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Rx Only

**BEXXAR®**

P/N 400009-B

**Tositumomab and  
Iodine I 131 Tositumomab**

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**WARNINGS**

8 **Hypersensitivity Reactions, including Anaphylaxis:** Serious hypersensitivity  
9 reactions, including some with fatal outcome, have been reported with the Bexxar  
10 therapeutic regimen. Medications for the treatment of severe hypersensitivity  
11 reactions should be available for immediate use. Patients who develop severe  
12 hypersensitivity reactions should have infusions of the BEXXAR therapeutic  
13 regimen discontinued and receive medical attention (see **WARNINGS**).

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

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

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

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**DESCRIPTION**

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The BEXXAR therapeutic regimen (Tositumomab and Iodine I 131 Tositumomab) is an anti-neoplastic radioimmunotherapeutic monoclonal antibody-based regimen composed of the monoclonal antibody, Tositumomab, and the radiolabeled monoclonal antibody, Iodine I 131 Tositumomab.

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**Tositumomab**

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

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

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**Iodine I 131 Tositumomab**

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Iodine I 131 Tositumomab is a radio-iodinated derivative of Tositumomab that has been covalently linked to Iodine-131. Unbound radio-iodine and other reactants have been removed by chromatographic purification steps. Iodine I 131 Tositumomab is supplied as a sterile, clear, preservative-free liquid for IV administration. The dosimetric dosage form is supplied at nominal protein and activity concentrations of 0.1 mg/mL and 0.61 mCi/mL (at date of calibration), respectively. The therapeutic dosage form is supplied at nominal protein and activity concentrations of 1.1 mg/mL and 5.6 mCi/mL (at date of calibration), respectively. The formulation for the dosimetric and the therapeutic dosage forms contains 4.4%–6.6% (w/v) povidone, 1–2 mg/mL maltose (dosimetric dose) or 9–15 mg/mL maltose

60 (therapeutic dose), 0.85–0.95 mg/mL sodium chloride, and 0.9–1.3 mg/mL  
61 ascorbic acid. The pH is approximately 7.0.

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### **BEXXAR Therapeutic Regimen**

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

#### **BEXXAR Dosimetric Packaging**

- 71 • A carton containing two single-use 225 mg vials and one single-use  
72 35 mg vial of Tositumomab supplied by McKesson BioServices and
- 73 • A package containing a single-use vial of Iodine I 131 Tositumomab  
74 (0.61 mCi/mL at calibration), supplied by MDS Nordion.

#### **BEXXAR Therapeutic Packaging**

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

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

84 Iodine-131 decays with beta and gamma emissions with a physical  
85 half-life of 8.04 days. The principal beta emission has a mean energy of  
86 191.6 keV and the principal gamma emission has an energy of 364.5 keV  
87 (Ref 1).

88 **External Radiation:** The specific gamma ray constant for Iodine-131 is  
89 2.2 R/millicurie hour at 1 cm. The first half-value layer is 0.24 cm lead

90 (Pb) shielding. A range of values is shown in Table 1 for the relative  
91 attenuation of the radiation emitted by this radionuclide that results from  
92 interposition of various thicknesses of Pb. To facilitate control of the  
93 radiation exposure from this radionuclide, the use of a 2.55 cm thickness  
94 of Pb will attenuate the radiation emitted by a factor of about 1,000.

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

Shield Thickness (Pb) cm	Attenuation Factor
0.24	0.5
0.89	$10^{-1}$
1.60	$10^{-2}$
2.55	$10^{-3}$
3.7	$10^{-4}$

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

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Fraction of remaining radioactivity of Iodine-131 after x days =  $2^{-(x/8.04)}$

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Physical decay is presented in Table 2.

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

Days	Fraction Remaining
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

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\*(Calibration day)

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**CLINICAL PHARMACOLOGY**

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**General Pharmacology**

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Tositumomab binds specifically to the CD20 (human B-lymphocyte-restricted differentiation antigen, Bp 35 or B1) antigen. This antigen is a transmembrane phosphoprotein expressed on pre-B lymphocytes and at higher density on mature B lymphocytes (Ref. 2). The antigen is also expressed on >90% of B-cell non-Hodgkin's lymphomas (NHL) (Ref. 3).

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The recognition epitope for Tositumomab is found within the extracellular 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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**Mechanism of Action:** Possible mechanisms of action of the BEXXAR therapeutic regimen include induction of apoptosis (Ref. 5), complement-dependent cytotoxicity (CDC) (Ref. 6), and antibody-dependent cellular cytotoxicity (ADCC) (Ref. 5) mediated by the antibody. Additionally, cell death is associated with ionizing radiation from the radioisotope.

**123 Pharmacokinetics/Pharmacodynamics**

124 The phase 1 study of Iodine I 131 Tositumomab determined that a 475 mg  
125 predose of unlabeled antibody decreased splenic targeting and increased  
126 the terminal half-life of the radiolabeled antibody. The median blood  
127 clearance following administration of 485 mg of Tositumomab in  
128 110 patients with NHL was 68.2 mg/hr (range: 30.2–260.8 mg/hr).  
129 Patients with high tumor burden, splenomegaly, or bone marrow  
130 involvement were noted to have a faster clearance, shorter terminal half-  
131 life, and larger volume of distribution. The total body clearance, as  
132 measured by total body gamma camera counts, was dependent on the  
133 same factors noted for blood clearance. Patient-specific dosing, based on  
134 total body clearance, provided a consistent radiation dose, despite  
135 variable pharmacokinetics, by allowing each patient's administered activity  
136 to be adjusted for individual patient variables. The median total body  
137 effective half-life, as measured by total body gamma camera counts, in  
138 980 patients with NHL was 67 hours (range: 28-115 hours).

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

143 Administration of the BEXXAR therapeutic regimen results in sustained  
144 depletion of circulating CD20 positive cells. The impact of administration  
145 of the BEXXAR therapeutic regimen on circulating CD20 positive cells was  
146 assessed in two clinical studies, one conducted in chemotherapy naïve  
147 patients and one in heavily pretreated patients. The assessment of  
148 circulating lymphocytes did not distinguish normal from malignant cells.  
149 Consequently, assessment of recovery of normal B cell function was not  
150 directly assessed. At seven weeks, the median number of circulating  
151 CD20 positive cells was zero (range: 0-490 cells/mm<sup>3</sup>). Lymphocyte  
152 recovery began at approximately 12 weeks following treatment. Among  
153 patients who had CD20 positive cell counts recorded at baseline and at 6  
154 months, 8 of 58 (14%) chemotherapy naïve patients had CD20 positive  
155 cell counts below normal limits at six months and 6 of 19 (32%) heavily  
156 pretreated patients had CD20 positive cell counts below normal limits at

157 six months. There was no consistent effect of the BEXXAR therapeutic  
158 regimen on post-treatment serum IgG, IgA, or IgM levels.

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#### 160 **Radiation Dosimetry**

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

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Table 3

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## Estimated Radiation-Absorbed Organ Doses

From Organ ROIs	BEXXAR	BEXXAR
	mGy/MBq	mGy/MBq
	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
<b>From Whole Body ROIs</b>		
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

Corixa Corporation: BEXXAR® (Tositumomab, Iodine I 131 Tositumomab)  
 BLA STN 125011

171 **CLINICAL STUDIES**

172 The efficacy of the BEXXAR therapeutic regimen was evaluated in 2  
173 studies conducted in patients with low-grade, transformed low-grade, or  
174 follicular large-cell lymphoma. Determination of clinical benefit of the  
175 BEXXAR therapeutic regimen was based on evidence of durable  
176 responses without evidence of an effect on survival. All patients had  
177 received prior treatment without an objective response or had progression  
178 of disease following treatment. Patients were required to have a  
179 granulocyte count  $>1500$  cells/mm<sup>3</sup>, a platelet count  $\geq 100,000$ /mm<sup>3</sup>, an  
180 average of  $\leq 25\%$  of the intratrabecular marrow space involved by  
181 lymphoma, and no evidence of progressive disease arising in a field  
182 irradiated with  $>3500$  cGy within 1 year of completion of irradiation.

183 Study 1 was a multicenter, single-arm study of 40 patients whose disease  
184 had not responded to or had progressed after at least four doses of  
185 Rituximab therapy. The median age was 57 (range: 35–78); the median  
186 time from diagnosis to protocol entry was 50 months (range: 12–170); and  
187 the median number of prior chemotherapy regimens was 4 (range: 1–11).  
188 The efficacy outcome data from this study, as determined by an  
189 independent panel that reviewed patient records and radiologic studies,  
190 are summarized in Table 4.

191 Among the forty patients in the study, twenty-four patients had disease  
192 that did not respond to their last treatment with Rituximab, 11 patients had  
193 disease that responded to Rituximab for less than 6 months, and five  
194 patients had disease that responded to Rituximab, with a duration of  
195 response of 6 months or greater. Overall, 35 of the 40 patients met the  
196 definition of "Rituximab refractory", defined as no response or a response  
197 of less than 6 months duration. In this subset of patients the overall  
198 objective response was 63% (95% confidence interval 45%, 79%) with a  
199 median duration of 25 months (range of 4 - 38+ months). The complete  
200 response in this subset of patients was 29% (95% CI of 15%, 46%) with a  
201 median duration of response not yet reached (range of 4 - 38+ months).

202 Study 2 was a multicenter, single arm, open-label study of 60  
203 chemotherapy refractory patients. The median age was 60 (range 38-82),

204 the median time from diagnosis to protocol entry was 53 months (range: 9-  
 205 334), and the median number of prior chemotherapy regimens was 4  
 206 (range 2-13). Fifty-three patients had not responded to prior therapy and  
 207 7 patients had responded with a duration of response of <6 months. The  
 208 efficacy outcome data from this study, as determined by an independent  
 209 panel that reviewed patient records and radiologic studies are also  
 210 summarized in Table 4. Investigators continued to follow eight patients  
 211 with complete response after the last independent review panel  
 212 assessment. The updated duration of ongoing response as per  
 213 investigators was reported to range from 42 to 85 months.

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 217 **Table 4: Efficacy Outcomes in Bexxar Clinical Studies**  
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	Study 1 (n=40)	Study 2 (n=60)
Overall Response Rate 95% CI <sup>a</sup>	68% (51%, 81%)	47% (34%, 60%)
Response Duration (mos) Median 95% CI <sup>a</sup> Range	16 (10, NR <sup>b</sup> ) 1+ to 38+	12 (7, 47) 2 to 47
Complete Response <sup>c</sup> Rate 95% CI <sup>a</sup>	33% (19%, 49%)	20% (11%, 32%)
Complete response <sup>c</sup> duration (mos) Median 95% CI <sup>a</sup> Range	NR <sup>b</sup> (15, NR) 4 to 38+	47 (47, NR) 9 to 47

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<sup>a</sup> CI = Confidence Interval

<sup>b</sup> NR = Not reached, Median duration of follow up: Study 1 = 26 months; Study 2 = 30 months

<sup>c</sup> Complete response rate = Pathologic and clinical complete responses

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The results of these studies were supported by demonstration of durable objective responses in three single-arm studies. In these studies, 130 patients with Rituximab-naïve follicular non-Hodgkin's lymphoma with or without transformation were evaluated for efficacy. All patients had relapsed following, or were refractory to, chemotherapy. The overall response rates ranged from 49% to 64% and the median durations of

230 response ranged from 13 to 16 months. Due to small sample sizes in the  
231 supportive studies, as in studies 1 and 2, the 95% confidence intervals for  
232 the median durations of response are wide.

233

#### 234 **INDICATIONS AND USAGE**

235 The BEXXAR therapeutic regimen (Tositumomab and Iodine I 131  
236 Tositumomab) is indicated for the treatment of patients with CD20 antigen-  
237 expressing relapsed or refractory, low grade, follicular, or transformed  
238 non-Hodgkin's lymphoma, including patients with Rituximab-refractory  
239 non-Hodgkin's lymphoma. Determination of the effectiveness of the  
240 BEXXAR therapeutic regimen is based on overall response rates in  
241 patients whose disease is refractory to chemotherapy alone or to  
242 chemotherapy and Rituximab. The effects of the BEXXAR therapeutic  
243 regimen on survival are not known.

244 The BEXXAR therapeutic regimen is not indicated for the initial treatment  
245 of patients with CD20 positive non-Hodgkin's lymphoma. (see **ADVERSE**  
246 **REACTIONS, Immunogenicity**)

247 The BEXXAR therapeutic regimen is intended as a single course of  
248 treatment. The safety of multiple courses of the BEXXAR therapeutic  
249 regimen, or combination of this regimen with other forms of irradiation or  
250 chemotherapy, has not been evaluated.

#### 251 **CONTRAINDICATIONS**

252 The BEXXAR therapeutic regimen is contraindicated in patients with  
253 known hypersensitivity to murine proteins or any other component of the  
254 BEXXAR therapeutic regimen.

#### 255 **PREGNANCY CATEGORY X**

256 Iodine I 131 Tositumomab (a component of the BEXXAR therapeutic  
257 regimen) is contraindicated for use in women who are pregnant. Iodine-  
258 131 may cause harm to the fetal thyroid gland when administered to  
259 pregnant women. Review of the literature has shown that transplacental

260 passage of radioiodide may cause severe, and possibly irreversible,  
261 hypothyroidism in neonates. While there are no adequate and well-  
262 controlled studies of the BEXXAR therapeutic regimen in pregnant  
263 animals or humans, use of the BEXXAR therapeutic regimen in women of  
264 childbearing age should be deferred until the possibility of pregnancy has  
265 been ruled out. If the patient becomes pregnant while being treated with  
266 the BEXXAR therapeutic regimen, the patient should be apprised of the  
267 potential hazard to the fetus (see **BOXED WARNING, Pregnancy**  
268 **Category X**).

## 269 **WARNINGS**

### 270 **Prolonged and Severe Cytopenias (see **BOXED WARNINGS;**** 271 **ADVERSE REACTIONS, Hematologic Events):**

272 The most common adverse reactions associated with the BEXXAR  
273 therapeutic regimen were severe or life-threatening cytopenias (NCI CTC  
274 grade 3 or 4) with 71% of the 230 patients enrolled in clinical studies  
275 experiencing grade 3 or 4 cytopenias. These consisted primarily of grade  
276 3 or 4 thrombocytopenia (53%) and grade 3 or 4 neutropenia (63%). The  
277 time to nadir was 4 to 7 weeks and the duration of cytopenias was  
278 approximately 30 days. Thrombocytopenia, neutropenia, and anemia  
279 persisted for more than 90 days following administration of the BEXXAR  
280 therapeutic regimen in 16 (7%), 15 (7%), and 12 (5%) patients  
281 respectively (this includes patients with transient recovery followed by  
282 recurrent cytopenia). Due to the variable nature in the onset of cytopenias,  
283 complete blood counts should be obtained weekly for 10-12 weeks. The  
284 sequelae of severe cytopenias were commonly observed in the clinical  
285 studies and included infections (45% of patients), hemorrhage (12%), a  
286 requirement for growth factors (12% G- or GM-CSF; 7% Epoetin alfa) and  
287 blood product support (15% platelet transfusions; 16% red blood cell  
288 transfusions). Prolonged cytopenias may also influence subsequent  
289 treatment decisions.

290 The safety of the BEXXAR therapeutic regimen has not been established  
291 in patients with >25% lymphoma marrow involvement, platelet count  
292 <100,000 cells/mm<sup>3</sup> or neutrophil count <1,500 cells/mm<sup>3</sup>.

293 **Hypersensitivity Reactions Including Anaphylaxis (see BOXED**  
294 **WARNINGS; ADVERSE REACTIONS, Hypersensitivity Reactions and**  
295 **Immunogenicity):** Serious hypersensitivity reactions, including some  
296 with fatal outcome, were reported during and following administration of  
297 the BEXXAR therapeutic regimen. Emergency supplies including  
298 medications for the treatment of hypersensitivity reactions, e.g.,  
299 epinephrine, antihistamines and corticosteroids, should be available for  
300 immediate use in the event of an allergic reaction during administration of  
301 the BEXXAR therapeutic regimen. Patients who have received murine  
302 proteins should be screened for human anti-mouse antibodies (HAMA).  
303 Patients who are positive for HAMA may be at increased risk of  
304 anaphylaxis and serious hypersensitivity reactions during administration of  
305 the BEXXAR therapeutic regimen.

306 **Secondary Malignancies:** Myelodysplastic syndrome (MDS) and/or  
307 acute leukemia were reported in 10% (24/230) of patients enrolled in the  
308 clinical studies and 3% (20/765) of patients included in expanded access  
309 programs, with median follow-up of 39 and 27 months, respectively.  
310 Among the 44 reported cases, the median time to development of  
311 MDS/leukemia was 31 months following treatment; however, the  
312 cumulative rate continues to increase.

313 Additional non-hematological malignancies were also reported in 54 of the  
314 995 patients enrolled in clinical studies or included in the expanded  
315 access program. Approximately half of these were non-melanomatous  
316 skin cancers. The remainder, which occurred in 2 or more patients,  
317 included colorectal cancer (7), head and neck cancer (6), breast cancer  
318 (5), lung cancer (4), bladder cancer (4), melanoma (3), and gastric cancer  
319 (2). The relative risk of developing secondary malignancies in patients  
320 receiving the BEXXAR therapeutic regimen over the background rate in  
321 this population cannot be determined, due to the absence of controlled  
322 studies (see **ADVERSE REACTIONS**).

323 **Pregnancy Category X:** (see **BOXED WARNINGS;**  
324 **CONTRAINDICATIONS**).

325 **Hypothyroidism:** Administration of the BEXXAR therapeutic regimen  
326 may result in hypothyroidism (see **ADVERSE REACTIONS,**  
327 **Hypothyroidism**). Thyroid-blocking medications should be initiated at  
328 least 24 hours before receiving the dosimetric dose and continued until  
329 14 days after the therapeutic dose (see **DOSAGE and**  
330 **ADMINISTRATION**). All patients must receive thyroid-blocking agents;  
331 any patient who is unable to tolerate thyroid-blocking agents should not  
332 receive the BEXXAR therapeutic regimen. Patients should be evaluated  
333 for signs and symptoms of hypothyroidism and screened for biochemical  
334 evidence of hypothyroidism annually.

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### 336 **PRECAUTIONS**

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

341 **Renal Function:** Iodine I 131 Tositumomab and Iodine-131 are excreted  
342 primarily by the kidneys. Impaired renal function may decrease the rate of  
343 excretion of the radiolabeled iodine and increase patient exposure to the  
344 radioactive component of the BEXXAR therapeutic regimen. There are no  
345 data regarding the safety of administration of the BEXXAR therapeutic  
346 regimen in patients with impaired renal function.

347 **Immunization:** The safety of immunization with live viral vaccines  
348 following administration of the BEXXAR therapeutic regimen has not been  
349 studied. The ability of patients who have received the BEXXAR  
350 therapeutic regimen to generate a primary or anamnestic humoral  
351 response to any vaccine has not been studied.

352 **Information for Patients:** Prior to administration of the BEXXAR  
353 therapeutic regimen, patients should be advised that they will have a  
354 radioactive material in their body for several days upon their release from  
355 the hospital or clinic. After discharge, patients should be provided with  
356 both oral and written instructions for minimizing exposure of family  
357 members, friends and the general public. Patients should be given a copy

358 of the written instructions for use as a reference for the recommended  
359 precautionary actions.

360 The pregnancy status of women of childbearing potential should be  
361 assessed and these women should be advised of the potential risks to the  
362 fetus (see **CONTRAINDICATIONS**). Women who are breastfeeding  
363 should be instructed to discontinue breastfeeding and should be apprised  
364 of the resultant potential harmful effects to the infant if these instructions  
365 are not followed.

366 Patients should be advised of the potential risk of toxic effects on the male  
367 and female gonads following the BEXXAR therapeutic regimen, and be  
368 instructed to use effective contraceptive methods during treatment and for  
369 12 months following the administration of the BEXXAR therapeutic  
370 regimen.

371 Patients should be informed of the risks of hypothyroidism and be advised  
372 of the importance of compliance with thyroid blocking agents and need for  
373 life-long monitoring.  
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375 Patients should be informed of the possibility of developing a HAMA  
376 immune response and that HAMA may affect the results of *in vitro* and  
377 *in vivo* diagnostic tests as well as results of therapies that rely on murine  
378 antibody technology.  
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380 Patients should be informed of the risks of cytopenias and symptoms  
381 associated with cytopenia, the need for frequent monitoring for up to  
382 12 weeks after treatment, and the potential for persistent cytopenias  
383 beyond 12 weeks.  
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385 Patients should be informed that MDS, secondary leukemia, and solid  
386 tumors have also been observed in patients receiving the BEXXAR  
387 therapeutic regimen.  
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389 Due to lack of controlled clinical studies, and high background incidence in  
390 the heavily pretreated patient population, the relative risk of development  
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392 of myelodysplastic syndrome/acute leukemia and solid tumors due to the  
393 BEXXAR therapeutic regimen cannot be determined.  
394

395 **Laboratory Monitoring:** A complete blood count (CBC) with differential  
396 and platelet count should be obtained prior to, and at least weekly  
397 following administration of the BEXXAR therapeutic regimen. Weekly  
398 monitoring of blood counts should continue for a minimum of 10 weeks or,  
399 if persistent, until severe cytopenias have completely resolved. More  
400 frequent monitoring is indicated in patients with evidence of moderate or  
401 more severe cytopenias (see **BOXED WARNINGS** and **WARNINGS**).  
402 Thyroid stimulating hormone (TSH) level should be monitored before  
403 treatment and annually thereafter. Serum creatinine levels should be  
404 measured immediately prior to administration of the BEXXAR therapeutic  
405 regimen.

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

411 **Drug/Laboratory Test Interactions:** Administration of the BEXXAR  
412 therapeutic regimen may result in the development of human anti-murine  
413 antibodies (HAMA). The presence of HAMA may affect the accuracy of the  
414 results of *in vitro* and *in vivo* diagnostic tests and may affect the toxicity  
415 profile and efficacy of therapeutic agents that rely on murine antibody  
416 technology. Patients who are HAMA positive may be at increased risk for  
417 serious allergic reactions and other side effects if they undergo *in vivo*  
418 diagnostic testing or treatment with murine monoclonal antibodies.

419 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No long-term  
420 animal studies have been performed to establish the carcinogenic or  
421 mutagenic potential of the BEXXAR therapeutic regimen or to determine  
422 its effects on fertility in males or females. However, radiation is a potential  
423 carcinogen and mutagen. Administration of the BEXXAR therapeutic  
424 regimen results in delivery of a significant radiation dose to the testes.

425 The radiation dose to the ovaries has not been established. There have  
426 been no studies to evaluate whether administration of the BEXXAR  
427 therapeutic regimen causes hypogonadism, premature menopause,  
428 azoospermia and/or mutagenic alterations to germ cells. There is a  
429 potential risk that the BEXXAR therapeutic regimen may cause toxic  
430 effects on the male and female gonads. Effective contraceptive methods  
431 should be used during treatment and for 12 months following  
432 administration of the BEXXAR therapeutic regimen.

433 **Pregnancy Category X: (see CONTRAINDICATIONS; WARNINGS).**

434 **Nursing Mothers:** Radioiodine is excreted in breast milk and may reach  
435 concentrations equal to or greater than maternal plasma concentrations.  
436 Immunoglobulins are also known to be excreted in breast milk. The  
437 absorption potential and potential for adverse effects of the monoclonal  
438 antibody component (Tositumomab) in the infant are not known.  
439 Therefore, formula feedings should be substituted for breast feedings  
440 before starting treatment. Women should be advised to discontinue  
441 nursing.

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

444 **Geriatric Use:** Clinical studies of the BEXXAR therapeutic regimen did  
445 not include sufficient numbers of patients aged 65 and over to determine  
446 whether they respond differently from younger patients. In clinical studies,  
447 230 patients received the BEXXAR therapeutic regimen at the  
448 recommended dose. Of these, 27% (61 patients) were age 65 or older  
449 and 4% (10 patients) were age 75 or older. Across all studies, the overall  
450 response rate was lower in patients age 65 and over (41% vs. 61%) and  
451 the duration of responses was shorter (10 months vs. 16 months);  
452 however, these findings are primarily derived from 2 of the 5 studies.  
453 While the incidence of severe hematologic toxicity was lower, the duration  
454 of severe hematologic toxicity was longer in those age 65 or older as  
455 compared to patients less than 65 years of age. Due to the limited  
456 experience greater sensitivity of some older individuals cannot be ruled  
457 out.

458        **ADVERSE REACTIONS**

459        The most serious adverse reactions observed in the clinical trials were  
460        severe and prolonged cytopenias and the sequelae of cytopenias which  
461        included infections (sepsis) and hemorrhage in thrombocytopenic patients,  
462        allergic reactions (bronchospasm and angioedema), secondary leukemia  
463        and myelodysplasia (see **BOXED WARNINGS** and **WARNINGS**).

464        The most common adverse reactions occurring in the clinical trials  
465        included neutropenia, thrombocytopenia, and anemia that are both  
466        prolonged and severe. Less common but severe adverse reactions  
467        included pneumonia, pleural effusion and dehydration.

468        Data regarding adverse events were primarily obtained in 230 patients  
469        with non-Hodgkin's lymphoma enrolled in five clinical trials using the  
470        recommended dose and schedule. Patients had a median follow-up of 39  
471        months and 79% of the patients were followed at least 12 months for  
472        survival and selected adverse events. Patients had a median of 3 prior  
473        chemotherapy regimens, a median age of 55 years, 60% male, 27% had  
474        transformation to a higher grade histology, 29% were intermediate grade  
475        and 2% high grade histology (IWF) and 68% had Ann Arbor stage IV  
476        disease. Patients enrolled in these studies were not permitted to have  
477        prior hematopoietic stem cell transplantation or irradiation to more than  
478        25% of the red marrow. In the expanded access program, which included  
479        765 patients, data regarding clinical serious adverse events and HAMA  
480        and TSH levels were used to supplement the characterization of delayed  
481        adverse events (see **ADVERSE REACTIONS, Hypothyroidism,**  
482        **Secondary Leukemia and Myelodysplastic Syndrome,**  
483        **Immunogenicity**).

484        Because clinical trials are conducted under widely varying conditions,  
485        adverse reaction rates observed in the clinical trials of a drug cannot be  
486        directly compared to rates in the clinical trials of another drug and may not  
487        reflect the rates observed in practice. The adverse reaction information  
488        from clinical trials does, however, provide a basis for identifying the  
489        adverse events that appear to be related to drug use and for  
490        approximating rates.

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

499 **Infectious Events:** One hundred and four of the 230 (45%) patients  
500 experienced one or more adverse events possibly related to infection.  
501 The majority were viral (e.g. rhinitis, pharyngitis, flu symptoms, or herpes)  
502 or other minor infections. Twenty of 230 (9%) patients experienced  
503 infections that were considered serious because the patient was  
504 hospitalized to manage the infection. Documented infections included  
505 pneumonia, bacteremia, septicemia, bronchitis, and skin infections.

506 **Hypersensitivity Reactions:** Fourteen patients (6%) experienced one or  
507 more of the following adverse events: allergic reaction, face edema,  
508 injection site hypersensitivity, anaphylactic reaction, laryngismus, and  
509 serum sickness. In the post-marketing setting, severe hypersensitivity  
510 reactions, including fatal anaphylaxis have been reported.

511 **Gastrointestinal Toxicity:** Eighty-seven patients (38%) experienced one  
512 or more gastrointestinal adverse events, including nausea, emesis,  
513 abdominal pain, and diarrhea. These events were temporally related to  
514 the infusion of the antibody. Nausea, vomiting, and abdominal pain were  
515 often reported within days of infusion, whereas diarrhea was generally  
516 reported days to weeks after infusion.

517 **Infusional Toxicity:** A constellation of symptoms, including fever, rigors  
518 or chills, sweating, hypotension, dyspnea, bronchospasm, and nausea,  
519 have been reported during or within 48 hours of infusion. Sixty-seven  
520 patients (29%) reported fever, rigors/chills, or sweating within 14 days  
521 following the dosimetric dose. Although all patients in the clinical studies  
522 received pretreatment with acetaminophen and an antihistamine, the  
523 value of premedication in preventing infusion-related toxicity was not

524 evaluated in any of the clinical studies. Infusional toxicities were managed  
525 by slowing and/or temporarily interrupting the infusion. Symptomatic  
526 management was required in more severe cases. Adjustment of the rate  
527 of infusion to control adverse reactions occurred in 16 patients (7%);  
528 seven patients required adjustments for only the dosimetric infusion, two  
529 required adjustments for only the therapeutic infusion, and seven required  
530 adjustments for both the dosimetric and the therapeutic infusions.  
531 Adjustments included reduction in the rate of infusion by 50%, temporary  
532 interruption of the infusion, and in 2 patients, infusion was permanently  
533 discontinued.

534 Table 5 lists clinical adverse events that occurred in  $\geq 5\%$  of patients.  
535 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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Corixa Corporation: BEXXAR® (Tositumomab, Iodine I 131 Tositumomab)  
BLA STN 125011

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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%

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<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>	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	5% (n=11)

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<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 hematology 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 programs were similar to the characteristics of patients enrolled in the clinical studies, except that the median number of prior chemotherapy regimens was fewer (2 vs. 3) and the proportion with low-grade histology

568 was higher (77% vs. 70%) in patients from the expanded access  
569 programs.

570 **Secondary Leukemia and Myelodysplastic Syndrome (MDS):** There  
571 were 44 cases of MDS/secondary leukemia reported among 995 (4.0%)  
572 patients included in clinical studies and expanded access programs, with a  
573 median follow-up of 29 months. The overall incidence of MDS/secondary  
574 leukemia among the 230 patients included in the clinical studies was 10%  
575 (24/230), with a median follow-up of 39 months and a median time to  
576 development of MDS of 34 months. The cumulative incidence of  
577 MDS/secondary leukemia in this patient population was 4.7% at 2 years  
578 and 15% at 5 years. The incidence of MDS/secondary leukemia among  
579 the 765 patients in the expanded access programs was 3% (20/765), with  
580 a median follow-up of 27 months and a median time to development of  
581 MDS of 31 months. The cumulative incidence of MDS/secondary  
582 leukemia in this patient population was 1.6% at 2 years and 6% at 5 years.

583 **Secondary Malignancies:** Of the 995 patients in clinical studies and the  
584 expanded access programs, there were 65 reports of second  
585 malignancies in 54 patients, excluding secondary leukemias. The most  
586 common included non-melanomatous skin cancers (26), colorectal cancer  
587 (7) head and neck cancer (6), breast cancer (5), lung cancer (4), bladder  
588 cancer (4), melanoma (3), and gastric cancer (2). Some of these events  
589 included recurrence of an earlier diagnosis of cancer.

590 **Hypothyroidism:** Of the 230 patients in the clinical studies, 203 patients  
591 did not have elevated TSH upon study entry. Of these, 137 patients had  
592 at least one post-treatment TSH value available and were not taking  
593 thyroid hormonal treatment upon study entry. With a median follow up  
594 period of 46 months, the incidence of hypothyroidism based on elevated  
595 TSH or initiation of thyroid replacement therapy in these patients was 18%  
596 with a median time to development of hypothyroidism of 16 months. The  
597 cumulative incidences of hypothyroidism at 2 and 5 years in these 137  
598 patients were 11% and 19% respectively. New events have been  
599 observed up to 90 months post treatment.

600 Of the 765 patients in the expanded access programs, 670 patients did  
601 not have elevated TSH upon study entry. Of these, 455 patients had at  
602 least one post-treatment TSH value available and were not taking thyroid  
603 hormonal treatment upon study entry. With a median follow up period of  
604 33 months, the incidence of hypothyroidism based on elevated TSH or  
605 initiation of thyroid replacement therapy in these 455 patients was 13%  
606 with a median time to development of hypothyroidism of 15 months. The  
607 cumulative incidences of hypothyroidism at 2 and 5 years in these patients  
608 were 9% and 17%, respectively.

609 **Immunogenicity:** One percent (11/989) of the chemotherapy-relapsed or  
610 refractory patients included in the clinical studies or the expanded access  
611 program had a positive serology for HAMA prior to treatment and six  
612 patients had no baseline assessment for HAMA. Of the 230 patients in  
613 the clinical studies, 220 patients were seronegative for HAMA prior to  
614 treatment, and 219 had at least one post-treatment HAMA value obtained.  
615 With a median observation period of 6 months, a total of 23 patients (11%)  
616 became seropositive for HAMA post-treatment. The median time of  
617 HAMA development was 6 months. The cumulative incidences of HAMA  
618 seropositivity at 6 months, 12 months, and 18 months were 6%, 17% and  
619 21% respectively.

620 Of the 765 patients in the expanded access programs, 758 patients were  
621 seronegative for HAMA prior to treatment, and 569 patients had at least  
622 one post-treatment HAMA value obtained. With a median observation  
623 period of 7 months, a total of 57 patients (10%) became seropositive for  
624 HAMA post-treatment. The median time of HAMA development was 5  
625 months. The cumulative incidences of HAMA seropositivity at 6 months,  
626 12 months, and 18 months were 7%, 12% and 13%, respectively.

627 In a study of 76 previously untreated patients with low-grade non-  
628 Hodgkin's lymphoma who received the BEXXAR therapeutic regimen, the  
629 incidence of conversion to HAMA seropositivity was 70%, with a median  
630 time to development of HAMA of 27 days.

631 The data reflect the percentage of patients whose test results were  
632 considered positive for HAMA in an ELISA assay that detects antibodies

633 to the Fc portion of IgG<sub>1</sub> murine immunoglobulin and are highly dependent  
634 on the sensitivity and specificity of the assay. Additionally, the observed  
635 incidence of antibody positivity in an assay may be influenced by several  
636 factors including sample handling, concomitant medications, and  
637 underlying disease. For these reasons, comparison of the incidence of  
638 HAMA in patients treated with the BEXXAR therapeutic regimen with the  
639 incidence of HAMA in patients treated with other products may be  
640 misleading.

#### 641 **OVERDOSAGE**

642 The maximum dose of the BEXXAR therapeutic regimen that was  
643 administered in clinical trials was 88 cGy. Three patients were treated with  
644 a total body dose of 85 cGy of Iodine I 131 Tositumomab in a dose  
645 escalation study. Two of the 3 patients developed Grade 4 toxicity of 5  
646 weeks duration with subsequent recovery. In addition, accidental  
647 overdose of the BEXXAR therapeutic regimen occurred in one patient at a  
648 total body dose of 88 cGy. The patient developed Grade 3 hematologic  
649 toxicity of 18 days duration. Patients who receive an accidental overdose  
650 of Iodine I 131 Tositumomab should be monitored closely for cytopenias  
651 and radiation-related toxicity. The effectiveness of hematopoietic stem  
652 cell transplantation as a supportive care measure for marrow injury has  
653 not been studied; however, the timing of such support should take into  
654 account the pharmacokinetics of the BEXXAR therapeutic regimen and  
655 decay rate of the Iodine-131 in order to minimize the possibility of  
656 irradiation of infused hematopoietic stem cells.

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#### 658 **DOSAGE AND ADMINISTRATION**

##### 659 **Recommended Dose**

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

663 Note: the safety of the BEXXAR therapeutic regimen was established only  
664 in the setting of patients receiving thyroid blocking agents and  
665 premedication to ameliorate/prevent infusion reactions (see **Concomitant**  
666 **Medications**).

667 **Dosimetric step**

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

679 **Therapeutic step**

680 Note: Do not administer the therapeutic step if biodistribution is altered  
681 (see **Assessment of Biodistribution of Iodine I 131 Tositumomab**).

- 682 • Tositumomab 450 mg intravenously in 50 ml 0.9% Sodium Chloride  
683 over 60 minutes. Reduce the rate of infusion by 50% for mild to  
684 moderate infusional toxicity; interrupt infusion for severe infusional  
685 toxicity. After complete resolution of severe infusional toxicity, infusion  
686 may be resumed with a 50% reduction in the rate of infusion.
- 687 • Iodine I 131 Tositumomab (see **CALCULATION OF IODINE-131**  
688 **ACTIVITY FOR THE THERAPEUTIC DOSE**). Reduce the rate of  
689 infusion by 50% for mild to moderate infusional toxicity; interrupt  
690 infusion for severe infusional toxicity. After complete resolution of  
691 severe infusional toxicity, infusion may be resumed with a 50%  
692 reduction in the rate of infusion.

693           • Patients with  $\geq 150,000$  platelets/ $\text{mm}^3$ : The recommended dose is  
694           the activity of Iodine-131 calculated to deliver 75 cGy total body  
695           irradiation and 35 mg Tositumomab, administered intravenously  
696           over 20 minutes.

697           • Patients with NCI Grade 1 thrombocytopenia (platelet counts  
698            $\geq 100,000$  but  $< 150,000$  platelets/ $\text{mm}^3$ ): The recommended dose is  
699           the activity of Iodine-131 calculated to deliver 65 cGy total body  
700           irradiation and 35 mg Tositumomab, administered intravenously  
701           over 20 minutes.

702           **Concomitant Medications:** The safety of the BEXXAR therapeutic  
703           regimen was established in studies in which all patients received the  
704           following concurrent medications:

705           • Thyroid protective agents: Saturated solution of potassium iodide  
706           (SSKI) 4 drops orally t.i.d.; Lugol's solution 20 drops orally t.i.d.; or  
707           potassium iodide tablets 130 mg orally q.d. Thyroid protective agents  
708           should be initiated at least 24 hours prior to administration of the Iodine  
709           I 131 Tositumomab dosimetric dose and continued until 2 weeks after  
710           administration of the Iodine I 131 Tositumomab therapeutic dose.

711           **Patients should not receive the dosimetric dose of Iodine I 131**  
712           **Tositumomab if they have not yet received at least three doses of**  
713           **SSKI, three doses of Lugol's solution, or one dose of 130 mg**  
714           **potassium iodide tablet (at least 24 hours prior to the dosimetric**  
715           **dose).**

716           • Acetaminophen 650 mg orally and diphenhydramine 50 mg orally 30  
717           minutes prior to administration of Tositumomab in the dosimetric and  
718           therapeutic steps.

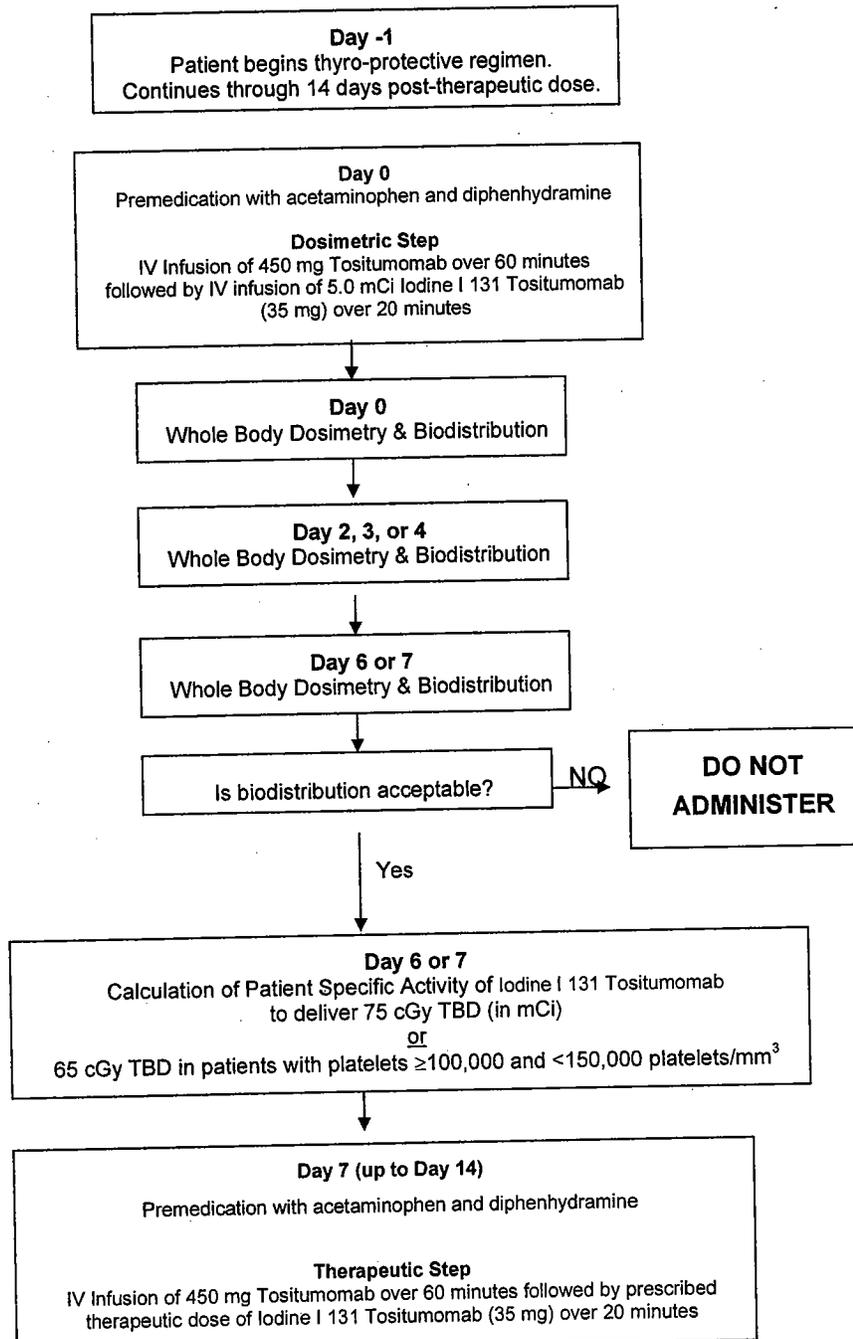
719           The BEXXAR therapeutic regimen is administered via an IV tubing set  
720           with an in-line 0.22 micron filter. **THE SAME IV TUBING SET AND**  
721           **FILTER MUST BE USED THROUGHOUT THE ENTIRE DOSIMETRIC**  
722           **OR THERAPEUTIC STEP. A CHANGE IN FILTER CAN RESULT IN**  
723           **LOSS OF DRUG.**

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Figure 1 shows an overview of the dosing schedule.

**Figure 1**  
**Dosing Schedule**

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773           **PREPARATION OF THE BEXXAR THERAPEUTIC REGIMEN**

774           **GENERAL**

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

777           **The Iodine I 131 Tositumomab dosimetric and therapeutic doses**  
778           **should be measured by a suitable radioactivity calibration system**  
779           **immediately prior to administration. The dose calibrator must be**  
780           **operated in accordance with the manufacturer's specifications and**  
781           **quality control for the measurement of Iodine-131.**

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

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

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

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794           **Preparation for the Dosimetric Step**

795           **Tositumomab Dose**

796           **Required materials not supplied:**

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

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

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

803 Method:

- 804 1. Withdraw and dispose of 32 mL of saline from a 50 mL bag of sterile  
805 0.9% Sodium Chloride for Injection, USP.
- 806 2. Withdraw the entire contents from each of the two 225 mg vials (a total  
807 of 450 mg Tositumomab in 32 mL) and transfer to the infusion bag  
808 containing 18 mL of 0.9% Sodium Chloride for Injection, USP to yield a  
809 final volume of 50 mL.
- 810 3. Gently mix the solution by inverting/rotating the bag. DO NOT SHAKE.
- 811 4. The diluted Tositumomab may be stored for up to 24 hours when  
812 stored refrigerated at 2°C–8°C (36°F–46°F) and for up to 8 hours at  
813 room temperature.

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

817 **Preparation of Iodine I 131 Tositumomab Dosimetric Dose**

818 Required materials not supplied:

- 819 A. Lead shielding for preparation vial and syringe pump
- 820
- 821 B. One 30 mL syringe with 18 gauge needle to withdraw the  
822 calculated volume of Iodine I 131 Tositumomab from the Iodine I  
823 131 Tositumomab vial. One 60 mL syringe with 18 gauge needle to  
824 withdraw the volume from the preparation vial for administration
- 825 C. One 20 mL syringe with attached needle, filled with 0.9% Sodium  
826 Chloride for Injection, USP
- 827 D. One 3 mL syringe with attached needle to withdraw Tositumomab  
828 from 35 mg vial
- 829 E. One sterile, 30 or 50 mL preparation vial
- 830 F. Two lead pots, both kept at room temperature. One pot is used to  
831 thaw the labeled antibody and the second pot is used to hold the  
832 preparation vial

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Method:

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1. Allow approximately 60 minutes for thawing (at ambient temperature) of the Iodine I 131 Tosiumomab 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 Tosiumomab activity of 5.0 mCi.

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3. Withdraw the calculated volume from the Iodine I 131 Tosiumomab 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 Tosiumomab at this time, based on the volume and the activity in the preparation vial. Recalculate the volume required for an Iodine I 131 Tosiumomab activity of 5.0 mCi. Using the same 30 mL syringe, add or subtract the appropriate volume from the Iodine I 131 Tosiumomab vial so that the preparation vial contains the volume required for an Iodine I 131 Tosiumomab 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 Tosiumomab contained in the solution of Iodine I 131 Tosiumomab 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 Tosiumomab needed to yield a total of 35 mg protein. Calculate the volume needed from the 35 mg vial of Tosiumomab, based on the protein concentration. Withdraw the calculated volume of Tosiumomab from the 35 mg vial of Tosiumomab, and transfer this volume to the shielded preparation vial. The preparation vial should now contain a total of 35 mg of Tosiumomab.

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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.

- 871 9. Withdraw the entire contents from the preparation vial into a 60 mL  
872 syringe using a large bore needle (18 gauge).
- 873 10. Assay and record the activity.

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**Administration of the Dosimetric Step**

877 Required materials not supplied: For questions about required materials call  
878 the BEXXAR Service Center at 1-877-423-9927.

- 879 A. One IV Filter set (0.22 micron filter), 15 inch with injection site (port)  
880 and luer lock
- 881 B. One Primary IV infusion set
- 882 C. One 100 mL bag of sterile 0.9% Sodium Chloride for Injection, USP
- 883 D. Two Secondary IV infusion sets
- 884 E. One IV Extension set, 30 inch luer lock
- 885 F. One 3-way stopcock
- 886 G. One 50 mL bag of sterile 0.9% Sodium Chloride for Injection, USP
- 887 H. One Infusion pump for Tositumomab infusion
- 888 I. One Syringe Pump for Iodine I 131 Tositumomab infusion
- 889 J. Lead shielding for use in the administration of the dosimetric dose

890 **Tositumomab Infusion:**

891 (See Figure 1 in the "**Workbook for Dosimetry Methodology and**  
892 **Administration Set-Up**" for diagrammatic illustration of the configuration of  
893 the infusion set components.)  
894

- 895 1. Attach a primary IV infusion set (Item B) to the 0.22 micron in-line filter set  
896 (Item A) and the 100 mL bag of sterile 0.9% Sodium Chloride for Injection,  
897 USP (Item C).
- 898 2. After priming the primary IV infusion set (Item B) and IV filter set (Item A),  
899 connect the infusion bag containing 450 mg Tositumomab (50 mL) via a  
900 secondary IV infusion set (Item D) to the primary IV infusion set (Item B) at  
901 a port distal to the 0.22 micron in-line filter. Infuse Tositumomab over 60  
902 minutes.

903

904 3. After completion of the Tositumomab infusion, disconnect the secondary  
905 IV infusion set (Item D) and flush the primary IV infusion set (Item B) and  
906 the in-line IV filter set (Item A) with sterile 0.9% Sodium Chloride for  
907 Injection, USP. Discard the Tositumomab bag and secondary IV infusion  
908 set.

909

910 **Iodine I 131 Tositumomab Dosimetric Infusion:**

911 (See Figure 2 in the "**Workbook for Dosimetry Methodology and**  
912 **Administration Set-Up**" for diagrammatic illustration of the configuration of  
913 the infusion set components.)

914 1. Appropriate shielding should be used in the administration of the  
915 dosimetric dose.

916 2. The dosimetric dose is delivered in a 60 mL syringe.

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

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

923 **(Note: You must use the same primary infusion set (Item B) and IV filter**  
924 **set (Item A) with pre-wetted filter that was used for the Tositumomab**  
925 **infusion. A change in filter can result in loss of up to 7% of the Iodine I**  
926 **131 Tositumomab dose.)**

927

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

930 6. Set syringe pump to deliver the entire 5.0 mCi (35 mg) dose of Iodine I  
931 131 Tositumomab over 20 minutes.

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

- 936 8. After the flush, disconnect the extension set (Item E), 3-way stopcock  
937 (Item F) and syringe. Disconnect the primary IV infusion set (Item B) and  
938 in-line filter set (Item A). Determine the combined residual activity of the  
939 syringe and infusion set components (stopcock, extension set, primary  
940 infusion set and in-line filter set) by assaying these items in a suitable  
941 radioactivity calibration system immediately following completion of  
942 administration of all components of the dosimetric step. Calculate and  
943 record the dose delivered to the patient by subtracting the residual activity  
944 in the syringe and the infusion set components from the activity of Iodine I  
945 <sup>131</sup>Tositumomab in the syringe prior to infusion.
- 946 9. Discard all materials used to deliver the Iodine I <sup>131</sup>Tositumomab (e.g.,  
947 syringes, vials, in-line filter set, extension set and infusion sets) in  
948 accordance with local, state, and federal regulations governing radioactive  
949 and biohazardous waste.

950 **Determination of Dose for the Therapeutic Step (see CALCULATION OF**  
951 **IODINE-131 ACTIVITY FOR THERAPEUTIC DOSE):**

952 The method for determining and calculating the patient-specific dose of  
953 Iodine-131 activity (mCi) to be administered in the therapeutic step is  
954 described below. The derived values obtained in steps 3 and 4 and  
955 calculation of the therapeutic dose as described in step 6 may be determined  
956 manually [see **Workbook for Dosimetry Methodology and Administration**  
957 **Set-up**] or calculated automatically using the Corixa proprietary software  
958 program [BEXXAR Patient Management Templates]. To receive training and  
959 to obtain the "BEXXAR Patient Management Templates" call the BEXXAR  
960 Service Center at 1-877-423-9927. For assistance with either manual or  
961 automated calculations call the BEXXAR Service Center at 1-877-423-9927.

- 962 1. Following infusion of the Iodine I <sup>131</sup>Tositumomab dosimetric dose,  
963 obtain total body gamma camera counts and whole body images at the  
964 following timepoints:
- 965 a. Within one hour of infusion and prior to urination
  - 966 b. 2-4 days after infusion of the dosimetric dose, following urination
  - 967 c. 6-7 days after infusion of the dosimetric dose, following urination
- 968 2. Assess biodistribution. If biodistribution is altered, the therapeutic step  
969 should not be administered.

- 970 3. Determine total body residence time (see Graph 1, "**Determination of**  
971 **Residence Time**", in the "**Workbook for Dosimetry Methodology and**  
972 **Administration Set-Up**").
- 973 4. Determine activity hours (see Table 2, "**Determination of Activity**  
974 **Hours**", in the "**Workbook for Dosimetry Methodology and**  
975 **Administration Set-Up**"), according to gender. Use actual patient mass  
976 (in kg) or maximum effective mass (in kg) whichever is lower (see Table 1,  
977 "**Determination of Maximum Effective Mass**", in the "**Workbook for**  
978 **Dosimetry Methodology and Administration Set-Up**").
- 979 5. Determine whether the desired total body dose should be reduced (to 65  
980 cGy) due to a platelet count of 100,000 to <150,000 cells/mm<sup>3</sup>.
- 981 6. Based on the total body residence time and activity hours, calculate the  
982 Iodine-131 activity (mCi) to be administered to deliver the therapeutic dose  
983 of 65 or 75 cGy.

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

986 Iodine-131 Activity (mCi) =  $\frac{\text{Activity Hours (mCi hr)}}{\text{Residence Time (hr)}} \times \frac{\text{Desired Total Body Dose (cGy)}}{75 \text{ cGy}}$   
987

988 **Preparation for the Therapeutic Step**989 **Tositumomab Dose**990 **Required materials not supplied:**

- 991 A. One 50 mL syringe with attached 18 gauge needle (to withdraw 450  
992 mg of Tositumomab from two vials each containing 225 mg  
993 Tositumomab)
- 994 B. One 50 mL bag of sterile 0.9% Sodium Chloride for Injection, USP
- 995 C. One 50 mL syringe for drawing up 32 mL of saline for disposal from the  
996 50 mL bag of sterile 0.9% Sodium Chloride for Injection USP

997 **Method:**

- 998 1. Withdraw and dispose of 32 mL of saline from a 50 mL bag of sterile 0.9%  
999 Sodium Chloride for Injection, USP.
- 1000 2. Withdraw the entire contents from each of the two 225 mg vials (a total of  
1001 450 mg Tositumomab in 32 mL) and transfer to the infusion bag  
1002 containing 18 mL of 0.9% Sodium Chloride for Injection, USP to yield a  
1003 final volume of 50 mL.
- 1004 3. Gently mix the solutions by inverting/rotating the bag. DO NOT SHAKE.
- 1005 4. The diluted Tositumomab may be stored for up to 24 hours when stored  
1006 refrigerated at 2°C–8°C (36°F–46°F) and for up to 8 hours at room  
1007 temperature.
- 1008 Note: Tositumomab solution may contain particulates that are generally  
1009 white in nature. The product should appear clear to opalescent, colorless  
1010 to slightly yellow.

1012 **Preparation of Iodine I 131 Tositumomab Therapeutic Dose**1014 **Required materials not supplied:**

- 1015 A. Lead shielding for preparation vial and syringe pump

- 1016 B. One or two 30 mL syringes with 18 gauge needles to withdraw the  
1017 calculated volume of Iodine I 131 Tositumomab from the Iodine I 131  
1018 Tositumomab vial(s). One or two 60 mL syringes with 18 gauge  
1019 needles to withdraw the volume from the preparation vial for  
1020 administration
- 1021 C. One 20 mL syringe with attached needle filled with 0.9% Sodium  
1022 Chloride for Injection, USP
- 1023 D. One 3 mL sterile syringe with attached needle to draw up  
1024 Tositumomab from the 35 mg vial
- 1025 E. One sterile, 30 or 50 mL preparation vial
- 1026 F. Two lead pots both kept at room temperature. One pot is used to thaw  
1027 the labeled antibody, and the second pot is used to hold the  
1028 preparation vial

1029 Method:

- 1030 1. Allow approximately 60 minutes for thawing (at ambient temperature) of  
1031 the Iodine I 131 Tositumomab therapeutic vial with appropriate lead  
1032 shielding.  
1033
- 1034 2. Calculate the dose of Iodine I 131 Tositumomab required (see  
1035 **CALCULATION OF IODINE-131 ACTIVITY FOR THERAPEUTIC DOSE**).
- 1036 3. Based on the activity concentration of the vial (see actual product  
1037 specification sheet for each vial supplied in the therapeutic package),  
1038 calculate the volume required for the Iodine I 131 Tositumomab activity  
1039 required for the therapeutic dose.
- 1040 4. Using one or more 30 mL syringes with an 18-gauge needle, withdraw the  
1041 calculated volume from the Iodine I 131 Tositumomab vial.
- 1042 5. Transfer this volume to the shielded preparation vial.
- 1043 6. Assay the dose to ensure that the appropriate activity (mCi) has been  
1044 prepared.
- 1045 a. If the assayed dose is the calculated dose (+/- 10%) needed for the  
1046 therapeutic step, proceed with step 7.

- 1047 b. If the assayed dose does not contain the desired dose (+/- 10%), re-  
1048 calculate the activity concentration of the Iodine I 131 Tositumomab at  
1049 this time, based on the volume and the activity in the preparation vial.  
1050 Re-calculate the volume required for an Iodine I 131 Tositumomab  
1051 activity for the therapeutic dose. Using the same 30 mL syringe, add  
1052 or subtract the appropriate volume from the Iodine I 131 Tositumomab  
1053 vial so that the preparation vial contains the volume required for the  
1054 Iodine I 131 Tositumomab activity required for the therapeutic dose.  
1055 Re-assay the preparation vial. Proceed to step 7.
- 1056 7. Calculate the amount of Tositumomab protein contained in the solution of  
1057 Iodine I 131 Tositumomab in the shielded preparation vial, based on the  
1058 volume and protein concentration (see product specification sheet).
- 1059 8. If the shielded preparation vial contains less than 35 mg, calculate the  
1060 amount of additional Tositumomab needed to yield a total of 35 mg  
1061 protein. Calculate the volume needed from the 35 mg vial of  
1062 Tositumomab, based on the protein concentration. Withdraw the  
1063 calculated volume of Tositumomab from the 35 mg vial of Tositumomab,  
1064 and transfer this volume to the shielded preparation vial. The preparation  
1065 vial should now contain a total of 35 mg of Tositumomab.
- 1066 **Note:** If the dose of Iodine I 131 Tositumomab requires the use of 2 vials  
1067 of Iodine I 131 Tositumomab or the entire contents of a single vial of  
1068 Iodine I 131 Tositumomab, there may be no need to add protein from the  
1069 35 mg vial of Tositumomab.
- 1070 9. Using the 20 mL syringe containing 0.9% Sodium Chloride for Injection,  
1071 USP, add a sufficient volume (if needed) to the shielded preparation vial to  
1072 yield a final volume of 30 mL. Gently mix the solution.
- 1073 10. Withdraw the entire volume from the preparation vial into a one or more  
1074 sterile 60 mL syringes using a large bore needle (18 gauge).
- 1075 11. Assay and record the activity.

1076  
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1078

#### **Administration of the Therapeutic Step**

1079  
1080 **Note:** Restrictions on patient contact with others and release from the  
1081 hospital must follow all applicable federal, state, and institutional regulations.

1082 **Required materials not supplied: For questions about required materials call**  
1083 **the BEXXAR Service Center at 1-877-423-9927.**

- 1084 A. One IV Filter set (0.22 micron, filter), 15 inch with injection site (port)  
1085 and luer lock
- 1086 B. One Primary IV infusion set

- 1087 C. One 100 mL bag of sterile 0.9% Sodium Chloride for Injection, USP  
1088 D. Two Secondary IV infusion sets  
1089 E. One IV extension set, 30 inch luer lock  
1090 F. One 3-way stopcock  
1091 G. One 50 mL bag of sterile 0.9% Sodium Chloride for Injection, USP  
1092 H. One Infusion pump for Tositumomab infusion  
1093 I. One Syringe Pump for Iodine I 131 Tositumomab infusion  
1094 J. Lead shielding for use in the administration of the therapeutic dose  
1095

1096 **Tositumomab Infusion:**

1097 (See Figure 1 in the "**Workbook for Dosimetry Methodology and**  
1098 **Administration Set-Up**" for diagrammatic illustration of the configuration of  
1099 the infusion set components.)

- 1100 1. Attach a primary IV infusion set (Item B) to the 0.22 micron in-line filter set  
1101 (Item A) and a 100 mL bag of sterile 0.9% Sodium Chloride for Injection,  
1102 USP (Item C).  
1103 2. After priming the primary IV infusion set (Item B) and filter set (Item A),  
1104 connect the infusion bag containing 450 mg Tositumomab (50 mL) via a  
1105 secondary IV infusion set (Item D) to the primary IV infusion set (Item B) at  
1106 a port distal to the 0.22 micron in-line filter. Infuse Tositumomab over 60  
1107 minutes.  
1108 3. After completion of the Tositumomab infusion, disconnect the secondary  
1109 IV infusion set (Item D) and flush the primary IV infusion set (Item B) and  
1110 the IV filter set (Item A) with sterile 0.9% Sodium Chloride for Injection,  
1111 USP. Discard the Tositumomab bag and secondary IV infusion set.

1112 **Iodine I 131 Tositumomab Therapeutic Infusion:**

1113 (See Figure 2 in the "**Workbook for Dosimetry Methodology and**  
1114 **Administration Set-Up**" for diagrammatic illustration of the configuration of  
1115 the infusion set components.)  
1116

- 1117 1. Appropriate shielding should be used in the administration of the  
1118 therapeutic dose.

- 1119 2. The therapeutic dose is delivered in one or more 60 mL syringes.
- 1120 3. Connect the extension set (Item E) to the 3-way stopcock (Item F).
- 1121 4. Connect the 50 mL bag of sterile 0.9% Sodium Chloride for Injection, USP  
1122 (Item G) to a secondary IV infusion set (Item D) and connect the infusion  
1123 set to the 3-way stopcock (Item F). Prime the secondary IV infusion set  
1124 (Item D) and the extension set (Item E). Connect the extension set (Item  
1125 E) to a port in the primary IV infusion set (Item B), distal to the filter.
- 1126 (Note: You must use the same primary infusion set (Item B) and IV filter  
1127 set (Item A) with pre-wetted filter that was used for the Tositumomab  
1128 infusion. A change in filter can result in loss of up to 7% of the Iodine I  
1129 131 Tositumomab dose.)
- 1130 5. Attach the syringe filled with the Iodine I 131 Tositumomab to the 3-way  
1131 stopcock (Item F).  
1132
- 1133 6. Set syringe pump to deliver the entire therapeutic dose of Iodine I 131  
1134 Tositumomab over 20 minutes. (Note: if more than one syringe is  
1135 required, remove the syringe and repeat steps 5 and 6.)
- 1136 7. After completion of the infusion of Iodine I 131 Tositumomab, close the  
1137 stopcock (Item F) to the syringe. Flush the secondary IV infusion set (Item  
1138 D) and the extension set (Item E) with 0.9% Sodium Chloride from the 50  
1139 mL bag of sterile, 0.9% Sodium Chloride for Injection, USP (Item G).
- 1140 8. After the flush, disconnect the extension set (Item E), 3-way stopcock  
1141 (Item F) and syringe. Disconnect the primary IV infusion set (Item B) and  
1142 in-line filter set (Item A). Determine the combined residual activity of the  
1143 syringe(s) and infusion set components (stopcock, extension set, primary  
1144 infusion set and in-line filter set) by assaying these items in a suitable  
1145 radioactivity calibration system immediately following completion of  
1146 administration of all components of the therapeutic step. Calculate and  
1147 record the dose delivered to the patient by subtracting the residual activity  
1148 in the syringe and infusion set components from the activity of Iodine I 131  
1149 Tositumomab in the syringe prior to infusion.
- 1150 9. Discard all materials used to deliver the Iodine I 131 Tositumomab (e.g.,  
1151 syringes, vials, in-line filter set, extension set and infusion sets) in  
1152 accordance with local, state, and federal regulations governing radioactive  
1153 and biohazardous waste.
- 1154

**1155 DOSIMETRY**

1156 The following sections describe the procedures for image acquisition for  
1157 collection of dosimetry data, interpretation of biodistribution images,  
1158 calculation of residence time, and calculation of activity hours. Please read  
1159 all sections carefully.

**1160 IMAGE ACQUISITION AND INTERPRETATION****1161 Gamma Camera and Dose Calibrator Procedures**

1162 Manufacturer-specific quality control procedures should be followed for the  
1163 gamma camera/computer system, the collimator, and the dose calibrator.  
1164 Less than 20% variance between maximum and minimum pixel count values  
1165 in the useful field of view is acceptable on Iodine-131 intrinsic flood fields and  
1166 variability <10% is preferable. Iodine-131-specific camera uniformity  
1167 corrections are strongly recommended, rather than applying lower energy  
1168 correction to the Iodine-131 window. Camera extrinsic uniformity should be  
1169 assessed at least monthly using <sup>99m</sup>Tc or <sup>57</sup>Co as a source with imaging at the  
1170 appropriate window.  
1171

1172 Additional (non-routine) quality control procedures are required. To assure  
1173 the accuracy and precision of the patient total body counts, the gamma  
1174 camera must undergo validation and daily quality control on each day it is  
1175 used to collect patient images.

1176  
1177  
1178 Use the same setup and region of interest (ROI) for calibration, determination  
1179 of background, and whole body patient studies.

**1180 Gamma Camera Set-Up**

1181 The **same** camera, collimator, scanning speed, energy window, and setup  
1182 must be used for all studies. The gamma camera must be capable of whole  
1183 body imaging and have a large or extra large field of view with a digital  
1184 interface. It must be equipped with a parallel-hole collimator rated to at least  
1185 364 keV by the manufacturer with a septal penetration for Iodine-131 of <7%.  
1186 The camera and computer must be set up for scanning as follows:  
1187

- 1188 • Parallel hole collimator rated to at least 364 keV with a septal penetration  
1189 for Iodine-131 of <7%
- 1190 • Symmetric window (20-25%) centered on the 364 keV photo peak of  
1191 Iodine-131 (314-414 keV)
- 1192 • Matrix: appropriate whole body matrix
- 1193 • Scanning speed: 10-30 cm/minute

1194

**1195 Counts from Calibrated Source for Quality Control**

- 1196 Camera sensitivity for Iodine-131 must be determined each day.
- 1197 Determination of the gamma camera's sensitivity is obtained by scanning a  
1198 calibrated activity of Iodine-131 (e.g., 200–250  $\mu$ Ci in at least 20 mL of saline  
1199 within a sealed pharmaceutical vial). The radioactivity of the Iodine-131  
1200 source is first determined using a NIST-traceable-calibrated clinical dose  
1201 calibrator at the Iodine-131 setting.

**1202 Background Counts**

- 1203 The background count is obtained from a scan with no radioactive source.
- 1204 This should be obtained following the count of the calibrated source and just  
1205 prior to obtaining the patient count.
- 1206 If abnormally high background counts are measured, the source should be  
1207 identified and, if possible, removed. If abnormally low background counts are  
1208 measured, the camera energy window setting and collimator should be  
1209 verified before repeating the background counts.

- 1210 The counts per  $\mu$ Ci are obtained by dividing the background-corrected source  
1211 count by the calibrated activity for that day. For a specific camera and  
1212 collimator, the counts per  $\mu$ Ci should be relatively constant. When values  
1213 vary more than 10% from the established ratio, the reason for the discrepancy  
1214 should be ascertained and corrected and the source count repeated.

**1215 Patient Total Body Counts**

- 1216 The source and background counts are obtained first and the camera  
1217 sensitivity (i.e., constant counting efficiency) is established prior to obtaining  
1218 the patient count. The same rectangular region of interest (ROI) must be

1219 used for the whole body counts, the quality control counts of the radioactive  
1220 source, and the background counts.

1221 Acquire anterior and posterior whole body images for gamma camera counts.  
1222 For any particular patient, the same gamma camera must be used for all  
1223 scans. To obtain proper counts, extremities must be included in the images,  
1224 and arms should not cross over the body. The scans should be centered on  
1225 the midline of the patient. Record the time of the start of the radiolabeled  
1226 dosimetric infusion and the time of the start of each count acquisition.

1227 Gamma camera counts will be obtained at the three imaging time points:

1228 • **Count 1: *Within an hour of end of the infusion*** of the Iodine I 131  
1229 Tositumomab dosimetric dose prior to patient voiding.

1230 • **Count 2:** Two to 4 days after administration of the Iodine I 131  
1231 Tositumomab dosimetric dose and immediately following patient voiding.

1232 • **Count 3:** Six to 7 days after the administration of the Iodine I 131  
1233 Tositumomab dosimetric dose and immediately following patient voiding.

#### 1234 **Assessment of Biodistribution of Iodine I 131 Tositumomab**

1235 The biodistribution of Iodine I 131 Tositumomab should be assessed by  
1236 determination of total body residence time and by visual examination of whole  
1237 body camera images from the first image taken at the time of Count 1 (within  
1238 an hour of the end of the infusion) and from the second image taken at the  
1239 time of Count 2 (at 2 to 4 days after administration). To resolve ambiguities,  
1240 an evaluation of the third image at the time of Count 3 (6 to 7 days after  
1241 administration) may be necessary. If either of these methods indicates that  
1242 the biodistribution is altered, the Iodine I 131 Tositumomab therapeutic dose  
1243 should not be administered.

#### 1244 **Expected Biodistribution**

- 1245 • On the first imaging timepoint: Most of the activity is in the blood pool  
1246 (heart and major blood vessels) and the uptake in normal liver and spleen  
1247 is less than in the heart.
- 1248 • On the second and third imaging timepoints: The activity in the blood pool  
1249 decreases significantly and there is decreased accumulation of activity in

1250 normal liver and spleen. Images may show uptake by thyroid, kidney, and  
1251 urinary bladder and minimal uptake in the lungs. Tumor uptake in soft  
1252 tissues and in normal organs is seen as areas of increased intensity.

1253

1254 **Results Indicating Altered Biodistribution**

- 1255 • On the first imaging timepoint: If the blood pool is not visualized or if there  
1256 is diffuse, intense tracer uptake in the liver and/or spleen or uptake  
1257 suggestive of urinary obstruction the biodistribution is altered. Diffuse lung  
1258 uptake greater than that of blood pool on the first day represents altered  
1259 biodistribution.
- 1260 • On the second and third imaging timepoints: uptake suggestive of urinary  
1261 obstruction and diffuse lung uptake greater than that of the blood pool  
1262 represent altered biodistribution.
- 1263 • Total body residence times of less than 50 hours and more than 150 hours.

1264

1265 **CALCULATION OF IODINE-131 ACTIVITY FOR THE THERAPEUTIC**  
1266 **DOSE**

1267 There are two options for calculation of the Iodine-131 activity for the  
1268 therapeutic dose. The derived values and calculation of the therapeutic dose  
1269 may be determined manually [see **Workbook for Dosimetry Methodology**  
1270 **and Administration Set-up**] or calculated automatically using the Corixa  
1271 proprietary software program [BEXXAR Patient Management Templates]. The  
1272 following describes in greater detail the stepwise method for manual  
1273 determination of the Iodine-131 activity for the therapeutic dose.

1274

1275 **Residence Time (hr)**

1276 For each time point, calculate the background corrected total body count at  
1277 each timepoint (defined as the geometric mean). The following equation is  
1278 used:

1279 Geometric mean of counts =  $\sqrt{(C_A - C_{BA})(C_P - C_{BP})}$

1280

1281 In this equation,  $C_A$  = the anterior counts,  $C_{BA}$  = the anterior background  
1282 counts,  $C_P$  = the posterior counts, and  $C_{BP}$  = the posterior background counts.

1283

1284 Once the geometric mean of the counts has been calculated for each of the 3  
1285 timepoints, the % injected activity remaining for each timepoint is calculated  
1286 by dividing the geometric mean of the counts from that timepoint by the  
1287 geometric mean of the counts from Day 0 and multiplying by 100.

1288

1289 The residence time (h) is then determined by plotting the time from the start of  
1290 infusion and the % injected activity values for the 3 imaging timepoints on  
1291 Graph 1 (see Worksheet "**Determination of Residence Time**" in the  
1292 "**Workbook for Dosimetry Methodology and Administration Set-Up**"  
1293 supplied with Dosimetric Dose Packaging). A best-fit line is then drawn from  
1294 100% (the pre-plotted Day 0 value) through the other 2 plotted points (if the  
1295 line does not intersect the two points, one point must lie above the best-fit line  
1296 and one point must lie below the best-fit line). The residence time (h) is read  
1297 from the x-axis of the graph at the point where the fitted line intersects with  
1298 the horizontal 37% injected activity line.

1299

#### 1300 **Activity Hours (mCi hr)**

1301 In order to determine the activity hours (mCi hr), look up the patient's  
1302 maximum effective mass derived from the patient's sex and height (see  
1303 Worksheet "**Determination of Maximum Effective Mass**" in the "**Workbook**  
1304 **for Dosimetry Methodology and Administration Set-Up**" supplied with  
1305 Dosimetric Dose Packaging). If the patient's actual weight is less than the  
1306 maximum effective mass, the actual weight should be used in the activity  
1307 hours table (see Worksheet "**Determination of Activity Hours**" in the  
1308 "**Workbook for Dosimetry Methodology and Administration Set-Up**"  
1309 supplied with Dosimetric Dose Packaging). If the patient's actual weight is  
1310 greater than the maximum effective mass, the mass from the worksheet for  
1311 "**Determination of Maximum Effective Mass**" should be used.

#### 1312 **Calculation of Iodine-131 Activity for the Therapeutic Dose**

1313 The following equation is used to calculate the activity of Iodine-131 required  
1314 for delivery of the desired total body dose of radiation.

1315

1316 
$$\text{Iodine-131 Activity (mCi)} = \frac{\text{Activity Hours (mCi hr)}}{\text{Residence Time (hr)}} \times \frac{\text{Desired Total Body Dose (cGy)}}{75 \text{ cGy}}$$

1317

1318 **HOW SUPPLIED**

1319 **TOSITUMOMAB DOSIMETRIC PACKAGING**

1320 The components of the dosimetric step will be shipped **ONLY** to individuals  
1321 who are participating in the certification program or have been certified in the  
1322 preparation and administration of the BEXXAR therapeutic regimen. The  
1323 components are shipped from separate sites; when ordering, ensure that the  
1324 components are scheduled to arrive on the same day. The components of  
1325 the Tositumomab Dosimetric Step include:

1326 1. Tositumomab: Two single-use 225 mg vials (16.1 mL) and one single-use  
1327 35 mg vial (2.5 mL) of Tositumomab at a protein concentration of 14 mg/mL  
1328 supplied by McKesson BioServices.

1329 NDC 67800-101-31

1330 2. Iodine I 131 Tositumomab: A single-use vial of Iodine I 131 Tositumomab  
1331 within a lead pot, supplied by MDS Nordion. Each single-use vial contains  
1332 not less than 20 mL of Iodine I 131 Tositumomab at nominal protein and  
1333 activity concentrations of 0.1 mg/mL and 0.61 mCi/mL (at calibration),  
1334 respectively. (Refer to the product specification sheet for the lot-specific  
1335 protein concentration, activity concentration, total activity and expiration date.)

1336 NDC 67800-111-10

1337

1338 **TOSITUMOMAB THERAPEUTIC PACKAGING**

1339 The components of the therapeutic step will be shipped **ONLY** to individuals  
1340 who are participating in the certification program or have been certified in the  
1341 preparation and administration of the BEXXAR therapeutic regimen for an  
1342 individual patient who has completed the Dosimetric Step. The components of  
1343 the therapeutic step are shipped from separate sites; when ordering, ensure  
1344 that the components are scheduled to arrive on the same day. The  
1345 components of the Tositumomab Therapeutic Step include:

Corixa Corporation: BEXXAR® (Tositumomab, Iodine I 131 Tositumomab)  
BLA STN 125011

1346 1. Tositumomab: Two single-use 225 mg vials (16.1 mL) and one single-use  
1347 35 mg vial (2.5 mL) of Tositumomab at a protein concentration of 14  
1348 mg/mL supplied by McKesson BioServices.

1349 NDC 67800-101-32

1350 2. Iodine I 131 Tositumomab: One or two single-use vials of Iodine I 131.  
1351 Tositumomab within a lead pot(s), supplied by MDS Nordion. Each single-  
1352 use vial contains not less than 20 mL of Iodine I 131 Tositumomab at  
1353 nominal protein and activity concentrations of 1.1 mg/mL and 5.6 mCi/mL  
1354 (at calibration), respectively. Refer to the product specification sheet for  
1355 the lot-specific protein concentration, activity concentration, total activity  
1356 and expiration date.

1357 NDC 67800-121-10

1358

1359 **STABILITY AND STORAGE**

1360 **TOSITUMOMAB**

1361 Vials of Tositumomab (35 mg and 225 mg) should be stored refrigerated at  
1362 2°C–8°C (36°F–46°F) prior to dilution. Do not use beyond expiration date.  
1363 Protect from strong light. **DO NOT SHAKE**. Do not freeze. Discard any  
1364 unused portions left in the vial.

1365 Solutions of diluted Tositumomab are stable for up to 24 hours when stored  
1366 refrigerated at 2°C–8°C (36°F–46°F) and for up to 8 hours at room  
1367 temperature. However, it is recommended that the diluted solution be stored  
1368 refrigerated at 2°C–8°C (36°F–46°F) prior to administration because it does  
1369 not contain preservatives. Any unused portion must be discarded. Do not  
1370 freeze solutions of diluted Tositumomab.

1371

1372 **IODINE I 131 TOSITUMOMAB**

1373 **Store frozen in the original lead pots.** The lead pot containing the product  
1374 must be stored in a freezer at a temperature of -20°C or below until it is  
1375 removed for thawing prior to administration to the patient. Do not use beyond  
1376 the expiration date on the label of the lead pot.

1377 Thawed dosimetric and therapeutic doses of Iodine I 131 Tositumomab are  
1378 stable for up to 8 hours at 2°C–8°C (36°F–46°F) or at room temperature.  
1379 Solutions of Iodine I 131 Tositumomab diluted for infusion contain no  
1380 preservatives and should be stored refrigerated at 2°C–8°C (36°F–46°F) prior  
1381 to administration (do not freeze). Any unused portion must be discarded  
1382 according to federal and state laws.

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