% of the red marrow. In the expanded access program, which included  
451 765 patients, data regarding clinical serious adverse events and HAMA  
452 and TSH levels were used to supplement the characterization of delayed  
453 adverse events. (See **ADVERSE REACTIONS, Hypothyroidism,**  
454 **Secondary Leukemia and Myelodysplastic Syndrome,**  
455 **Immunogenicity.**)

456 Because clinical trials are conducted under widely varying conditions,  
457 adverse reaction rates observed in the clinical trials of a drug cannot be  
458 directly compared to rates in the clinical trials of another drug and may not  
459 reflect the rates observed in practice. The adverse reaction information  
460 from clinical trials does, however, provide a basis for identifying the  
461 adverse events that appear to be related to drug use and for  
462 approximating rates.

463 **Hematologic Events:** Hematologic toxicity was the most frequently  
464 observed adverse event in clinical trials with the BEXXAR therapeutic  
465 regimen (Table 6). Sixty-three (27%) of 230 patients received one or  
466 more hematologic supportive care measures following the therapeutic  
467 dose: 12% received G-CSF; 7% received Epoetin alfa; 15% received  
468 platelet transfusions; and 16% received packed red blood cell  
469 transfusions. Twenty-eight (12%) patients experienced hemorrhagic  
470 events; the majority were mild to moderate.

471 **Infectious Events:** One hundred and four of the 230 (45%) patients  
472 experienced one or more adverse events possibly related to infection.  
473 The majority were viral (e.g. rhinitis, pharyngitis, flu symptoms, or herpes)  
474 or other minor infections. Nineteen of 230 (8%) patients experienced  
475 infections that were considered serious because the patient was  
476 hospitalized to manage the infection. Documented infections included  
477 pneumonia, bacteremia, septicemia, bronchitis, and skin infections.

478 **Hypersensitivity Reactions:** Fourteen patients (6%) experienced one or  
479 more of the following adverse events: allergic reaction, face edema,

480 injection site hypersensitivity, anaphylactoid reaction, laryngismus, and  
481 serum sickness.

482

483 **Gastrointestinal toxicity:** Eighty-seven patients (38%) experienced one  
484 or more gastrointestinal adverse events, including nausea, emesis,  
485 abdominal pain, and diarrhea. These events were temporally related to  
486 the infusion of the antibody. Nausea, vomiting, and abdominal pain were  
487 often reported within days of infusion, whereas diarrhea was generally  
488 reported days to weeks after infusion.

489

490 **Infusional Toxicity:** A constellation of symptoms, including fever, rigors  
491 or chills, sweating, hypotension, dyspnea, bronchospasm, and nausea,  
492 have been reported during or within 48 hours of infusion. Sixty-seven  
493 patients (29%) reported fever, rigors/chills, or sweating within 14 days  
494 following the dosimetric dose. Although all patients in the clinical studies  
495 received pretreatment with acetaminophen and an antihistamine, the  
496 value of premedication in preventing infusion-related toxicity was not  
497 evaluated in any of the clinical studies. Infusional toxicities were managed  
498 by slowing and/or temporarily interrupting the infusion. Symptomatic  
499 management was required in more severe cases. Adjustment of the rate  
500 of infusion to control adverse reactions occurred in 16 patients (7%);  
501 seven patients required adjustments for only the dosimetric infusion, two  
502 required adjustments for only the therapeutic infusion, and seven required  
503 adjustments for both the dosimetric and the therapeutic infusions.  
504 Adjustments included reduction in the rate of infusion by 50%, temporary  
505 interruption of the infusion, and in 2 patients, infusion was permanently  
506 discontinued.

507 Table 5 lists clinical adverse events that occurred in  $\geq 5\%$  of patients.

508 Table 6 provides a detailed description of the hematologic toxicity.

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**Table 5**  
**Incidence of Clinical Adverse Experiences Regardless of Relationship to**  
**Study Drug Occurring in  $\geq 5\%$  of the Patients Treated with BEXXAR**  
**Therapeutic Regimen<sup>a</sup>**  
**(N = 230)**

Body System Preferred Term	All Grades	Grade 3/4
Total	(96%)	(48%)
<b>Non-Hematologic AEs</b>		
<b>Body as a Whole</b>	81%	12%
Asthenia	46%	2%
Fever	37%	2%
Infection <sup>b</sup>	21%	<1%
Pain	19%	1%
Chills	18%	1%
Headache	16%	0%
Abdominal pain	15%	3%
Back pain	8%	1%
Chest pain	7%	0%
Neck pain	6%	1%
<b>Cardiovascular System</b>	26%	3%
Hypotension	7%	1%
Vasodilatation	5%	0%
<b>Digestive System</b>	56%	9%
Nausea	36%	3%
Vomiting	15%	1%
Anorexia	14%	0%
Diarrhea	12%	0%
Constipation	6%	1%
Dyspepsia	6%	<1%
<b>Endocrine System</b>	7%	0%
Hypothyroidism	7%	0%
<b>Metabolic and Nutritional Disorders</b>	21%	3%
Peripheral edema	9%	0%
Weight loss	6%	<1%
<b>Musculoskeletal System</b>	23%	3%
Myalgia	13%	<1%
Arthralgia	10%	1%
<b>Nervous System</b>	26%	3%
Dizziness	5%	0%
Somnolence	5%	0%

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**Table 5 (cont'd)**  
**Incidence of Clinical Adverse Experiences Regardless of Relationship to**  
**Study Drug Occurring in  $\geq 5\%$  of the Patients Treated with BEXXAR**  
**Therapeutic Regimen<sup>a</sup>**  
**(N =230)**

<b>Respiratory System</b>	44%	8%
Cough increased	21%	1%
Pharyngitis	12%	0%
Dyspnea	11%	3%
Rhinitis	10%	0%
Pneumonia	6%	0%
<b>Skin and Appendages</b>	44%	5%
Rash	17%	<1%
Pruritus	10%	0%
Sweating	8%	<1%

<sup>a</sup> Excludes laboratory derived hematologic adverse events (See Table 6).

<sup>b</sup> The COSTART term for infection includes a subset of infections (e.g., upper respiratory infection). Other terms are mapped to preferred terms (e.g., pneumonia and sepsis). For a more inclusive summary see ADVERSE REACTIONS, Infectious Events.

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**Table 6**  
**Hematologic Toxicity<sup>a</sup> (N=230)**

Endpoint	Values
<b><u>Platelets</u></b>	
Median nadir (cells/mm <sup>3</sup> )	43,000
Per patient incidence <sup>a</sup> platelets <50,000/mm <sup>3</sup>	53% (n=123)
Median <sup>b</sup> duration of platelets <50,000/mm <sup>3</sup> (days)	32
Grade 3/4 without recovery to Grade 2, N (%)	16 (7%)
Per patient incidence <sup>c</sup> platelets <25,000/mm <sup>3</sup>	21% (n=47)
<b><u>ANC</u></b>	
Median nadir (cells/mm <sup>3</sup> )	690
Per patient incidence <sup>a</sup> ANC<1,000 cells/mm <sup>3</sup> (%)	63% (n=145)
Median <sup>b</sup> duration of ANC<1,000 cells/mm <sup>3</sup> (days)	31
Grade 3/4 without recovery to Grade 2, N (%)	15 (7%)
Per patient incidence <sup>c</sup> ANC< 500 cells/mm <sup>3</sup> , N (%)	25% (n=57)
<b><u>Hemoglobin</u></b>	
Median nadir (gm/dL)	10
Per patient incidence <sup>a</sup> < 8 gm/dL	29% (n=66)
Median <sup>b</sup> duration of hemoglobin < 8.0 gm/dL (days)	23
Grade 3/4 without recovery to Grade 2, N (%)	12 (5%)
Per patient incidence <sup>c</sup> hemoglobin <6.5 gm/dL, N (%)	5% (n=11)
<sup>a</sup> Grade 3/4 toxicity was assumed if patient was missing 2 or more weeks of hematology data between Week 5 and Week 9. <sup>b</sup> Duration of grade 3/4 of 1000+ days (censored) was assumed for those patients with undocumented grade 3/4 and no hematologic data on or after Week 9. <sup>c</sup> Grade 4 toxicity was assumed if patient had documented Grade 3 toxicity and was missing 2 or more weeks of hematology data between Week 5 and Week 9.	

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### **Delayed Adverse Reactions**

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Delayed adverse reactions, including hypothyroidism, HAMA, and myelodysplasia/leukemia, were assessed in 230 patients included in clinical studies and 765 patients included in expanded access programs. The entry characteristics of patients included from the expanded access

532 programs were similar to the characteristics of patients enrolled in the  
533 clinical studies, except that the median number of prior chemotherapy  
534 regimens was fewer (2 vs. 3) and the proportion with low-grade histology  
535 was higher (77% vs. 70%) in patients from the expanded access  
536 programs.

537 **Secondary Leukemia and Myelodysplastic Syndrome (MDS):** There  
538 were 32 new cases of MDS/secondary leukemia reported among 994  
539 (3.2%) patients included in clinical studies and expanded access  
540 programs, with a median follow-up of 21 months. The overall incidence of  
541 MDS/secondary leukemia among the 229 patients included in the clinical  
542 studies, was 8.3% (19/229), with a median follow-up of 35 months and a  
543 median time to development of MDS of 30 months. The cumulative  
544 incidence of MDS/secondary leukemia was 4.2% at 2 years and 10.7% at  
545 4 years. Among the 765 patients included in the expanded access  
546 program, where the median duration of follow-up was shorter (20 months),  
547 the overall incidence of MDS/secondary leukemia was 1.7% (13/765) and  
548 the median time to development of MDS was 23 months. In the expanded  
549 access population, the cumulative incidence of MDS/secondary leukemia  
550 was 1.4% at 2 years and 4.8% at 4 years.

551 **Secondary Malignancies:** There were 52 reports of second  
552 malignancies, excluding secondary leukemias. The most common  
553 included non-melanomatous skin cancers, breast, lung, bladder, and head  
554 and neck cancers. Some of these events included recurrence of an earlier  
555 diagnosis of cancer.

556 **Hypothyroidism:** Twelve percent (27/230) of the patients included from  
557 the clinical studies had an elevated TSH level (8%) or no TSH level  
558 obtained (4%) prior to treatment. Of the 203 patients documented to be  
559 euthyroid at entry, 137 (67%) patients had at least one follow-up TSH  
560 value. The overall incidence of hypothyroidism, in the clinical study  
561 patients was 14% with cumulative incidences of 4.2% at 6 months and  
562 8.1%, 12.6%, and 15.0% at 1, 2, and 4 years, respectively. New events  
563 have been observed up to 72 months post treatment. Twelve percent  
564 (117/990) of the patients included in clinical studies or the expanded  
565 access programs had an elevated TSH level (8%) or a history of



566           hypothyroidism (4%) prior to treatment and 5 patients had no baseline  
567           information. Of the 873 who were euthyroid at entry, 583 (67%) had at  
568           least one post-treatment TSH value obtained. With a median observation  
569           period of 18 months, 54 patients (9%) became hypothyroid as determined  
570           by elevated TSH. The cumulative incidence of hypothyroidism in the  
571           combined populations was 9.1% and 17.4% at 2 and 4 years, respectively.

572           **Immunogenicity:** Two percent (4/230) of the chemotherapy-relapsed or  
573           refractory patients included in the clinical studies had a positive serology  
574           for HAMA prior to treatment and six patients had no baseline assessment  
575           for HAMA. Of the 220 patients who were seronegative prior to treatment,  
576           219 (99.5%) had at least one post-treatment HAMA value obtained. With  
577           a median observation period for HAMA seroconversion of 6 months, 23  
578           patients (11%) seroconverted to HAMA positivity. The median time to  
579           development of HAMA was 6 months. In a study of 77 patients who were  
580           chemotherapy-naïve, the incidence of conversion to HAMA seropositivity  
581           was 70%, with a median time to development of HAMA of 27 days.

582           One percent (11/989) of the chemotherapy-relapsed or refractory patients  
583           included in the clinical studies or the expanded access program had a  
584           positive serology for HAMA prior to treatment and six patient had no  
585           baseline assessment for HAMA. Of the 978 patients who were  
586           seronegative for HAMA prior to treatment, 785 (80%) had at least one  
587           post-treatment HAMA value obtained. With a median observation period  
588           of 6 months, a total of 76 patients (10%) became seropositive for HAMA  
589           post-treatment. The median time of HAMA development was 148 days,  
590           with 45 (59%) patients seropositive for HAMA by 6 months. No patient  
591           became seropositive for HAMA more than 30 months after administration  
592           of the BEXXAR therapeutic regimen.

593           The data reflect the percentage of patients whose test results were  
594           considered positive for HAMA in an ELISA assay that detects antibodies  
595           to the Fc portion of IgG<sub>1</sub> murine immunoglobulin and are highly dependent  
596           on the sensitivity and specificity of the assay. Additionally, the observed  
597           incidence of antibody positivity in an assay may be influenced by several  
598           factors including sample handling, concomitant medications, and  
599           underlying disease. For these reasons, comparison of the incidence of

600 HAMA in patients treated with the BEXXAR therapeutic regimen with the  
601 incidence of HAMA in patients treated with other products may be  
602 misleading.

### 603 **OVERDOSAGE**

604 The maximum dose of the BEXXAR therapeutic regimen that was  
605 administered in clinical trials was 88 cGy. Three patients were treated with  
606 a total body dose of 85 cGy of Iodine I 131 Tositumomab in a dose  
607 escalation study. Two of the 3 patients developed Grade 4 toxicity of 5  
608 weeks duration with subsequent recovery. In addition, accidental  
609 overdose of the BEXXAR therapeutic regimen occurred in one patient at  
610 total body doses of 88 cGy. The patient developed Grade 3 hematologic  
611 toxicity of 18 days duration. Patients who receive an accidental overdose  
612 of Iodine I 131 Tositumomab should be monitored closely for cytopenias  
613 and radiation-related toxicity. The effectiveness of hematopoietic stem  
614 cell transplantation as a supportive care measure for marrow injury has  
615 not been studied; however, the timing of such support should take into  
616 account the pharmacokinetics of the BEXXAR therapeutic regimen and  
617 decay rate of the Iodine-131 in order to minimize the possibility of  
618 irradiation of infused hematopoietic stem cells.

619

### 620 **DOSAGE AND ADMINISTRATION**

#### 621 **Recommended Dose**

622 The BEXXAR therapeutic regimen consists of four components  
623 administered in two discrete steps: the dosimetric step, followed 7-14 days  
624 later by a therapeutic step.

625 Note: the safety of the BEXXAR therapeutic regimen was established only  
626 in the setting of patients receiving thyroid blocking agents and  
627 premedication to ameliorate/prevent infusion reactions (See **Concomitant**  
628 **Medications**).

#### 629 **Dosimetric step**

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- Tositumomab 450 mg intravenously in 50 ml 0.9% Sodium Chloride over 60 minutes. Reduce the rate of infusion by 50% for mild to moderate infusional toxicity; interrupt infusion for severe infusional toxicity. After complete resolution of severe infusional toxicity, infusion may be resumed with a 50% reduction in the rate of infusion.
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- 640
- Iodine I 131 Tositumomab (containing 5.0 mCi I-131 and 35 mg tositumomab) intravenously in 30 ml 0.9% Sodium Chloride over 20 minutes. Reduce the rate of infusion by 50% for mild to moderate infusional toxicity; interrupt infusion for severe infusional toxicity. After complete resolution of severe infusional toxicity, infusion may be resumed with a 50% reduction in the rate of infusion.

641 **Therapeutic step**

642 Note: Do not administer the therapeutic step if biodistribution is altered.  
643 (See **Assessment of Biodistribution of Iodine I 131 Tositumomab**)

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- 648
- Tositumomab 450 mg intravenously in 50 ml 0.9% Sodium Chloride over 60 minutes. Reduce the rate of infusion by 50% for mild to moderate infusional toxicity; interrupt infusion for severe infusional toxicity. After complete resolution of severe infusional toxicity, infusion may be resumed with a 50% reduction in the rate of infusion.
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- 654
- Iodine I 131 Tositumomab (See **CALCULATION OF IODINE-131 ACTIVITY FOR THE THERAPEUTIC DOSE**). Reduce the rate of infusion by 50% for mild to moderate infusional toxicity; interrupt infusion for severe infusional toxicity. After complete resolution of severe infusional toxicity, infusion may be resumed with a 50% reduction in the rate of infusion.
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- 656
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- 658
- Patients with  $\geq 150,000$  platelets/mm<sup>3</sup>: The recommended dose is the activity of Iodine-131 calculated to deliver 75cGy total body irradiation and 35 mg Tositumomab, administered intravenously over 20 minutes.
- 659
- 660
- Patients with NCI Grade 1 thrombocytopenia (platelet counts  $\geq 100,000$  but  $<150,000$  platelets/mm<sup>3</sup>): the recommended dose is the

661 activity of Iodine-131 calculated to deliver 65 cGy total body  
662 irradiation and 35 mg Tositumomab, administered intravenously  
663 over 20 minutes.

664 **Concomitant Medications:** The safety of the BEXXAR therapeutic  
665 regimen was established in studies in which all patients received the  
666 following concurrent medications:

667 • Thyroid protective agents: Saturated solution of potassium iodide  
668 (SSKI) 4 drops orally t.i.d; Lugol's solution 20 drops orally t.i.d.; or  
669 Potassium iodide tablets 130 mg orally q.d. Thyroid protective agents  
670 should be initiated at least 24 hours prior to administration of the  
671 Iodine-131 Tositumomab dosimetric dose and continued until 2 weeks  
672 after administration of the Iodine I 131 Tositumomab therapeutic dose.

673 **Patients should not receive the dosimetric dose of Iodine I 131**  
674 **Tositumomab if they have not yet received at least 3 doses of**  
675 **SSKI, three doses of Lugol's solution, or one dose of 130 mg**  
676 **potassium iodide tablet (at least 24 hours prior to the dosimetric**  
677 **dose).**

678 • Acetaminophen 650 mg orally and diphenhydramine 50 mg orally 30  
679 minutes prior to administration of Tositumomab in the dosimetric and  
680 therapeutic steps.

681 The BEXXAR therapeutic regimen is administered via an IV tubing set  
682 with an in-line 0.22  $\mu$  filter. **THE SAME IV TUBING SET AND FILTER**  
683 **MUST BE USED THROUGHOUT THE ENTIRE DOSIMETRIC OR**  
684 **THERAPEUTIC STEP. A CHANGE IN FILTER CAN RESULT IN LOSS**  
685 **OF DRUG.**

686 Figure 1 shows an overview of the dosing schedule.

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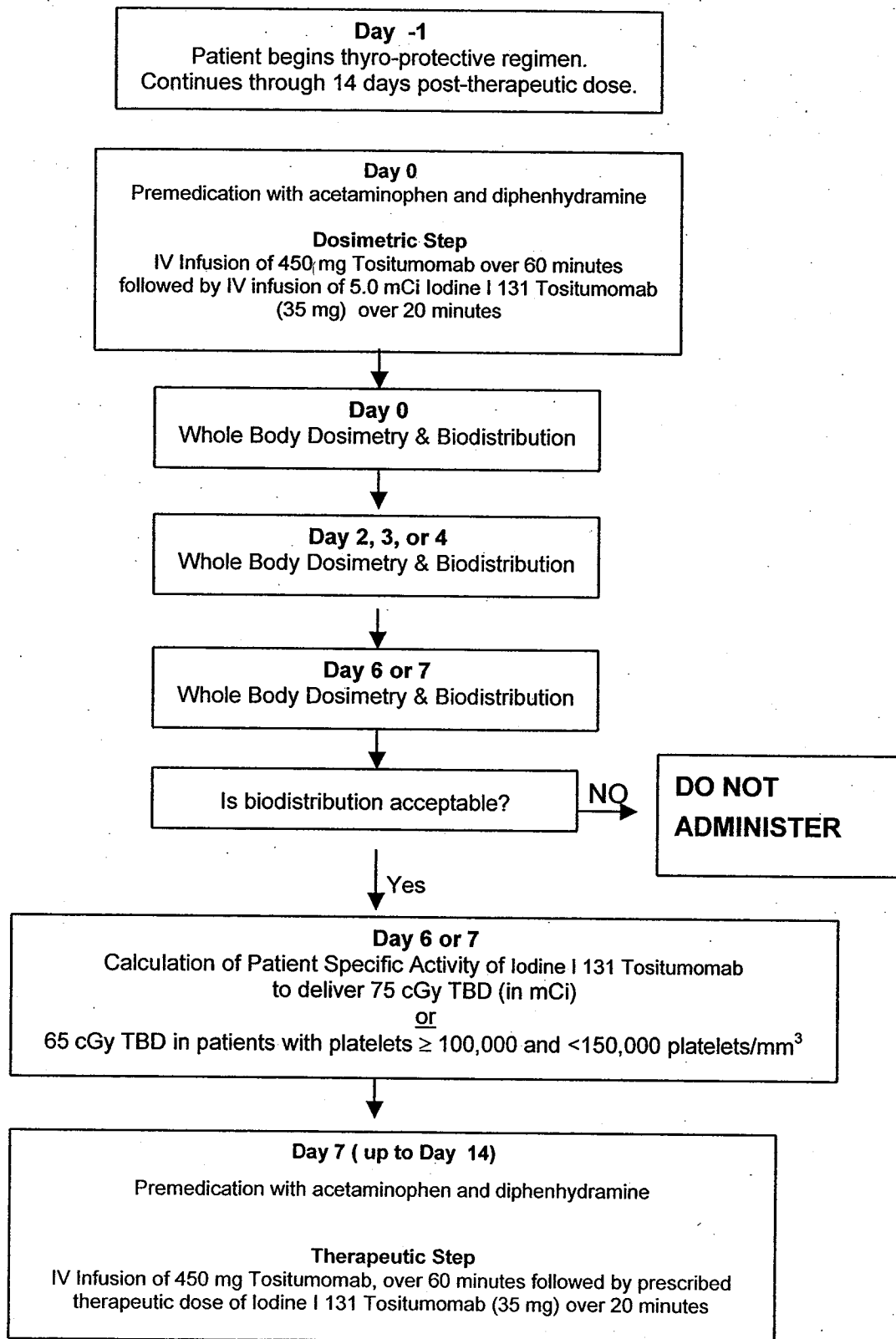
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### Figure 1 Dosing Schedule



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## **PREPARATION OF THE BEXXAR THERAPEUTIC REGIMEN**

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### **GENERAL**

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**Read all directions thoroughly and assemble all materials before preparing the dose for administration.**

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**The Iodine I 131 Tositumomab dosimetric and therapeutic doses 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 Iodine-131.**

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**All supplies for preparation and administration of the BEXXAR therapeutic regimen should be sterile. Use appropriate aseptic technique and radiation precautions for the preparation of the components of the BEXXAR therapeutic regimen.**

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Waterproof gloves should be utilized in the preparation and administration of the product. Iodine I 131 Tositumomab doses should be prepared, assayed, and administered by personnel who are licensed to handle and/or administer radionuclides. Appropriate shielding should be used during preparation and administration of the product.

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Restrictions on patient contact with others and release from the hospital must follow all applicable federal, state, and institutional regulations.

756

### **Preparation for the Dosimetric Step**

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#### **Tositumomab Dose**

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#### **Required materials not supplied**

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761

A. One 50 mL syringe with attached 18 gauge needle (to withdraw 450 mg of Tositumomab from two vials each containing 225 mg Tositumomab)

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B. One 50 mL bag of sterile 0.9% Sodium Chloride for Injection, USP.

763 C. One 50 mL syringe for drawing up 32 mL of saline for disposal from the  
764 50 mL bag of sterile 0.9% Sodium Chloride for Injection, USP

765 Method

- 766 1. Withdraw and dispose of 32 mL of saline from a 50 mL bag of sterile  
767 0.9% Sodium Chloride for Injection, USP.
- 768 2. Withdraw the entire contents from each of the two 225-mg vials (a total  
769 of 450 mg Tositumomab in 32 mL) and transfer to the infusion bag  
770 containing 18 mL of 0.9% Sodium Chloride for Injection, USP to yield a  
771 final volume of 50 mL.
- 772 3. Gently mix the solution by inverting/rotating the bag. DO NOT SHAKE.
- 773 4. The diluted Tositumomab may be stored for up to 24 hours when  
774 stored refrigerated at 2°C–8°C (36°F–46°F) and for up to 8 hours at  
775 room temperature.

776 Note: Tositumomab solution may contain particulates that are generally  
777 white in nature. The product should appear clear to opalescent, colorless  
778 to slightly yellow.

779 Preparation of Iodine I 131 Tositumomab Dosimetric Dose

780 **Required materials not supplied:**

- 781
- 782 A. Lead shielding for preparation vial and syringe pump
- 783 B. Two 30 mL syringes with 18 gauge needles: one to withdraw the  
784 calculated volume of Iodine I 131 Tositumomab from the Iodine I 131  
785 Tositumomab vial and one to withdraw the volume from the  
786 preparation vial into a syringe for administration.
- 787 C. One 20 mL syringe with attached needle, filled with 0.9% Sodium  
788 Chloride for Injection, USP
- 789 D. One 3 mL syringe with attached needle to withdraw Tositumomab from  
790 35-mg vial
- 791 E. One sterile, 30 or 50 mL preparation vial
- 792 F. Two lead pots, both kept at room temperature. One pot is used to  
793 thaw the labeled antibody and the second pot is used to hold the  
794 preparation vial.

795

**Method:**

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1. Allow approximately 60 minutes for thawing (at ambient temperature) of the Iodine I 131 Tosutumomab dosimetric vial with appropriate lead shielding.

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2. Based on the activity concentration of the vial (see actual product specification sheet for the vial supplied in the dosimetric package), calculate the volume required for an Iodine I 131 Tosutumomab activity of 5.0 mCi.

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3. Withdraw the calculated volume from the Iodine I 131 Tosutumomab vial.

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4. Transfer this volume to the shielded preparation vial.

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5. Assay the dose to ensure that the appropriate activity (mCi) has been prepared.

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- a. If the assayed dose is 5.0 mCi (+/- 10%) proceed with step 6.

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- b. If the assayed dose does not contain 5.0 mCi (+/- 10%) recalculate the activity concentration of the Iodine I 131 Tosutumomab at this time, based on the volume and the activity in the preparation vial. Recalculate the volume required for an Iodine I 131 Tosutumomab activity of 5.0 mCi. Using the same 30 mL syringe, add or subtract the appropriate volume from the Iodine I 131 Tosutumomab vial so that the preparation vial contains the volume required for an Iodine I 131 Tosutumomab activity of 5.0 mCi (+/- 10%). Re-assay the preparation vial and proceed with step 6.

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6. Calculate the amount of Tosutumomab contained in the solution of Iodine I 131 Tosutumomab in the shielded preparation vial, based on the volume and protein concentration (see actual product specification sheet supplied in the dosimetric package).

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7. If the shielded preparation vial contains less than 35 mg, calculate the amount of additional Tosutumomab needed to yield a total of 35 mg protein. Calculate the volume needed from the 35 mg vial of Tosutumomab, based on the protein concentration. Withdraw the calculated volume of Tosutumomab from the 35 mg vial of Tosutumomab, and transfer this volume to the shielded preparation vial. The preparation vial should now contain a total of 35 mg of Tosutumomab.

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8. Using the 20 mL syringe containing 0.9% Sodium Chloride for Injection, USP, add a sufficient quantity to the shielded preparation vial to yield a final volume of 30 mL. Gently mix the solutions.



833 9. Withdraw the entire contents from the preparation vial into a 30 mL  
834 syringe using a large bore needle (18 gauge).

835 10. Assay and record the activity.

836

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### Administration of the Dosimetric Step

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#### 840 **Required materials not supplied:**

841 A. One I.V. Filter set (0.22  $\mu$ m filter), 15 inch with injection site (port) and  
842 luer lock

843 B. One Primary IV infusion set

844 C. One 100 mL bag of sterile 0.9% Sodium Chloride for Injection, USP

845 D. Two Secondary I.V infusion sets

846 E. One I.V. Extension set, 30 inch luer lock

847 F. One 3-way stopcock

848 G. One 50 mL bag of sterile 0.9% Sodium Chloride for Injection, USP

849 H. One Infusion pump for Tositumomab infusion

850 I. One Syringe Pump for Iodine I 131 Tositumomab infusion

851 J. Lead shielding for use in the administration of the dosimetric dose

#### 852 **Tositumomab Infusion:**

853 (See Figure 1 in the "**Workbook for Dosimetry Methodology and**  
854 **Administration Set-Up**" for diagrammatic illustration of the configuration of  
855 the infusion set components).  
856

857 1. Attach a primary IV infusion set (Item B) to the 0.22 micron in-line filter set  
858 (Item A) and the 100 mL bag of sterile 0.9% Sodium Chloride for Injection,  
859 USP (Item C).

860 2. After priming the primary IV infusion set (Item B) and IV filter set (Item A),  
861 connect the infusion bag containing 450 mg Tositumomab (50 mL) via a  
862 secondary IV infusion set (Item D) to the primary IV infusion set (Item B) at  
863 a port distal to the 0.22 micron in-line filter. Infuse Tositumomab over 60  
864 minutes.

865

866 3. After completion of the Tositumomab infusion, disconnect the secondary  
867 IV infusion set (Item D) and flush the primary IV infusion set (Item B) and  
868 the in-line IV filter set (Item A) with 0.9% Sodium Chloride. Discard the  
869 Tositumomab bag and secondary IV infusion set.

870

### 871 **Iodine I 131 Tositumomab Dosimetric Infusion**

872 (See Figure 2 in the “**Workbook for Dosimetry Methodology and**  
873 **Administration Set-Up**” for diagrammatic illustration of the configuration of  
874 the infusion set components).

875 1. Appropriate shielding should be used in the administration of the  
876 dosimetric dose.

877 2. The dosimetric dose is delivered in a 30 mL syringe.

878 3. Connect the extension set (Item E) to the 3-way stopcock (Item F).

879 4. Connect the 50 mL bag of sterile 0.9% Sodium Chloride for Injection, USP  
880 (Item G) to a secondary IV infusion set (Item D) and connect the infusion  
881 set to the 3-way stopcock (Item F). Prime the secondary IV infusion set  
882 (Item D) and the extension set (Item E). Connect the extension set (Item  
883 E) to a port in the primary IV infusion set (Item B), distal to the filter.

884 (**Note:** You **must** use the same primary infusion set (Item B) and IV filter set  
885 (Item A) with pre-wetted filter that was used for the Tositumomab infusion. A  
886 change in filter can result in loss of up to 7% of the Iodine I 131 Tositumomab  
887 dose.)

888

889 5. Attach the syringe filled with the Iodine I 131 Tositumomab to the 3-way  
890 stopcock (Item F).

891 6. Set syringe pump to deliver the entire 5.0 mCi (35 mg) dose of Iodine I  
892 131 Tositumomab over 20 minutes.

893 7. After completion of the infusion of Iodine I 131 Tositumomab, close the  
894 stopcock (Item F) to the syringe. Flush the extension set (Item E) and the  
895 secondary IV infusion set (Item D) with 0.9% Sodium Chloride for  
896 Injection, USP from the 50 mL bag (Item G).

- 897 8. After the flush, disconnect the extension set (Item E), 3-way stopcock  
 898 (Item F) and syringe. Disconnect the primary IV infusion set (Item B) and  
 899 in-line filter set (Item A). Determine the combined residual activity of the  
 900 syringe and infusion set components (stopcock, extension set, primary  
 901 infusion set and in-line filter set) by assaying these items in a suitable  
 902 radioactivity calibration system immediately following completion of  
 903 administration of all components of the dosimetric step. Calculate and  
 904 record the dose delivered to the patient by subtracting the residual activity  
 905 in the syringe and the infusion set components from the activity of Iodine I  
 906 <sup>131</sup>Tositumomab in the syringe prior to infusion.
- 907 9. Discard all materials used to deliver the Iodine I <sup>131</sup>Tositumomab (e.g.,  
 908 syringes, vials, in-line filter set, extension set and infusion sets) in  
 909 accordance with local, state, and federal regulations governing radioactive  
 910 and biohazardous waste.

911

912 **Determination of Dose for the Therapeutic Step (See CALCULATION OF**  
 913 **IODINE-131 ACTIVITY FOR THERAPEUTIC DOSE)**

914 The methodology for determining and calculating the patient-specific dose of  
 915 Iodine I <sup>131</sup> activity (mCi) to be administered in the therapeutic step involves  
 916 the following steps:

- 917 1. Following infusion of the Iodine I <sup>131</sup> Tositumomab dosimetric dose,  
 918 obtain total body gamma camera counts and whole body images at the  
 919 following timepoints:
- 920 a. Within one hour of infusion and prior to urination
  - 921 b. 2-4 days after infusion of the dosimetric dose, following urination
  - 922 c. 6-7 days after infusion of the dosimetric dose, following urination
- 923 2. Assess biodistribution. If biodistribution is altered, the therapeutic step  
 924 should not be administered.
- 925 3. Determine total body residence time (See Graph 1, "**Determination of**  
 926 **Residence Time**", in the "**Workbook for Dosimetry Methodology and**  
 927 **Administration Set-Up**").
- 928 4. Determine activity hours, (See Table 2, "**Determination of Activity**  
 929 **Hours**", in the "**Workbook for Dosimetry Methodology and**  
 930 **Administration Set-Up**") according to gender. Use actual patient mass  
 931 (in kg) or maximum effective mass (in kg) whichever is lower (See  
 932 Table 1, "**Determination of Maximum Effective Mass**", in the  
 933 "**Workbook for Dosimetry Methodology and Administration Set-Up**").

- 934 5. Determine whether the desired total body dose should be reduced (to 65  
935 cGy) due to a platelet count of 100,000 to <150,000 cells/mm<sup>3</sup>.
- 936 6. Based on the total body residence time and activity hours, calculate the  
937 Iodine-131 activity (mCi) to be administered to deliver the therapeutic dose  
938 of 65 or 75 cGy.

939 The following equation is used to calculate the activity of Iodine-131 required  
940 for delivery of the desired total body dose of radiation.

941

942 
$$\text{Iodine-131 Activity (mCi)} = \frac{\text{Activity Hours (mCi hr)}}{\text{Residence Time (hr)}} \times \frac{\text{Desired Total Body Dose (cGy)}}{75 \text{ cGy}}$$

943

944 **Preparation for the Therapeutic Step**

945 **Tositumomab Dose**

946 **Required materials not supplied**

- 947 A. One 50 mL syringe with attached 18 gauge needle (to withdraw 450  
948 mg of Tositumomab from two vials each containing 225 mg  
949 Tositumomab)
- 950 B. One 50 mL bag of sterile 0.9% Sodium Chloride for Injection, USP
- 951 C. One 50 mL syringe for drawing up 32 mL of saline for disposal from the  
952 50 mL bag of sterile 0.9% Sodium Chloride for Injection USP

953 **Method**

- 954 1. Withdraw and dispose of 32 mL of saline from a 50 mL bag of sterile 0.9%  
955 Sodium Chloride for Injection, USP.
- 956 2. Withdraw the entire contents from each of the two 225-mg vials (a total of  
957 450 mg Tositumomab in 32 mL) and transfer to the infusion bag  
958 containing 18 mL of 0.9% Sodium Chloride for Injection, USP to yield a  
959 final volume of 50 mL.
- 960 3. Gently mix the solutions by inverting/rotating the bag. DO NOT SHAKE.

961 4. The diluted Tositumomab may be stored for up to 24 hours when stored  
962 refrigerated at 2°C–8°C (36°F–46°F) and for up to 8 hours at room  
963 temperature.

964 Note: Tositumomab solution may contain particulates that are generally  
965 white in nature. The product should appear clear to opalescent, colorless  
966 to slightly yellow.

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968  
969

#### **Preparation of Iodine I 131 Tositumomab Therapeutic Dose**

970 **Required materials not supplied:**

- 971 A. Lead shielding for preparation vial and syringe pump
- 972 B. Two or four 30 mL syringes with 18 gauge needles: one or two to  
973 withdraw the calculated volume of Iodine I 131 Tositumomab from  
974 the Iodine I 131 Tositumomab vial(s) and one or two to withdraw  
975 the volume from the preparation vial into a syringe for  
976 administration.
- 977 C. One 20 mL syringe with attached needle filled with 0.9% Sodium  
978 Chloride for Injection, USP
- 979 D. One 3 mL sterile syringe with attached needle to draw up  
980 Tositumomab from the 35 mg vial
- 981 E. One sterile, 30 or 50 mL preparation vial
- 982 F. Two lead pots both kept at room temperature. One pot is used to  
983 thaw the labeled antibody, and the second pot is used to hold the  
984 preparation vial.

985 **Method:**

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1. Allow approximately 60 minutes for thawing (at ambient temperature)  
of the Iodine I 131 Tositumomab therapeutic vial with appropriate lead  
shielding.

990 2. Calculate the dose of Iodine I 131 Tositumomab required (See  
991 **CALCULATION OF IODINE-131 ACTIVITY FOR THERAPEUTIC**  
992 **DOSE)**

993 3. Based on the activity concentration of the vial (see actual product  
994 specification sheet for each vial supplied in the therapeutic package),  
995 calculate the volume required for the Iodine I 131 Tositumomab activity  
996 required for the therapeutic dose.

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4. Using one or more 30 mL syringes with an 18-gauge needle, withdraw the calculated volume from the Iodine I 131 Tositumomab vial.
  5. Transfer this volume to the shielded preparation vial.
  6. Assay the dose to ensure that the appropriate activity (mCi) has been prepared.
    - a. If the assayed dose is the calculated dose (+/- 10%) needed for the therapeutic step, proceed with step 7.
    - b. If the assayed dose does not contain the desired dose (+/- 10%), re-calculate the activity concentration of the Iodine I 131 Tositumomab at this time, based on the volume and the activity in the preparation vial. Re-calculate the volume required for an Iodine I 131 Tositumomab activity for the therapeutic dose. Using the same 30 mL syringe, add or subtract the appropriate volume from the Iodine I 131 Tositumomab vial so that the preparation vial contains the volume required for the Iodine I 131 Tositumomab activity required for the therapeutic dose. Re-assay the preparation vial. Proceed to step 7.
  7. Calculate the amount of Tositumomab protein contained in the solution of Iodine I 131 Tositumomab in the shielded preparation vial, based on the volume and protein concentration. (See product specification sheet.)
  8. If the shielded preparation vial contains less than 35 mg, calculate the amount of additional Tositumomab needed to yield a total of 35 mg protein. Calculate the volume needed from the 35 mg vial of Tositumomab, based on the protein concentration. Withdraw the calculated volume of Tositumomab from the 35 mg vial of Tositumomab, and transfer this volume to the shielded preparation vial. The preparation vial should now contain a total of 35 mg of Tositumomab.

**Note:** If the dose of Iodine I 131 Tositumomab requires the use of 2 vials of Iodine I 131 Tositumomab or the entire contents of a single vial of Iodine I 131 Tositumomab, there may be no need to add protein from the 35 mg vial of Tositumomab.
  9. Using the 20 mL syringe containing 0.9% Sodium Chloride for Injection, USP, add a sufficient volume (if needed) to the shielded preparation vial to yield a final volume of 30 mL. Gently mix the solution.
  10. Withdraw the entire volume from the preparation vial into a one or more sterile 30 mL syringes using a large bore needle (18 gauge).

1036 11. Assay and record the activity.

1037

1038

1039

**Administration of the Therapeutic Step**

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**Note:** Restrictions on patient contact with others and release from the hospital must follow all applicable federal, state, and institutional regulations.

1042

1043

**Required materials not supplied:**

1044

A. One I.V. Filter set (0.22 µm filter), 15 inch with injection site (port) and luer lock

1045

1046

B. One Primary I.V. infusion set

1047

C. One 100 mL bag of sterile 0.9% Sodium Chloride for Injection, USP

1048

D. Two Secondary I.V. infusion sets

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E. One I.V. extension set, 30 inch luer lock

1050

F. One 3-way stopcock

1051

G. One 50 mL bag of sterile 0.9% Sodium Chloride for Injection, USP

1052

H. One Infusion pump for Tositumomab infusion

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I. One Syringe Pump for Iodine I 131 Tositumomab infusion

1054

J. Lead shielding for use in the administration of the therapeutic dose

1055

1056

**Tositumomab Infusion:**

1057

(See Figure 1 in the “**Workbook for Dosimetry Methodology and**

1058

**Administration Set-Up**” for diagrammatic illustration of the configuration of the infusion set components).

1059

1060

1. Attach a primary IV infusion set (Item B) to the 0.22 micron in-line filter set (Item A) and a 100 mL bag of sterile 0.9% Sodium Chloride for Injection, USP (Item C).

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2. After priming the primary IV infusion set (Item B) and filter set (Item A), connect the infusion bag containing 450 mg Tositumomab (50 mL) via a secondary IV infusion set (Item D) to the primary IV infusion set (Item B) at a port distal to the 0.22 micron in-line filter. Infuse Tositumomab over 60 minutes.

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1068 3. After completion of the Tositumomab infusion, disconnect the secondary  
1069 IV infusion set (Item D) and flush the primary IV infusion set (Item B) and  
1070 the IV filter set (Item A) with 0.9% Sodium Chloride. Discard the  
1071 Tositumomab bag and secondary IV infusion set.

1072

1073 **Iodine I 131 Tositumomab Therapeutic Infusion:**

1074 (See Figure 2 in the “**Workbook for Dosimetry Methodology and**  
1075 **Administration Set-Up**” for diagrammatic illustration of the configuration of  
1076 the infusion set components).

1077

1078 1. Appropriate shielding should be used in the administration of the  
1079 therapeutic dose.

1080 2. The therapeutic dose is delivered in one or more 30 mL syringes.

1081 3. Connect the extension set (Item E) to the 3-way stopcock (Item F).

1082 4. Connect the 50 mL bag of sterile 0.9% Sodium Chloride for Injection, USP  
1083 (Item G) to a secondary IV infusion set (Item D) and connect the infusion  
1084 set to the 3-way stopcock (Item F). Prime the secondary IV infusion set  
1085 (Item D) and the extension set (Item E). Connect the extension set (Item  
1086 E) to a port in the primary IV infusion set (Item B), distal to the filter.

1087 (Note: You **must** use the same primary infusion set (Item B) and IV filter set  
1088 (Item A) with pre-wetted filter that was used for the Tositumomab infusion. A  
1089 change in filter can result in loss of up to 7% of the Iodine I 131 Tositumomab  
1090 dose.)

1091

1092 5. Attach the syringe filled with the Iodine I 131 Tositumomab to the 3-way  
1093 stopcock (Item F).

1094 6. Set syringe pump to deliver the entire therapeutic dose of Iodine I 131  
1095 Tositumomab over 20 minutes. (Note: if more than one syringe is  
1096 required, remove the syringe and repeat steps 5 and 6.)

1097 7. After completion of the infusion of Iodine I 131 Tositumomab, close the  
1098 stopcock (Item F) to the syringe. Flush the secondary IV infusion set (Item  
1099 D) and the extension set (Item E) with 0.9% Sodium Chloride from the 50  
1100 mL bag of sterile, 0.9% Sodium Chloride for Injection, USP (Item G).



- 1101 8. After the flush, disconnect the extension set (Item E), 3-way stopcock  
1102 (Item F) and syringe. Disconnect the primary IV infusion set (Item B) and  
1103 in-line filter set (Item A). Determine the combined residual activity of the  
1104 syringe(s) and infusion set components (stopcock, extension set, primary  
1105 infusion set and in-line filter set) by assaying these items in a suitable  
1106 radioactivity calibration system immediately following completion of  
1107 administration of all components of the therapeutic step. Calculate and  
1108 record the dose delivered to the patient by subtracting the residual activity  
1109 in the syringe and infusion set components from the activity of Iodine I 131  
1110 Tositumomab in the syringe prior to infusion.
- 1111 9. Discard all materials used to deliver the Iodine I 131 Tositumomab (e.g.,  
1112 syringes, vials, in-line filter set, extension set and infusion sets) in  
1113 accordance with local, state, and federal regulations governing radioactive  
1114 and biohazardous waste.

1115

## 1116 **DOSIMETRY**

1117 The following sections describe the procedures for image acquisition for  
1118 collection of dosimetry data, interpretation of biodistribution images,  
1119 calculation of residence time, and calculation of activity hours. Please read  
1120 all sections carefully.

1121

1122

## 1123 **IMAGE ACQUISITION AND INTERPRETATION**

### 1124 **Gamma Camera and Dose Calibrator Procedures**

1125 Manufacturer-specific quality control procedures should be followed for the  
1126 gamma camera/computer system, the collimator, and the dose calibrator.  
1127 Less than 20% variance between maximum and minimum pixel count values  
1128 in the useful field of view is acceptable on Iodine-131 intrinsic flood fields and  
1129 variability <10% is preferable. Iodine-131-specific camera uniformity  
1130 corrections are strongly recommended, rather than applying lower energy  
1131 correction to the Iodine-131 window. Camera extrinsic uniformity should be  
1132 assessed at least monthly using <sup>99m</sup>Tc or <sup>57</sup>Co as a source with imaging at  
1133 the appropriate window.

1134 Additional (non-routine) quality control procedures are required. To assure  
1135 the accuracy and precision of the patient total body counts, the gamma  
1136 camera must undergo validation and daily quality control on each day it is  
1137 used to collect patient images.

1138 Use the same setup and region of interest (ROI) for calibration, determination  
1139 of background, and whole body patient studies.

#### 1140 **Gamma Camera Set-Up**

1141 The **same** camera, collimator, region of interest (ROI), scanning speed,  
1142 energy window, and setup must be used for all studies. The gamma camera  
1143 must be capable of whole body imaging and have a large or extra large field  
1144 of view with a digital interface. It must be equipped with a parallel-hole  
1145 collimator rated to at least 364 keV by the manufacturer with a septal  
1146 penetration for Iodine-131 of <7%.

1147 The camera and computer must be set up for scanning as follows:

1148

1149 • Parallel hole collimator rated to at least 364 keV with a septal penetration  
1150 for Iodine-131 of <7%

1151 • Symmetric window (20-25%) centered on the 364 keV photo peak of  
1152 Iodine-131 (314 - 414 keV)

1153 • Matrix: minimum 128 x 128

1154 • Scanning speed: 10-30 cm/minute

1155

#### 1156 **Counts from Calibrated Source for Quality Control**

1157 Camera sensitivity for Iodine-131 must be determined each day.

1158 Determination of the gamma camera's sensitivity is obtained by scanning a  
1159 calibrated activity of Iodine-131 (e.g., 200–250  $\mu$ Ci in at least 20 mL of saline  
1160 within a sealed pharmaceutical vial). The radioactivity of the Iodine-131  
1161 source is first determined using a NIST-traceable-calibrated clinical dose  
1162 calibrator at the Iodine-131 setting.

1163

#### 1164 **Background Counts**

1165 The background count is obtained from a scan with no radioactive source.

1166 This should be obtained following the count of the calibrated source and just  
1167 prior to obtaining the patient count.

1168 If abnormally high background counts are measured, the source should be  
1169 identified and, if possible, removed. If abnormally low background counts are

1170 measured, the camera energy window setting and collimator should be  
1171 verified before repeating the background counts.

1172 The counts per  $\mu\text{Ci}$  are obtained by dividing the background-corrected source  
1173 count by the calibrated activity for that day. For a specific camera and  
1174 collimator, the counts per  $\mu\text{Ci}$  should be relatively constant. When values  
1175 vary more than 10% from the established ratio, the reason for the discrepancy  
1176 should be ascertained and corrected and the source count repeated.

### 1177 **Patient Total Body Counts**

1178 The source and background counts are obtained first and the camera  
1179 sensitivity (i.e., constant counting efficiency) is established prior to obtaining  
1180 the patient count. The same rectangular region of interest (ROI) must be  
1181 used for the whole body counts, the quality control counts of the radioactive  
1182 source, and the background counts.

1183 Acquire anterior and posterior whole body images for gamma camera counts.  
1184 For any particular patient, the same gamma camera must be used for all  
1185 scans. To obtain proper counts, extremities must be included in the images,  
1186 and arms should not cross over the body. The scans should be centered on  
1187 the midline of the patient. Record the time of the start of the radiolabeled  
1188 dosimetric infusion and the time of the start of each count acquisition.

1189 Gamma camera counts will be obtained at the three imaging time points:

- 1190 • **Count 1:** *Within an hour of end of the infusion* of the Iodine I 131  
1191 Tositumomab dosimetric dose prior to patient voiding.
- 1192 • **Count 2:** Two to 4 days after administration of the Iodine I 131  
1193 Tositumomab dosimetric dose and immediately following patient voiding.
- 1194 • **Count 3:** Six to 7 days after the administration of the Iodine I 131  
1195 Tositumomab dosimetric dose and immediately following patient voiding

### 1196 **Assessment of Biodistribution of Iodine I 131 Tositumomab**

1197 The biodistribution of Iodine I 131 Tositumomab should be assessed by  
1198 determination of total body residence time and by visual examination of whole

1199 body camera images from the first image taken at the time of Count 1 (within  
1200 an hour of the end of the infusion) and from the second image taken at the  
1201 time of Count 2 (at 2 to 4 days after administration). To resolve ambiguities,  
1202 an evaluation of the third image at the time of Count 3 (6 to 7 days after  
1203 administration) may be necessary. If either of these methods indicates that  
1204 the biodistribution is altered, the Iodine I 131 Tositumomab therapeutic dose  
1205 should not be administered.

#### 1206 Expected Biodistribution

- 1207 • On the first imaging timepoint: Most of the activity is in the blood pool  
1208 (heart and major blood vessels) and the uptake in normal liver and spleen is  
1209 less than in the heart.
- 1210 • On the second and third imaging timepoints: The activity in the blood pool  
1211 decreases significantly and there is decreased accumulation of activity in  
1212 normal liver and spleen. Images may show uptake by thyroid, kidney, and  
1213 urinary bladder and minimal uptake in the lungs. Tumor uptake in soft tissues  
1214 and in normal organs is seen as areas of increased intensity.

1215

#### 1216 Results Indicating Altered Biodistribution

- 1217 • On the first imaging timepoint: If the blood pool is not visualized or if there  
1218 is diffuse, intense tracer uptake in the liver and/or spleen or uptake  
1219 suggestive of urinary obstruction the biodistribution is altered. Diffuse lung  
1220 uptake greater than that of blood pool on the first day represents altered  
1221 biodistribution.
- 1222 • On the second and third imaging timepoints: uptake suggestive of urinary  
1223 obstruction and diffuse lung uptake greater than that of the blood pool  
1224 represent altered biodistribution.
- 1225 • Total body residence times of less than 50 hours and more than 150  
1226 hours.

1227

#### 1228 **CALCULATION OF IODINE-131 ACTIVITY FOR THE THERAPEUTIC** 1229 **DOSE**

1230 The methods for determining the residence time (hr) and activity hours (mCi  
1231 hr) are described below.

1232

1233 **Residence Time (hr)**

1234 For each time point, calculate the background corrected total body count at  
1235 each timepoint (defined as the geometric mean). The following equation is  
1236 used:

1237 Geometric mean of counts =  $\sqrt{(C_A - C_{BA})(C_P - C_{BP})}$

1238

1239 In this equation,  $C_A$  = the anterior counts,  $C_{BA}$  = the anterior background  
1240 counts,  $C_P$  = the posterior counts, and  $C_{BP}$  = the posterior background counts.

1241

1242 Once the geometric mean of the counts has been calculated for each of the 3  
1243 timepoints, the % injected activity remaining for each timepoint is calculated  
1244 by dividing the geometric mean of the counts from that timepoint by the  
1245 geometric mean of the counts from Day 0 and multiplying by 100.

1246

1247 The residence time (h) is then determined by plotting the time from the start of  
1248 infusion and the % injected activity values for the 3 imaging timepoints on  
1249 Graph 1 (See Worksheet "**Determination of Residence Time**" in the  
1250 "**Workbook for Dosimetry Methodology and Administration Set-Up**"  
1251 supplied with Dosimetric Dose Packaging). A best-fit line is then drawn from  
1252 100% (the pre-plotted Day 0 value) through the other 2 plotted points (if the  
1253 line does not intersect the two points, one point must lie above the best-fit line  
1254 and one point must lie below the best-fit line). The residence time (h) is read  
1255 from the x-axis of the graph at the point where the fitted line intersects with  
1256 the horizontal 37% injected activity line.

1257

1258 **Activity Hours (mCi hr)**

1259 In order to determine the activity hours (mCi hr), look up the patient's  
1260 maximum effective mass derived from the patient's sex and height (See  
1261 Worksheet "**Determination of Maximum Effective Mass**" in the "**Workbook**  
1262 **for Dosimetry Methodology and Administration Set-Up**" supplied with  
1263 Dosimetric Dose Packaging). If the patient's actual weight is less than the  
1264 maximum effective mass, the actual weight should be used in the activity  
1265 hours table (See Worksheet "**Determination of Activity Hours**" in the

1266 **“Workbook for Dosimetry Methodology and Administration Set-Up”**  
1267 supplied with Dosimetric Dose Packaging). If the patient’s actual weight is  
1268 greater than the maximum effective mass, the mass from the worksheet for  
1269 **“Determination of Maximum Effective Mass”** should be used.

### 1270 **Calculation of Iodine-131 Activity for the Therapeutic Dose**

1271 The following equation is used to calculate the activity of Iodine-131 required  
1272 for delivery of the desired total body dose of radiation.

1273

1274 **Iodine-131 Activity (mCi) =** 
$$\frac{\text{Activity Hours (mCi hr)}}{\text{Residence Time (hr)}} \times \frac{\text{Desired Total Body Dose (cGy)}}{75 \text{ cGy}}$$

1275

### 1276 **HOW SUPPLIED**

#### 1277 **TOSITUMOMAB DOSIMETRIC PACKAGING**

1278 The components of the dosimetric step will be shipped **ONLY** to individuals  
1279 who are participating in the certification program or have been certified in the  
1280 preparation and administration of the BEXXAR therapeutic regimen. The  
1281 components are shipped from separate sites; when ordering, ensure that the  
1282 components are scheduled to arrive on the same day. The components of  
1283 the Tositumomab Dosimetric Step include:

1284 1. Tositumomab: Two single-use 225 mg vials (16.1 mL) and one single-use  
1285 35 mg vial (2.5 mL) of Tositumomab at a protein concentration of 14 mg/mL  
1286 supplied by McKesson Biosciences.

1287 NDC 67800-101-31

1288 2. Iodine I 131 Tositumomab: A single-use vial of Iodine I 131 Tositumomab  
1289 within a lead pot, supplied by MDS Nordion. Each single-use vial contains  
1290 not less than 20 mL of Iodine I 131 Tositumomab at nominal protein and  
1291 activity concentrations of 0.1 mg/mL and 0.61 mCi/mL (at calibration),  
1292 respectively. (Refer to the product specification sheet for the lot-specific  
1293 protein concentration, activity concentration, total activity and expiration date.)

1294 NDC 67800-111-10

1295

1296 **TOSITUMOMAB THERAPEUTIC PACKAGING**

1297 The components of the therapeutic step will be shipped **ONLY** to individuals  
1298 who are participating in the certification program or have been certified in the  
1299 preparation and administration of the BEXXAR therapeutic regimen for an  
1300 individual patient who has completed the Dosimetric Step. The components of  
1301 the therapeutic step are shipped from separate sites; when ordering, ensure  
1302 that the components are scheduled to arrive on the same day. The  
1303 components of the Tositumomab Therapeutic Step include:

1304 1. Tositumomab: Two single-use 225 mg vials (16.1 mL) and one single-use  
1305 35 mg vial (2.5 mL) of Tositumomab at a protein concentration of 14 mg/mL  
1306 supplied by McKesson Biosciences.

1307 NDC 67800-101-32

1308 2. One or two single-use vials of Iodine I 131 Tositumomab within a lead pot,  
1309 supplied by MDS Nordion. Each single-use vial contains not less than 20 mL  
1310 of Iodine I 131 Tositumomab at nominal protein and activity concentrations of  
1311 1.1 mg/mL and 5.6 mCi/mL (at calibration), respectively. Refer to the product  
1312 specification sheet for the lot-specific protein concentration, activity  
1313 concentration, total activity and expiration date.

1314 NDC 67800-121-10.

1315

1316 **STABILITY AND STORAGE**

1317 **TOSITUMOMAB**

1318 Vials of Tositumomab (35 mg and 225 mg) should be stored refrigerated at  
1319 2°C-8°C (36°F-46°F) prior to dilution. Do not use beyond expiration date.  
1320 Protect from strong light. **DO NOT SHAKE.** Do not freeze. Discard any  
1321 unused portions left in the vial.

1322 Solutions of diluted Tositumomab are stable for up to 24 hours when stored  
1323 refrigerated at 2°C-8°C (36°F-46°F) and for up to 8 hours at room  
1324 temperature. However, it is recommended that the diluted solution be stored

1325 refrigerated at 2°C–8°C (36°F–46°F) prior to administration because it does  
1326 not contain preservatives. Any unused portion must be discarded. Do not  
1327 freeze solutions of diluted Tositumomab.

1328

### 1329 IODINE I 131 TOSITUMOMAB

1330 **Store frozen in the original lead pots.** The lead pot containing the product  
1331 must be stored in a freezer at a temperature of -20°C or below until it is  
1332 removed for thawing prior to administration to the patient. Do not use beyond  
1333 the expiration date on the label of the lead pot.

1334 Thawed dosimetric and therapeutic doses of Iodine I 131 Tositumomab are  
1335 stable for up to 8 hours at 2°C–8°C (36°F–46°F) or at room temperature.  
1336 Solutions of Iodine I 131 Tositumomab diluted for infusion contain no  
1337 preservatives and should be stored refrigerated at 2°C–8°C (36°F–46°F) prior  
1338 to administration (do not freeze). Any unused portion must be discarded  
1339 according to federal and state laws.

1340

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