

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BEXXAR safely and effectively. See full prescribing information for BEXXAR.

**BEXXAR (tositumomab and iodine I 131 tositumomab)**

**Injection, for intravenous infusion**

**Initial U.S. Approval: 2003**

**WARNING: SERIOUS ALLERGIC REACTIONS/ANAPHYLAXIS, PROLONGED AND SEVERE CYTOPENIAS, AND RADIATION EXPOSURE**

See full prescribing information for complete boxed warning.

- **Serious Allergic Reactions:** Immediately interrupt infusion and permanently discontinue the BEXXAR therapeutic regimen for serious allergic reactions (5.1)
- **Prolonged and severe cytopenias occur in most patients. BEXXAR should not be administered to patients with >25% lymphoma marrow involvement, platelet count <100,000 cells/mm<sup>3</sup>, or neutrophil count <1,500 cells/mm<sup>3</sup> (5.2, 6.1)**
- **Radiation Exposure:** The BEXXAR therapeutic regimen is supplied only to certified healthcare professionals. Follow institutional radiation safety practices and applicable federal guidelines to minimize radiation exposure to household contacts and medical staff. (5.3)

### RECENT MAJOR CHANGES

Contraindications (4) removal 02/2012  
Warnings and Precautions, Embryo-fetal Toxicity (5.6) 02/2012

### INDICATIONS AND USAGE

BEXXAR (tositumomab and Iodine I 131 tositumomab) is a CD20-directed radiotherapeutic antibody indicated for the treatment of patients with CD20-positive, relapsed or refractory, low-grade, follicular, or transformed non-Hodgkin's lymphoma, including patients with rituximab-refractory non-Hodgkin's lymphoma. (1.1)

Determination of the effectiveness of the BEXXAR therapeutic regimen is based on overall response rates. The effects of the BEXXAR therapeutic regimen on survival are not known. (1.1)

#### Important Limitation of Use

- BEXXAR therapeutic regimen is only indicated for a single course of treatment and is not indicated for a first-line treatment. (1.2)

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#### DOSAGE AND ADMINISTRATION

The BEXXAR therapeutic regimen consists of a 2-part dosimetric step, followed 7 to 14 days later by a 2-part therapeutic step. (2.1)

#### DOSAGE FORMS AND STRENGTHS

- Tositumomab 225 mg solution (14 mg per mL), single use vial
- Tositumomab 35 mg solution (14 mg per mL), single use vial
- Iodine I 131 tositumomab solution containing 12-18 mCi Iodine-131 per vial (not less than 0.61 mCi per mL at calibration) and 2.0-6.1 mg tositumomab per vial (not less than 0.1 mg per mL), single use vial
- Iodine I 131 tositumomab solution containing 112-168 mCi Iodine-131 per vial (not less than 5.6 mCi per mL at calibration) and 22-61 mg tositumomab per vial (not less than 1.1 mg per mL), single use vial

#### CONTRAINDICATIONS

None

#### WARNINGS AND PRECAUTIONS

- **Secondary Malignancies:** Hematological and non-hematological secondary malignancies have been reported. (5.4)
- **Hypothyroidism:** Thyroid-blocking medication is required prior to administration of the BEXXAR therapeutic regimen. Evaluate for clinical evidence of hypothyroidism and thyroid-stimulating hormone (TSH) level before treatment and annually thereafter. (5.5)
- **Embryo-fetal Toxicity:** Administration to a pregnant woman can cause embryo-fetal harm including severe, and possibly irreversible, neonatal hypothyroidism. Females and males of reproductive potential should use effective contraception to avoid pregnancy during treatment and for 12 months after the therapeutic dose. (5.6, 8.1, 8.7)

#### ADVERSE REACTIONS

The most common adverse reactions (≥ 25%) are neutropenia, thrombocytopenia, anemia, infections, infusion reactions, asthenia, fever, and nausea. (6)

**To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

#### USE IN SPECIFIC POPULATIONS

- **Nursing Mothers:** Discontinue nursing. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 02/2012

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\*Sections or subsections omitted from the full prescribing information are not listed.

1 **FULL PRESCRIBING INFORMATION**

2 **WARNING: SERIOUS ALLERGIC REACTIONS (INCLUDING ANAPHYLAXIS),**  
3 **PROLONGED AND SEVERE CYTOPENIAS, AND RADIATION EXPOSURE**

4 **Serious Allergic Reactions (Including Anaphylaxis):** Serious, including fatal, allergic  
5 reactions have occurred during or following administration of the BEXXAR therapeutic  
6 regimen. Have medications for the treatment of allergic reactions available for immediate  
7 use. Permanently discontinue the BEXXAR therapeutic regimen for serious allergic  
8 reactions and administer appropriate medical treatment [*see Warnings and Precautions*  
9 (5.1)].

10 **Prolonged and Severe Cytopenias:** The BEXXAR therapeutic regimen resulted in  
11 severe and prolonged thrombocytopenia and neutropenia in more than 70% of the patients  
12 in clinical studies. The BEXXAR therapeutic regimen should not be administered to  
13 patients with greater than 25% lymphoma marrow involvement, platelet count less than  
14 100,000 cells/mm<sup>3</sup> or neutrophil count less than 1,500 cells/mm<sup>3</sup> [*see Warnings and*  
15 *Precautions (5.2), Adverse Reactions (6.1)*].

16 **Radiation Exposure:** The BEXXAR therapeutic regimen may be administered only  
17 under the supervision of physicians who are certified under or participating in the  
18 BEXXAR therapeutic regimen certification program and who are authorized under the  
19 Radioactive Materials License at their clinical site. Follow institutional radiation safety  
20 practices and applicable federal guidelines to minimize radiation exposure during handling  
21 and after administration of the BEXXAR therapeutic regimen [*see Warnings and*  
22 *Precautions (5.3)*].

23 **1 INDICATIONS AND USAGE**

24 **1.1 Relapsed or Refractory CD20-Positive, Non-Hodgkin's Lymphoma**

25 The BEXXAR<sup>®</sup> therapeutic regimen (tositumomab and iodine I 131 tositumomab) is  
26 indicated for the treatment of patients with CD20-positive relapsed or refractory, low grade,  
27 follicular, or transformed non-Hodgkin's lymphoma, including patients with rituximab-refractory  
28 non-Hodgkin's lymphoma.

29 Determination of the effectiveness of the BEXXAR therapeutic regimen is based on  
30 overall response rates. The effects of the BEXXAR therapeutic regimen on survival are not  
31 known.

32  
33 **1.2 Important Limitations of Use**

- 34 • The BEXXAR therapeutic regimen is only indicated for a single course of treatment.
- 35 • The safety and efficacy of additional courses of the BEXXAR therapeutic regimen have  
36 not been established.
- 37 • The BEXXAR therapeutic regimen is not indicated for first-line treatment of patients  
38 with CD20-positive non-Hodgkin's lymphoma.

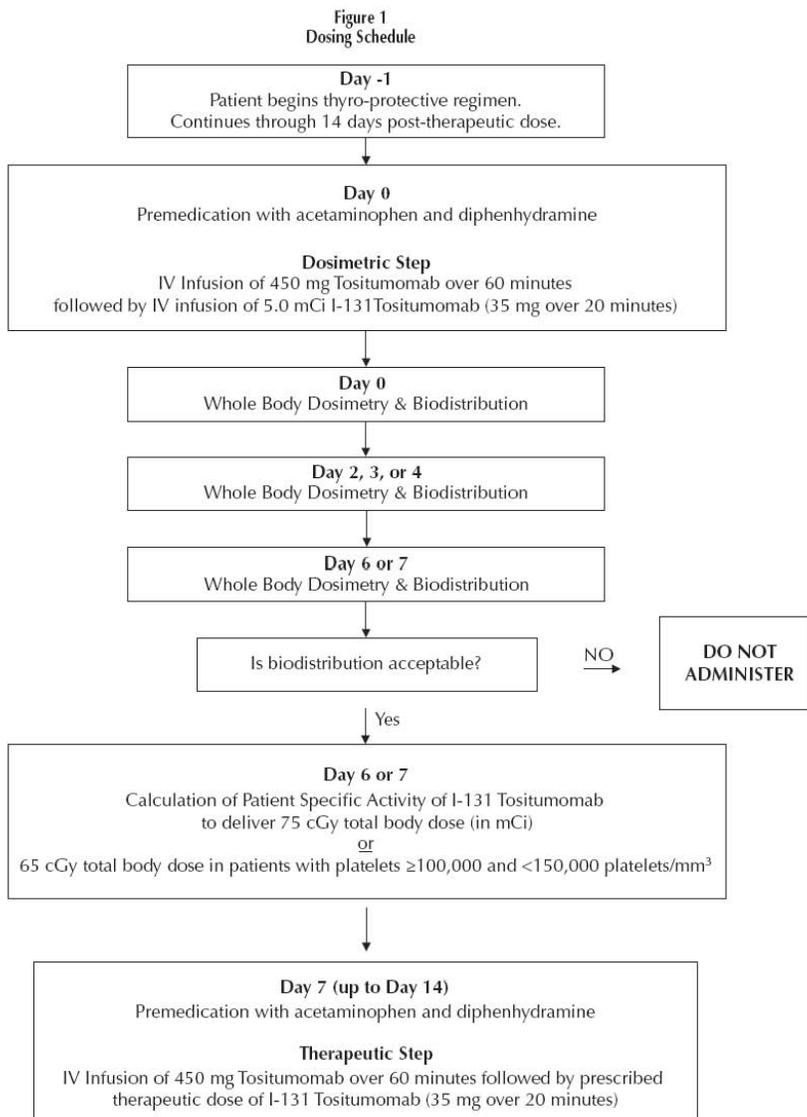
39 **2 DOSAGE AND ADMINISTRATION**

40 The BEXXAR therapeutic regimen consists of 2 separate components (tositumomab and  
41 iodine I 131 tositumomab) administered in 2 separate steps (dosimetric dose and therapeutic  
42 dose) separated by 7 to 14 days.

43 Parenteral drug products should be inspected for particulate matter prior to  
44 administration, whenever solution and container permit [see Description (11)].

45

46 **2.1 Overview of Dosing Schedule**



47  
48

49 **2.2 Recommended Dose**

50 Dosimetric dose

- 51 (1) Tositumomab 450 mg by intravenous infusion  
52 (2) I-131 tositumomab (5 mCi I-131 and 35 mg protein) by intravenous infusion

53 Therapeutic dose (administered 7-14 days after dosimetric dose)

54 (1) Tositumomab 450 mg by intravenous infusion.

55 (2) I-131 tositumomab (35 mg) by intravenous infusion. The iodine-131 dose is calculated  
56 based on 1) assessment of dosimetry and biodistribution obtained following the  
57 dosimetric dose, and 2) platelet counts obtained within 28 days prior to dosing.

58 *If platelet counts are 150,000 platelets/mm<sup>3</sup> or greater:*

59 The recommended dose (mCi) is the activity of Iodine-131 calculated to deliver 75 cGy  
60 total body irradiation

61 *If platelet counts are 100,000 to 149,000 platelets/mm<sup>3</sup>:*

62 The recommended dose is the activity of Iodine-131 calculated to deliver 65 cGy total  
63 body irradiation

64

## 65 **2.3 Preparation of Dosimetric Dose**

### 66 Tositumomab Dosimetric Dose

67 (1) Withdraw and discard 32 mL from a 50-mL bag 0.9% Sodium Chloride for Injection,  
68 USP.

69 (2) Withdraw and transfer entire contents from each of the two 225-mg tositumomab vials (a  
70 total of 450 mg tositumomab in 32 mL) to remaining 18 mL in bag of 0.9% Sodium  
71 Chloride for Injection, USP to yield a final volume of 50 mL.

72 (3) DO NOT SHAKE. Gently mix the solution by inverting/rotating the bag. The  
73 tositumomab solution is clear to opalescent, colorless to slightly yellow, and may contain  
74 white particulates.

75 (4) Diluted tositumomab may be stored at 36°F to 46°F (2°C to 8°C) for 24 hours or at room  
76 temperature for 8 hours. Discard unused solution.

### 77 I-131 Tositumomab Dosimetric Dose

78 Required materials (not supplied):

- 79 • Lead shielding for preparation vial and syringe pump
- 80 • One sterile 30-mL preparation vial
- 81 • Two lead pots at room temperature

### 82 Method

83 (1) Thaw contents (approximately 60 minutes) of I-131 tositumomab dosimetric vial at room  
84 temperature with appropriate lead shielding. Thawed undiluted I-131 tositumomab may  
85 be stored up to 8 hours at 36°F to 46°F (2°C to 8°C) or at room temperature.

86 (2) Calculate the volume required for I-131 tositumomab activity of 5.0 mCi, based on the  
87 activity concentration of dosimetric vial (refer to product specification sheet provided in  
88 dosimetric carton).

89 (3) Withdraw and transfer the calculated volume from I-131 tositumomab vial to the shielded  
90 preparation vial.

- 91 (4) Assay preparation vial to confirm activity is 5.0 mCi ( $\pm 10\%$ ) using a suitable  
92 radioactivity calibration system operated in accordance with the manufacturer's  
93 specifications and quality control for the measurement of Iodine-131.
- 94 • If the preparation vial contains the calculated activity ( $\pm 10\%$ ), proceed to step 5.
  - 95 • If the preparation vial does not contain the calculated activity (5 mCi  $\pm 10\%$ ),  
96 determine the activity concentration of the I-131 tositumomab based on the  
97 volume and the activity in the preparation vial. Add or subtract the appropriate  
98 volume of I-131 tositumomab to the preparation vial to achieve the desired  
99 activity of 5.0 mCi ( $\pm 10\%$ ). Re-assay to confirm.
- 100 (5) Calculate the amount of tositumomab in the shielded preparation vial, based on the  
101 volume and labeled protein concentration of the I-131 tositumomab dosimetric vial (see  
102 product specification sheet provided in dosimetric carton). If less than 35 mg, add  
103 additional tositumomab from the non-radioactive vial to the shielded vial to yield a total  
104 of 35 mg tositumomab in the shielded vial.
- 105 (6) Add a sufficient quantity of 0.9% Sodium Chloride for Injection, USP to the shielded  
106 preparation vial to yield a final volume of 30 mL. Gently mix contents.
- 107 (7) Withdraw the entire contents from the preparation vial into a 60-mL syringe using a large  
108 bore needle (18-gauge) and shield contents of syringe and syringe pump.
- 109 (8) Assay and record the activity.

110

## 111 **2.4 Administration of Dosimetric Dose**

112 Thyroid Protective Pre-medication: Initiate thyroid protective drugs 24 hours prior to the  
113 dosimetric dose and continue daily dosing for a minimum of 14 days following the therapeutic dose. The  
114 following regimens are recommended:

- 115 • saturated solution of potassium iodide (SSKI) 4 drops orally 3 times daily or
- 116 • Lugol's solution 20 drops orally 3 times daily or
- 117 • potassium iodide tablets 130 mg orally once daily

118 Do not administer the dosimetric dose unless the patient has received at least 3 doses of  
119 SSKI, 3 doses of Lugol's solution, or 1 dose of 130-mg potassium iodide tablet.

### 120 Tositumomab

- 121 (1) Premedicate with oral diphenhydramine 50 mg and oral acetaminophen 650 mg, 30  
122 minutes prior to initiation of the dosimetric dose.
- 123 (2) Administer 450 mg tositumomab in 50 mL 0.9% sodium chloride by intravenous infusion  
124 through a 0.22 micron in-line filter over 60 minutes (refer to *Site Training Manual* for  
125 diagram showing assembly of the infusion set components). Decrease the rate of infusion  
126 by 50% for mild to moderate infusion reactions. Discontinue for serious allergic  
127 reactions; interrupt for severe infusion reactions. If severe infusion reaction completely  
128 resolves, the infusion may be continued at 50% of the previous infusion rate.

### 129 I-131 Tositumomab

- 130 (3) Attach the shielded syringe containing the I-131 tositumomab dose in a syringe pump to  
131 the intravenous line containing the in-line filter used in step 2 above. A change in filter  
132 can result in loss of up to 7% of the I-131 tositumomab dose.
- 133 (4) Set syringe pump to deliver the entire dose of I-131 tositumomab over 20 minutes,  
134 immediately following completion of the tositumomab infusion. Decrease the rate of  
135 infusion by 50% for mild to moderate infusion reactions. Discontinue for serious allergic  
136 reactions; interrupt for severe infusion reactions. If severe infusion reaction completely  
137 resolves, the infusion may be continued at 50% of the previous infusion rate.
- 138 (5) Upon completion of the I-131 tositumomab infusion, flush the IV line with 0.9% Sodium  
139 Chloride for Injection, USP.
- 140 (6) Determine the combined residual activity of the syringe and infusion set components  
141 (stopcock, extension set, primary infusion set, and in-line filter set) by assaying these  
142 items in a suitable radioactivity calibration system immediately following completion of  
143 administration of all components of the dosimetric dose.
- 144 (7) Calculate and record the dose delivered to the patient by subtracting the residual activity  
145 in the syringe and the infusion set components from the activity of I-131 tositumomab in  
146 the syringe prior to infusion.
- 147 (8) Discard unused portion of Iodine I-131 tositumomab and infusion set components  
148 according to federal and state laws regarding radioactive and biohazardous waste.

149

## 150 **2.5 Assessment of Dosimetry and Biodistribution**

151 Additional copies of templates for recording dosimetry and calculation of the I-131  
152 tositumomab therapeutic dose and the *Site Training Manual* may be obtained from the  
153 GlaxoSmithKline Pharma Service Center (1-877-423-9927).

154 Obtain total body gamma camera counts and whole body images at the following  
155 timepoints:

- 156 (1) Count 1 (Day 0): Within 1 hour following the end of the I-131 tositumomab infusion and  
157 prior to urination, obtain total body gamma camera count and whole body images
- 158 (2) Count 2 (Day 2, 3, or 4): Obtain total body gamma camera counts and whole body  
159 images, immediately following urination.
- 160 (3) Count 3 (Day 6 or 7): Obtain total body gamma camera counts and whole body images,  
161 immediately following urination.

162 Verify that the expected biodistribution is present.

163 Assess Biodistribution: Determine total body residence time and examine whole body  
164 camera images done at Count 1 and Count 2. Examine image performed at Count 3 as needed to  
165 resolve ambiguities.

166 Expected biodistribution characteristics:

167 Count 1 (day of dosimetric dose)

- 168 • Most of the activity is in the blood pool (heart and major blood vessels). Uptake in  
169 normal liver and spleen is less than in the heart.

170 Count 2 (day 2, 3, or 4) and Count 3 (day 6 or 7)  
171 • Activity in the blood pool decreases significantly. Decreased accumulation of activity in  
172 normal liver and spleen. Possible uptake present in thyroid, kidney, and urinary bladder  
173 with minimal uptake in the lungs. Possible increased intensity at known lymphoma sites.  
174 Biodistribution is altered if any of the following is present:

175 Count 1:

- 176 • blood pool is not visualized
- 177 • diffuse, intense tracer uptake in the liver and/or spleen or uptake suggestive of urinary  
178 obstruction,
- 179 • diffuse uptake in normal lung greater than that of blood pool.

180 Count 2 and Count 3:

- 181 • uptake is suggestive of urinary obstruction
- 182 • diffuse uptake in normal lung which is greater than that of the blood pool
- 183 • total body residence time is less than 50 hours
- 184 • total body residence time is more than 150 hours.

185

## 186 2.6 Calculation of I-131 Therapeutic Dose

187 The therapeutic dose may be calculated manually using the total body residence time and  
188 activity hours (refer to the *Site Training Manual*). The therapeutic dose may also be derived by  
189 using the GlaxoSmithKline BEXXAR therapeutic regimen Patient Management Templates (refer  
190 to the *Site Training Manual*). For assistance with either manual or automated calculations call  
191 the GlaxoSmithKline Pharma Service Center at 1-877-423-9927.

192 The following equation is used to calculate the activity of Iodine-131 required for  
193 delivery of the desired total body dose of radiation:

$$\text{Iodine-131 Activity (mCi)} = \frac{\text{Activity Hours (mCi hr)}}{\text{Residence Time (hr)}} \times \frac{\text{Desired Total Body Dose (65cGy or 75cGy)}}{75\text{cGy}}$$

194

## 195 2.7 Preparation of Therapeutic Dose

### 196 Tositumomab

197 A 450-mg dose of tositumomab should be prepared as previously described [*see Dosage*  
198 *and Administration (2.3)*].

### 199 I-131 tositumomab

200 Required materials (not supplied):

201 Lead shielding for preparation vial and syringe pump

202 One sterile 50-mL preparation vial

203 Two lead pots at room temperature.

### 204 Method

205 Thaw contents (approximately 60 minutes) of I-131 tositumomab therapeutic vial at room  
206 temperature with appropriate lead shielding. Thawed, undiluted I-131 tositumomab may be

207 stored up to 8 hours at 36°F to 46°F (2°C to 8°C) or at room temperature. Do not freeze solutions  
208 of diluted I-131 tositumomab; store refrigerated until time of use.

- 209 (1) Calculate the volume (see activity concentration on the product specification sheet  
210 provided with the therapeutic vial) of I-131 tositumomab activity required to deliver  
211 either 75cGy or 65cGy total body irradiation [see *Dosage and Administration (2.6)*].
- 212 (2) Withdraw and transfer the calculated volume from I-131 tositumomab vial to the shielded  
213 preparation vial.
- 214 (3) Assay preparation vial to confirm calculated activity using a suitable radioactivity  
215 calibration system operated in accordance with the manufacturer's specifications and  
216 quality control for the measurement of Iodine-131.
  - 217 • If the assayed dose in the preparation vial contains the calculated activity ( $\pm 10\%$ ),  
218 proceed to step 5.
  - 219 • If the assayed dose in the preparation vial does not contain the calculated activity  
220 ( $\pm 10\%$ ), determine the activity concentration of I-131 tositumomab based on the  
221 volume and the activity in the preparation vial. Add or subtract the appropriate  
222 volume of I-131 tositumomab to the preparation vial to achieve the required I-131  
223 tositumomab activity. Re-assay the preparation vial contents to confirm.
- 224 (4) Calculate the amount of tositumomab in the shielded preparation vial, based on the  
225 volume and protein concentration of I-131 tositumomab (refer to product specification  
226 sheet for the vial in the therapeutic carton). If the amount of tositumomab in the  
227 preparation vial is less than 35 mg, add additional tositumomab from the non-radioactive  
228 35-mg vial to the shielded preparation vial to yield a total of 35 mg tositumomab in the  
229 shielded vial.
- 230 (5) Add a sufficient quantity of 0.9% Sodium Chloride for Injection, USP to the shielded  
231 preparation vial to yield a final volume of 30 mL. Gently mix contents.
- 232 (6) Withdraw the entire contents from the shielded preparation vial into a 60-mL syringe  
233 using a large bore needle (18-gauge) and shield contents of syringe and syringe pump.
- 234 (7) Assay and record activity.

235

## 236 **2.8 Administration of Therapeutic Dose**

237 **Do not administer the therapeutic dose if biodistribution is altered [see *Dosage and***  
238 ***Administration (2.5)*].**

### 239 Tositumomab

240 Premedicate with oral diphenhydramine 50 mg and oral acetaminophen 650 mg 30  
241 minutes prior to initiation of the therapeutic dose.

242 Administer 450 mg tositumomab in 50 mL 0.9% sodium chloride by intravenous infusion  
243 through a 0.22 micron in-line filter over 60 minutes (refer to *Site Training Manual* for diagram  
244 showing assembly of the infusion set components). Decrease the rate of infusion by 50% for  
245 mild to moderate infusion reactions. Discontinue for serious allergic reactions; interrupt for

246 severe infusion reactions. If severe infusion reaction completely resolves, the infusion may be  
247 continued at 50% of the previous infusion rate.

### 248 I-131 Tositumomab

249 Attach the shielded syringe containing the I-131 tositumomab therapeutic dose to the  
250 intravenous line containing the in-line filter used in step 2 above. **A change in filter can result**  
251 **in loss of up to 7% of the I-131 tositumomab dose.** Set syringe pump to deliver the entire dose  
252 of I-131 tositumomab over 20 minutes, immediately following completion of the tositumomab  
253 infusion. Decrease the rate of infusion by 50% for mild to moderate infusion reactions.  
254 Discontinue for serious allergic reactions; interrupt for severe infusion reactions. If severe  
255 infusion reaction completely resolves, the infusion may be continued at 50% of the previous  
256 infusion rate.

257 (1) Upon completion of I-131 tositumomab infusion, flush the IV line with 0.9% Sodium  
258 Chloride for Injection, USP.

259 (2) Determine the combined residual activity of the syringe and infusion set components  
260 (stopcock, extension set, primary infusion set and in-line filter set) by assaying these  
261 items in a suitable radioactivity calibration system immediately following completion of  
262 administration of all components of the therapeutic dose.

263 (3) Calculate and record the dose delivered to the patient by subtracting the residual activity  
264 in the syringe and the infusion set components from the activity of I-131 tositumomab in  
265 the syringe prior to infusion.

266 (4) Discard unused portion of Iodine I-131 tositumomab and infusion set components  
267 according to federal and state laws regarding radioactive and biohazardous waste.

268

### 269 **2.9 Radiation Dosimetry**

270 Estimations of radiation-absorbed doses for I-131 tositumomab were performed using  
271 sequential whole body images and the MIRDOSE 3 software program. Patients with apparent  
272 thyroid, stomach, or intestinal imaging were selected for organ dosimetry analyses. The  
273 estimated radiation-absorbed doses to organs and marrow from a course of the BEXXAR  
274 therapeutic regimen are presented in Table 1.

275

**Table 1. Estimated Radiation-Absorbed Organ Doses**

	The BEXXAR therapeutic regimen mGy/MBq Median	The BEXXAR therapeutic regimen mGy/MBq Range
<b>Organ Regions of Interest (ROIs)</b>		
Thyroid	2.71	1.4 - 6.2
Kidneys	1.96	1.5 - 2.5
Upper large intestine wall	1.34	0.8 - 1.7
Lower large intestine 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
Marrow space	0.65	0.5 - 1.1
Stomach wall	0.40	0.2 - 0.8
<b>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

278 **3 DOSAGE FORMS AND STRENGTHS**

279 Tositumomab 225-mg solution (14 mg per mL), single-use vial

280 Tositumomab 35-mg solution (14 mg per mL), single-use vial

281 I-131 tositumomab solution containing 12-18 mCi Iodine-131 per vial (not less than 20  
282 mL containing not less than 0.61 mCi per mL at calibration) and 2.0-6.1 mg tositumomab per  
283 vial (not less than 0.1 mg per mL protein concentration), single-use vial

284 I-131 tositumomab solution containing 112-168 mCi Iodine-131 per vial (not less than 20  
285 mL containing not less than 5.6 mCi per mL at calibration) and 22-61 mg tositumomab per vial  
286 (not less than 1.1 mg per mL protein concentration), single-use vial

#### 287 **4 CONTRAINDICATIONS**

288 None

#### 289 **5 WARNINGS AND PRECAUTIONS**

##### 290 **5.1 Serious Allergic Reactions, Including Anaphylaxis**

291 The BEXXAR therapeutic regimen can cause severe, including fatal, allergic reactions  
292 [see *Adverse Reactions (6.1) and (6.3)*]. Premedicate with acetaminophen and diphenhydramine  
293 [see *Dosage and Administration (2.1), (2.4), and (2.8)*]. Have medications for the treatment of  
294 allergic reactions available for immediate use during administration. Signs and symptoms of  
295 severe allergic reactions may include fever, rigors or chills, sweating, hypotension, dyspnea,  
296 bronchospasm, and nausea during or within 48 hours of infusion. Immediately interrupt  
297 BEXXAR infusions for severe reactions and provide appropriate medical and supportive care  
298 measures. Permanently, discontinue the BEXXAR therapeutic regimen in patients who develop  
299 serious allergic reactions.

300

##### 301 **5.2 Prolonged and Severe Cytopenias**

302 Patients receiving the BEXXAR therapeutic regimen experienced severe (NCI CTC  
303 grade 3-4) and prolonged neutropenia (63%), thrombocytopenia (53%), and anemia (29%) [see  
304 *Adverse Reactions (6.1)*]. The time to nadir was 4 to 7 weeks and the duration of cytopenias was  
305 approximately 30 days. Due to the variable nature of the onset of cytopenias, monitor patients  
306 with weekly complete blood counts for up to 12 weeks.

307 The BEXXAR therapeutic regimen should not be administered to patients with >25%  
308 lymphoma marrow involvement, platelet count <100,000 cells/mm<sup>3</sup>, or neutrophil count  
309 <1,500 cells/mm<sup>3</sup>.

310

##### 311 **5.3 Radiation Exposure**

312 The BEXXAR therapeutic regimen contains Iodine-131. Follow institutional radiation  
313 safety practices and applicable federal guidelines to minimize radiation exposure during handling  
314 and after administration of the BEXXAR therapeutic regimen. Advise patients of the risks of  
315 radiation exposure of household contacts, pregnant women, and small children and of the steps to  
316 be taken to reduce these risks.

317 The BEXXAR therapeutic regimen should be administered only by physicians enrolled in  
318 the certification program for dose calculation and administration of the BEXXAR therapeutic

319 regimen. Further information regarding the BEXXAR therapeutic regimen certification program  
320 is available by phone at 1-877-423-9927.

321

#### 322 **5.4 Secondary Malignancies**

323 Myelodysplastic syndrome (MDS) or acute leukemia may occur with the use of the  
324 BEXXAR therapeutic regimen and were reported in 10% of patients enrolled in clinical trials  
325 and 3% of patients enrolled in the expanded access program (median follow-up of 39 and 27  
326 months, respectively). The median time to development of MDS or leukemia was 31 months [*see*  
327 *Adverse Reactions (6.1)*].

328 Non-hematologic malignancies may occur with the use of the BEXXAR therapeutic  
329 regimen and were reported in 5% of patients enrolled in clinical trials or the expanded access  
330 program. In the absence of controlled studies, the relative risk of secondary malignancies in  
331 patients receiving the BEXXAR therapeutic regimen cannot be determined [*see Adverse*  
332 *Reactions (6.1)*].

333

#### 334 **5.5 Hypothyroidism**

335 The BEXXAR therapeutic regimen can cause hypothyroidism [*see Adverse Reactions*  
336 *(6.1)*]. Initiate thyroid-blocking medications at least 24 hours before administering the dosimetric  
337 dose and continue until 14 days after the therapeutic dose [*see Dosage and Administration (2.4)*].  
338 The risk of hypothyroidism is likely to be increased in patients who do not complete the  
339 recommended thyroid-protective regimen. Evaluate for clinical evidence of hypothyroidism and  
340 thyroid-stimulating hormone (TSH) level before treatment and annually thereafter.

341

#### 342 **5.6 Embryo-fetal Toxicity**

343 The BEXXAR therapeutic regimen can cause fetal harm when administered to a pregnant  
344 woman including severe, and possibly irreversible, neonatal hypothyroidism. Inform patients  
345 who are pregnant or become pregnant after the BEXXAR therapeutic regimen about the potential  
346 hazard to a fetus. Evaluate infants born to mothers treated with the BEXXAR therapeutic  
347 regimen during pregnancy for hypothyroidism at time of delivery and during the neonatal period  
348 [*see Use in Specific Populations (8.1)*].

349 Males and females of reproductive potential should use effective contraception during  
350 treatment with the BEXXAR therapeutic regimen and for 12 months after the therapeutic dose  
351 [*see Use in Specific Populations (8.7)*].

352

#### 353 **5.7 Excessive Radiation Exposure in Patients With Impaired Renal Function**

354 There are no data regarding the safety of administration of the BEXXAR therapeutic  
355 regimen in patients with impaired renal function. Since the BEXXAR therapeutic regimen is  
356 primarily cleared through the kidneys, the rate of excretion of radiolabeled iodine is expected to  
357 be decreased in patients with impaired renal function or obstructive uropathy, which may result

358 in increased patient exposure to I-131 tositumomab. [See Use in Specific Populations (8.6),  
359 Clinical Pharmacology (12.3).]

360

## 361 **5.8 Immunization**

362 The safety of immunization with live viral vaccines following administration of the  
363 BEXXAR therapeutic regimen and the ability of patients who have received the BEXXAR  
364 therapeutic regimen to generate a primary or anamnestic humoral response to any vaccine have  
365 not been studied. Do not administer live viral vaccines to patients recently treated with  
366 BEXXAR.

## 367 **6 ADVERSE REACTIONS**

368 The following serious adverse reactions are discussed in greater detail in other sections of  
369 the label:

- 370 • Serious Allergic Reactions, Including Anaphylaxis [see Boxed Warning, Warnings  
371 and Precautions (5.1)]
- 372 • Prolonged and Severe Cytopenias [see Warnings and Precautions (5.2)]
- 373 • Secondary malignancies [see Warnings and Precautions (5.4)]
- 374 • Hypothyroidism [see Warnings and Precautions (5.5)]

375 The most common adverse reactions in patients receiving the BEXXAR therapeutic  
376 regimen (per-patient incidence greater than 25%) were neutropenia, thrombocytopenia, anemia,  
377 infections (including pneumonia, bacteremia, septicemia, bronchitis, and skin infections),  
378 infusion reactions, asthenia, fever, and nausea [see Boxed Warning, Warnings and Precautions  
379 (5.1, 5.2)].

380 The most common serious adverse reactions in patients receiving the BEXXAR  
381 therapeutic regimen were severe and prolonged cytopenias, infections (including pneumonia,  
382 bacteremia, septicemia, bronchitis, and skin infections), serious allergic reactions (including  
383 bronchospasm and angioedema), infusion reactions, and secondary leukemia and  
384 myelodysplastic syndrome [see Boxed Warning, Warnings and Precautions (5.1, 5.2, 5.4)].

385

### 386 **6.1 Clinical Trials Experience**

387 Because clinical trials are conducted under widely varying conditions, adverse reaction  
388 rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical  
389 trials of another drug and may not reflect the rates observed in clinical practice.

390 The reported safety data reflects exposure to the BEXXAR therapeutic regimen in 230  
391 patients with non-Hodgkin's lymphoma enrolled in 5 clinical trials using the recommended dose  
392 and schedule. Patients were followed for a median of 39 months; 79% were followed for at least  
393 12 months for survival and selected adverse reactions. Patients had a median of 3 prior  
394 chemotherapy regimens, a median age of 55 years, and 60% were male. Twenty-seven percent  
395 (27%) had transformation to a higher grade histology; 29% had intermediate-grade histology,  
396 and 2% had high-grade histology (IWF); 68% had Ann Arbor stage IV disease. Patients enrolled

397 in these studies were not permitted to have prior hematopoietic stem cell transplantation or  
 398 irradiation to more than 25% of the marrow space.

399 Data on serious adverse reactions and human anti-mouse antibodies (HAMA) and TSH  
 400 levels were obtained from an additional 765 patients enrolled in the expanded access program  
 401 and used to supplement the characterization of delayed adverse reactions. Patients in the  
 402 expanded access program had fewer prior chemotherapy regimens (2 versus 3) and a higher  
 403 proportion had low-grade histology (77% versus 70%) compared to patients in clinical trials.  
 404

405 **Table 2. Incidence of Non-Hematologic Adverse Reactions Occurring in ≥5% of Patients**  
 406 **Treated With the BEXXAR Therapeutic Regimen (N = 230)**

Body System Preferred Term	All Grades	Grade <sup>3</sup> / <sub>4</sub>
Total	96%	48%
<b>Body as a Whole</b>	81%	12%
Asthenia	46%	2%
Fever	37%	2%
Infection <sup>a</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%
<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%

407 <sup>a</sup> The COSTART term for infection includes a subset of infections (e.g., upper respiratory  
408 infection). Other types of infections are mapped to preferred terms (e.g., pneumonia and  
409 sepsis).  
410

411 **Table 3. Hematologic Toxicity<sup>a</sup> (N = 230)**

Parameter	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>	32 days
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>Absolute Neutrophil Count (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>	31 days
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	23 days
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)

412 <sup>a</sup> Grade 3/4 toxicity was assumed if patient was missing 2 or more weeks of hematology data  
 413 between Week 5 and Week 9.

414 <sup>b</sup> Duration of Grade 3/4 of 1,000+ days (censored) was assumed for those patients with  
 415 undocumented Grade 3/4 and no hematologic data on or after Week 9.

416 <sup>c</sup> Grade 4 toxicity was assumed if patient had documented Grade 3 toxicity and was missing 2  
 417 or more weeks of hematology data between Week 5 and Week 9.

418  
 419 **Prolonged and Severe Cytopenias:** The incidence and duration of severe cytopenias are  
 420 shown in Table 3. Sixty-three (27%) patients received one or more hematologic supportive care  
 421 measures following the therapeutic dose including G-CSF, epoetin alfa, platelet transfusions, and  
 422 packed red blood cell transfusions. Twenty-eight (12%) patients experienced hemorrhagic  
 423 adverse reactions.

424 **Infections:** One hundred and four patients (45%) patients experienced one or more  
 425 infections. Twenty (9%) experienced serious infections including pneumonia, bacteremia,  
 426 septicemia, bronchitis, and skin infections.

427 **Allergic (Hypersensitivity) Reactions:** Fourteen patients (6%) experienced one or more of  
 428 the following adverse reactions: allergic reaction, facial edema, injection site hypersensitivity,  
 429 anaphylactic reaction, laryngismus, and serum sickness.

430 **Infusion-related Adverse Reactions:** Infusion reactions including fever, rigors or chills,  
 431 sweating, hypotension, dyspnea, bronchospasm, and nausea occurred during or within 48 hours

432 of infusion. Sixty-seven patients (29%) experienced fever, rigors/chills, or sweating within 14  
 433 days following the dosimetric dose. All patients in the clinical studies received pretreatment with  
 434 acetaminophen and an antihistamine.

435 Myelodysplastic Syndrome (MDS)/Secondary Leukemia: The incidence of  
 436 MDS/secondary leukemia among the 230 patients included in the clinical studies was 10%  
 437 (24/230), with a median follow-up of 39 months and a median time to development of 34  
 438 months. The cumulative incidence of MDS/secondary leukemia was 4.7% at 2 years and 15% at  
 439 5 years. The incidence of MDS/secondary leukemia among the 765 patients in the expanded  
 440 access program was 3% (20/765), with a median follow-up of 27 months and a median time to  
 441 development of 31 months. The cumulative incidence of MDS/secondary leukemia in this patient  
 442 population was 1.6% at 2 years and 6% at 5 years.

443 Secondary Malignancies: Of the 995 patients in clinical studies and the expanded access  
 444 programs, there were 65 secondary malignancies reported in 54 patients (5%) in clinical studies  
 445 and the expanded access program. These included non-melanoma skin cancers (26), colorectal  
 446 cancer (7), head and neck cancer (6), breast cancer (5), lung cancer (4), bladder cancer (4),  
 447 melanoma (3), and gastric cancer (2).

448 Hypothyroidism: Of the 230 patients in the clinical studies, 203 patients did not have  
 449 elevated TSH at study entry. Of these, 137 patients had at least one post-treatment TSH value  
 450 available and were not taking thyroid hormonal treatment at study entry. With a median follow-  
 451 up period of 46 months, the incidence of hypothyroidism (elevated TSH or initiation of thyroid  
 452 replacement therapy) was 18% with a median time to development of 16 months. The  
 453 cumulative incidences of hypothyroidism at 2 and 5 years in these 137 patients were 11% and  
 454 19%, respectively. Onset of hypothyroidism has occurred up to 90 months post-treatment. The  
 455 cumulative incidence and median time to development of hypothyroidism were similar in the  
 456 expanded access program.

457

## 458 **6.2 Immunogenicity**

459 There is a potential for immunogenicity with therapeutic proteins such as tositumomab.  
 460 Serum samples from 989 chemotherapy-relapsed or refractory patients included in the clinical  
 461 studies or the expanded access program were tested by an enzyme-linked immunosorbent assay  
 462 (ELISA) that detects antibodies to the Fc portion of IgG<sub>1</sub> murine immunoglobulin. One percent  
 463 of the patients (11/989) had a positive serology for HAMA prior to treatment. The post-treatment  
 464 incidence of HAMA seropositivity is summarized in Table 4.

465

466 **Table 4. Incidence of HAMA Seropositivity Among Patients With Chemotherapy-**  
 467 **refractory or Relapsed Non-Hodgkin’s Lymphoma Receiving the BEXXAR Therapeutic**  
 468 **Regimen**

Chemotherapy- refractory or relapsed	Percent HAMA positive	Kaplan-Meier estimate of HAMA positivity		
		6 months	12 months	18 months

<b>patients</b>				
In clinical trials	23/219 (11%)	6%	17%	21%
In expanded-access program	57/569 (10%)	7%	12%	13%

469

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

473 Immunogenicity assay results are highly dependent on several factors including assay  
 474 sensitivity and specificity, assay methodology, sample handling, timing of sample collection,  
 475 concomitant medications, and underlying disease. For these reasons, comparison of incidence of  
 476 antibodies to BEXXAR with the incidence of antibodies to other products may be misleading.

477

478 **6.3 Postmarketing Experience**

479 The following adverse reactions have been identified during post-approval use of the  
 480 BEXXAR therapeutic regimen. Because these reactions are reported voluntarily from a  
 481 population of uncertain size, it is not always possible to reliably estimate their frequency or  
 482 establish a causal relationship to drug exposure.

483 Immune system disorders: Hypersensitivity reactions including fatal anaphylaxis.

484 Nervous system disorders: Axonal neuropathy leading to quadriparesis.

485 **7 DRUG INTERACTIONS**

486 No formal drug-drug interaction studies have been conducted with tositumomab or I-131  
 487 tositumomab.

488 **8 USE IN SPECIFIC POPULATIONS**

489 **8.1 Pregnancy**

490 Pregnancy: Category D [see Warnings and Precautions (5.6)]: There are no studies  
 491 of the BEXXAR therapeutic regimen in pregnant women or animals. Based on the transplacental  
 492 passage of I-131, administration of the BEXXAR therapeutic regimen to a pregnant woman can  
 493 cause fetal harm including severe and possibly irreversible neonatal hypothyroidism. Limited  
 494 data suggest an increased risk of miscarriage up to a year following I-131 treatment.

495 Inform patients who are pregnant or become pregnant after the BEXXAR therapeutic  
 496 regimen about the potential hazard to a fetus. Evaluate infants born to mothers treated with the  
 497 BEXXAR therapeutic regimen for hypothyroidism at the time of delivery and during the  
 498 neonatal period.

499

500 **8.3 Nursing Mothers**

501 Because immunoglobulins are secreted in human milk, it is expected that tositumomab  
 502 would be present in human milk. Radiolabeled iodine is excreted in breast milk and may reach  
 503 concentrations equal to or greater than maternal plasma concentrations. Because of the potential

504 for serious adverse reactions in nursing infants from the BEXXAR therapeutic regimen, advise  
505 women to discontinue nursing or to consider alternative treatment, taking into account the  
506 importance of the BEXXAR therapeutic regimen to the mother.

507

#### 508 **8.4 Pediatric Use**

509 The safety and effectiveness of the BEXXAR therapeutic regimen have not been  
510 established in children.

511

#### 512 **8.5 Geriatric Use**

513 Clinical studies of the BEXXAR therapeutic regimen did not include sufficient numbers  
514 of subjects aged 65 years and older to determine whether they respond differently from younger  
515 subjects.

516

#### 517 **8.6 Renal Impairment**

518 Use of the BEXXAR therapeutic regimen has not been studied in patients with renal  
519 impairment [*see Warnings and Precautions (5.6), Clinical Pharmacology (12.3)*].

520

#### 521 **8.7 Females and Males of Reproductive Potential**

522 Contraception: Females of reproductive potential should use effective contraception  
523 during treatment with the BEXXAR therapeutic regimen and for 12 months after treatment ends  
524 to avoid the embryo-fetal effects of the radioisotope and the risk of increased pregnancy loss  
525 during that time period.

526 The BEXXAR therapeutic regimen exposes the testes to radiation [*see Dosage and*  
527 *Administration (2.9)*]. Because of the potential for mutagenesis in male gametes, males of  
528 reproductive potential should use effective contraception during treatment with the BEXXAR  
529 therapeutic regimen and for 12 months after treatment ends.

530 Infertility: The BEXXAR therapeutic regimen results in radiation exposure of the ovaries  
531 and testes. Based on published studies examining patients treated with I-131, the BEXXAR  
532 therapeutic regimen may cause transient ovarian or testicular dysfunction. Radiation effects may  
533 persist for up to 12 months following treatment.

### 534 **10 OVERDOSAGE**

535 The maximum radiation activity of the I-131 component of the BEXXAR therapeutic  
536 regimen, administered to 4 patients, were doses calculated to deliver between 85 cGy and 88 cGy  
537 total body irradiation. The incidence of NCI Grade 4 cytopenias was increased in these 4 patients  
538 compared to patients who received the recommended therapeutic dose for the BEXXAR  
539 therapeutic regimen.

### 540 **11 DESCRIPTION**

541 The BEXXAR therapeutic regimen is composed of the monoclonal antibody  
542 tositumomab, and the radiolabeled monoclonal antibody, I-131 tositumomab.

543 Tositumomab is a murine IgG<sub>2a</sub> lambda monoclonal antibody directed against the CD20  
544 antigen, produced in mammalian cells. The approximate molecular weight of tositumomab is 150  
545 kD.

546 Tositumomab is supplied as a sterile, pyrogen-free, clear to opalescent, colorless to  
547 slightly yellow, preservative-free solution that must be diluted before intravenous administration.  
548 The formulation contains 100 mg/mL maltose, 8.5 mg/mL sodium chloride, 1 mg/mL phosphate,  
549 1 mg/mL potassium hydroxide, and Water for Injection, USP. The pH is approximately 7.2.

550 I-131 tositumomab is tositumomab covalently linked to Iodine-131. I-131 tositumomab is  
551 supplied as a sterile, clear, preservative-free liquid. The formulation for I-131 tositumomab  
552 contains 0.9 to 1.3 mg/mL ascorbic acid, 1 to 2 mg/mL maltose (dosimetric dose) or 9 to 15  
553 mg/mL maltose (therapeutic dose), 4.4% to 6.6% (w/v) povidone, and 8.5 to 9.5 mg/mL sodium  
554 chloride. The pH is approximately 7.0.

555 Physical/Radiochemical Characteristics of Iodine-131: Iodine-131 decays with beta and  
556 gamma emissions with a physical half-life of 8.04 days. The principal beta emission has a mean  
557 energy of 191.6 keV, and the principal gamma emission has energy of 364.5 keV.

558 External Radiation: The specific gamma ray constant for Iodine-131 is 2.2 R/millicurie  
559 hour at 1 cm. Use a 2.55 cm thickness of Pb (to attenuate the radiation emitted by a factor of  
560 about 1,000) to minimize radiation exposure from this radionuclide.

561 The fraction of Iodine-131 radioactivity that remains in the vial x days after the date of  
562 calibration is  $2^{-(x/8.04)}$ .

563 Physical decay is presented in Table 5.

564  
565

**Table 5. Physical Decay Chart: Iodine-131: Half-Life 8.04 Days**

Days	Fraction Remaining
0 <sup>a</sup>	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

566 <sup>a</sup> Calibration day.

567 **12 CLINICAL PHARMACOLOGY**

568 **12.1 Mechanism of Action**

569 Tositumomab binds specifically to an epitope within the extracellular domain of the  
570 CD20 molecule. The CD20 molecule is expressed on normal B lymphocytes (pre-B lymphocytes  
571 to mature B lymphocytes) and on B-cell non-Hodgkin's lymphomas. The CD20 molecule is not  
572 shed from the cell surface and is not internalized following antibody binding. The BEXXAR  
573 therapeutic regimen induces cell death by emitting ionizing radiation to CD20-expressing  
574 lymphocytes or neighboring cells. In addition to cell death mediated by the radioisotope, other  
575 possible mechanisms of action include antibody-dependent cellular cytotoxicity, complement-  
576 dependent cytotoxicity, and CD20-mediated apoptosis.

577

578 **12.2 Pharmacodynamics**

579 In two clinical studies (one in chemotherapy-naive patients and one in heavily pretreated  
580 patients), the administration of the BEXXAR therapeutic regimen resulted in sustained depletion  
581 of circulating CD20-positive cells. The assessment of circulating lymphocytes in these patients  
582 did not distinguish normal from malignant cells; consequently, recovery of normal B cell  
583 numbers was not directly assessed. At 7 weeks following treatment, the median number of  
584 circulating CD20-positive cells was zero (range: 0 to 490 cells/mm<sup>3</sup>) with recovery beginning at  
585 approximately 12 weeks. At 6 months following treatment, 8 (14%) of 58 chemotherapy-naive  
586 patients and 6 (32%) of 19 heavily pretreated patients had CD20-positive cell counts below  
587 normal limits. There was no consistent effect of the BEXXAR therapeutic regimen on post-  
588 treatment serum IgG, IgA, or IgM levels.

589

590 **12.3 Pharmacokinetics**

591 A pharmacokinetic study of I-131 tositumomab determined that a 475-mg predose of  
592 unlabeled antibody decreased splenic targeting and increased the terminal half-life of the  
593 radiolabeled antibody. The median blood clearance following administration of 485 mg of  
594 tositumomab in 110 patients with non-Hodgkin's lymphomas was 68.2 mg/hr (range: 30.2 to  
595 260.8 mg/hr). Patients with high tumor burden, splenomegaly, or bone marrow involvement were  
596 noted to have a larger volume of distribution, faster clearance, and shorter terminal half-life. The  
597 total body clearance, as measured by total body gamma camera counts, was dependent on the  
598 same factors noted for blood clearance. Patient-specific dosing, based on total body clearance,  
599 provided a consistent radiation dose despite variable pharmacokinetics, by allowing each  
600 patient's administered activity to be adjusted for individual patient variables. The median total  
601 body effective half-life, as measured by total body gamma camera counts, in 980 patients with  
602 non-Hodgkin's lymphoma was 67 hours (range: 28 to 115 hours).

603 Elimination of Iodine-131 occurs by decay (Table 5) and excretion in the urine. Five days  
604 following the dose, the whole body clearance was 67% of the injected dose. Ninety-eight percent  
605 (98%) of the clearance was accounted for in the urine.

606 **13 NONCLINICAL TOXICOLOGY**

607 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

608 No long-term animal studies have been performed to establish the carcinogenic or  
609 mutagenic potential of the BEXXAR therapeutic regimen or to determine its effects on fertility  
610 in males or females. However, Iodine I-131 is a potential carcinogen and mutagen.

611 Administration of the BEXXAR therapeutic regimen exposes the testes and ovaries to  
612 radiation [*see Dosage and Administration (2.9)*].

613 **14 CLINICAL STUDIES**

614 The clinical benefit of the BEXXAR therapeutic regimen was established in 2 single-arm  
615 clinical trials conducted in 100 patients with low-grade, transformed low-grade, or follicular  
616 large-cell lymphoma. Patients had a Karnofsky performance status of at least 60%, a granulocyte  
617 count of 1500 cells/mm<sup>3</sup>, a platelet count greater than or equal to 100,000/mm<sup>3</sup>, less than or  
618 equal to 25% of the intra-trabecular marrow space involved by lymphoma, and no evidence of  
619 progressive disease arising in a field irradiated with >3500 cGy within one year of completion of  
620 irradiation.

621 Study 1 enrolled 40 patients with low-grade or transformed low-grade or follicular large-  
622 cell lymphoma whose disease had not responded to, or had progressed following, at least 4 doses  
623 of rituximab therapy. The median age was 57 years (range: 35 to 78 years); the median time from  
624 diagnosis to protocol entry was 50 months (range: 12 to 170 months); and the median number of  
625 prior chemotherapy regimens was 4 (range: 1 to 11). Overall, 35 of the 40 patients were  
626 rituximab-refractory (defined as no response or a response of less than 6 months' duration  
627 following rituximab therapy).

628 Study 2 enrolled 60 rituximab-naïve patients who had relapsed following or were  
629 refractory to chemotherapy. The median age was 60 years (range: 38 to 82 years), the median  
630 time from diagnosis to protocol entry was 53 months (range: 9 to 334 months), and the median  
631 number of prior chemotherapy regimens was 4 (range: 2 to 13). Fifty-three patients had not  
632 responded to prior therapy and 7 patients had responded with duration of response of less than 6  
633 months.

634 The main outcome measure in Study 1 and Study 2 was overall response rate as  
635 determined by an independent panel that reviewed patient records and radiologic studies (Table  
636 6).

637

638

**Table 6. Efficacy Outcomes for the BEXXAR Therapeutic Regimen**

	Study 1 (n = 40)	Study 2 (n = 60)
Overall Response		
Rate	68%	47%
95% CI <sup>a</sup>	(51%, 81%)	(34%, 60%)
Response Duration (months)		
Median	16	12
95% CI <sup>a</sup>	(10, NR <sup>b</sup> )	(7, 47)
Range	1+ to 38+	2 to 47
Complete Response <sup>c</sup>		
Rate	33%	20%
95% CI <sup>a</sup>	(19%, 49%)	(11%, 32%)
Complete Response <sup>c</sup> Response Duration (months)		
Median	NR <sup>b</sup>	47
95% CI <sup>a</sup>	(15, NR)	(47, NR)
Range	4 to 38+	9 to 47

639 <sup>a</sup> CI = confidence interval640 <sup>b</sup> NR = not reached, median duration of follow-up: Study 1 = 26 months, Study 2 = 30 months641 <sup>c</sup> Complete response rate = pathologic and clinical complete responses

642

643 The results of these studies were supported by demonstration of durable objective  
644 responses in 3 additional small, single-arm studies enrolling 130 rituximab-naïve patients with  
645 follicular non-Hodgkin's lymphoma with or without transformation. All patients had relapsed  
646 following, or were refractory to, chemotherapy. The overall response rates ranged from 49% to  
647 64% and the median durations of response ranged from 13 to 16 months.

648 **16 HOW SUPPLIED/STORAGE AND HANDLING**

649 The BEXXAR therapeutic regimen is supplied as 2 separate units: dosimetric step  
650 components and therapeutic step components. The components of the dosimetric step are  
651 shipped from separate sites; when ordering, ensure that the components are scheduled to arrive  
652 on the same day. Similarly, the components of the therapeutic step are shipped from separate  
653 sites; when ordering, ensure that the components are scheduled to arrive on the same day.

654

655 **16.1 Dosimetric Dose Components**

- 656 • A carton (NDC 0007-3260-31) containing 2 single-use 225-mg vials (NDC 0007-3260-  
657 01) and 1 single-use 35-mg vial (NDC 0007-3260-21) of tositumomab solution each at a  
658 nominal concentration of 14 mg/mL

- 659 • One single-use vial (NDC 0007-3261-01) containing not less than 20 mL of I-131  
660 tositumomab solution at not less than protein and activity concentrations of 0.1 mg/mL  
661 and 0.61 mCi/mL (at calibration)  
662

## 663 **16.2 Therapeutic Dose Components**

- 664 • A carton (NDC 0007-3260-36) containing 2 single-use 225-mg vials (NDC 0007-3260-  
665 01) and 1 single-use 35-mg vial (NDC 007-3260-21) of tositumomab solution each at a  
666 nominal concentration of 14 mg/mL
- 667 • One or 2 single-use vials (NDC 0007-3262-01) each containing not less than 20 mL of I-  
668 131 tositumomab solution at not less than protein and activity concentrations of 1.1  
669 mg/mL and 5.6 mCi/mL (at calibration)  
670

## 671 **16.3 Storage**

672 Tositumomab: Store vials (including diluted vials) of tositumomab (35 mg and 225 mg)  
673 at 36°F to 46°F (2°C to 8°C). Protect from strong light. **Do not shake; do not freeze.** Diluted  
674 tositumomab solutions are stable for up to 24 hours when stored refrigerated and for up to 8  
675 hours at room temperature. Discard unused portions.

676 I-131 tositumomab: Store vials of I-131 tositumomab in the original lead pot at a  
677 temperature of -4°F (-20°C) or below until thawed prior to administration.

678 Thawed dosimetric and therapeutic doses of I-131 tositumomab (including diluted vials)  
679 are stable for up to 8 hours at 36°F to 46°F (2°C to 8°C) or at room temperature. I-131  
680 tositumomab does not contain a preservative. **Do not shake; do not freeze.** Discard unused  
681 portions according to federal and state laws regarding radioactive and biohazardous waste.

## 682 **17 PATIENT COUNSELING INFORMATION**

683 Advise patients:

- 684 • To take premedications, including thyroid-blocking agents as prescribed [*see Warnings*  
685 *and Precautions (5.5)*].
- 686 • To contact a healthcare professional if they experience signs and symptoms of allergic  
687 reactions [*see Warnings and Precautions (5.1)*].
- 688 • To report to a health care professional any signs of cytopenias (bleeding, easy bruising,  
689 petechiae or purpura, pallor, weakness or fatigue, or symptoms of infection such as fever)  
690 [*see Warnings and Precautions (5.2)*].
- 691 • Of the need for frequent monitoring for up to 3 months after treatment, and the potential  
692 for persistent cytopenias beyond 3 months.
- 693 • Concerning the risk of radiation exposure to household contacts, pregnant women and  
694 small children from radioactive materials remaining in the patient's body following the  
695 BEXXAR therapeutic regimen. Provide patient-specific advice orally and in writing [*see*  
696 *Warnings and Precautions (5.3)*].

- 697 • Of the need for life-long monitoring for hypothyroidism [*see Warnings and Precautions*
- 698 [*5.5*].
- 699 • Who are pregnant that the BEXXAR therapeutic regimen can cause hypothyroidism in
- 700 the infant [*see Warnings and Precautions (5.6), Use in Special Populations (8.7)*].
- 701 • To check with their physicians before receiving live virus vaccinations [*see Warnings*
- 702 *and Precautions (5.8)*].
- 703 • Who are of reproductive potential to use effective contraceptive methods during
- 704 treatment and for a minimum of 12 months following the BEXXAR therapeutic regimen
- 705 [*see Use in Special Populations (8.7)*].
- 706 • To discontinue nursing during and after the BEXXAR therapeutic regimen [*see Use in*
- 707 *Special Populations (8.3)*].

708  
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