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^3, or neutrophil count <1,500 cells/mm^3 (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)

---------- 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.

---------- USE IN SPECIFIC POPULATIONS ----------

- Nursing Mothers: Discontinue nursing. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 02/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

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

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

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

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

1 INDICATIONS AND USAGE

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

The BEXXAR® therapeutic regimen (tositumomab and iodine I 131 tositumomab) is 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.

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.

1.2 Important Limitations of Use

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

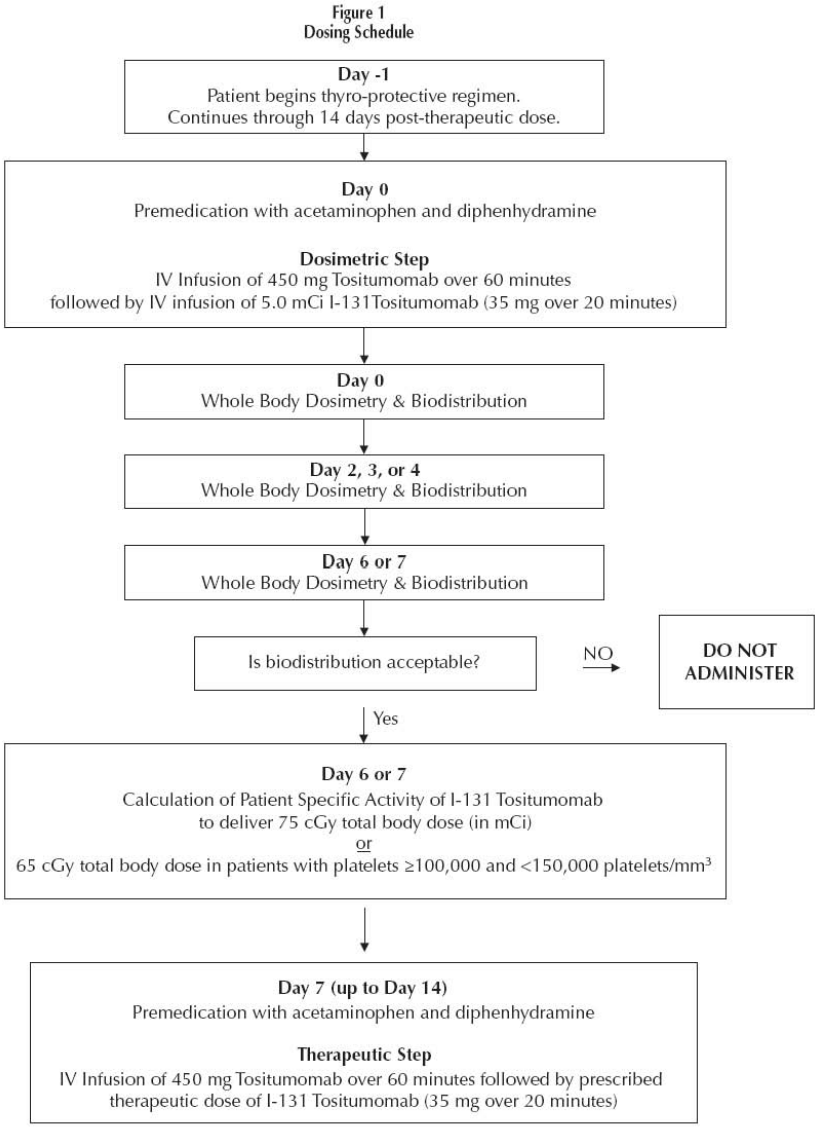
2 DOSAGE AND ADMINISTRATION

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

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

2.1 Overview of Dosing Schedule

Figure 1
Dosing Schedule



2.2 Recommended Dose

Dosimetric dose

(1) Tositumomab 450 mg by intravenous infusion

(2) I-131 tositumomab (5 mCi I-131 and 35 mg protein) by intravenous infusion

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

(1) Tositumomab 450 mg by intravenous infusion.

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

If platelet counts are 150,000 platelets/mm^3 or greater:

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

If platelet counts are 100,000 to 149,000 platelets/mm^3:

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

2.3 Preparation of Dosimetric Dose

Tositumomab Dosimetric Dose

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

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

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

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

I-131 Tositumomab Dosimetric Dose

Required materials (not supplied):

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

Method

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

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

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

(4) Assay preparation vial to confirm activity is 5.0 mCi (± 10%) using a suitable radioactivity calibration system operated in accordance with the manufacturer's specifications and quality control for the measurement of Iodine-131.
- If the preparation vial contains the calculated activity (±10%), proceed to step 5.
- If the preparation vial does not contain the calculated activity (5 mCi ±10%), determine the activity concentration of the I-131 tositumomab based on the volume and the activity in the preparation vial. Add or subtract the appropriate volume of I-131 tositumomab to the preparation vial to achieve the desired activity of 5.0 mCi (±10%). Re-assay to confirm.

(5) Calculate the amount of tositumomab in the shielded preparation vial, based on the volume and labeled protein concentration of the I-131 tositumomab dosimetric vial (see product specification sheet provided in dosimetric carton). If less than 35 mg, add additional tositumomab from the non-radioactive vial to the shielded vial to yield a total of 35 mg tositumomab in the shielded vial.

(6) Add a sufficient quantity of 0.9% Sodium Chloride for Injection, USP to the shielded preparation vial to yield a final volume of 30 mL. Gently mix contents.

(7) Withdraw the entire contents from the preparation vial into a 60-mL syringe using a large bore needle (18-gauge) and shield contents of syringe and syringe pump.

(8) Assay and record the activity.

2.4 Administration of Dosimetric Dose

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

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

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

Tositumomab

(1) Premedicate with oral diphenhydramine 50 mg and oral acetaminophen 650 mg, 30 minutes prior to initiation of the dosimetric dose.

(2) Administer 450 mg tositumomab in 50 mL 0.9% sodium chloride by intravenous infusion through a 0.22 micron in-line filter over 60 minutes (refer to *Site Training Manual* for diagram showing assembly of the infusion set components). Decrease the rate of infusion by 50% for mild to moderate infusion reactions. Discontinue for serious allergic reactions; interrupt for severe infusion reactions. If severe infusion reaction completely resolves, the infusion may be continued at 50% of the previous infusion rate.

I-131 Tositumomab

(3) Attach the shielded syringe containing the I-131 tositumomab dose in a syringe pump to the intravenous line containing the in-line filter used in step 2 above**.** A change in filter can result in loss of up to 7% of the I-131 tositumomab dose.

(4) Set syringe pump to deliver the entire dose of I-131 tositumomab over 20 minutes, immediately following completion of the tositumomab infusion. Decrease the rate of infusion by 50% for mild to moderate infusion reactions. Discontinue for serious allergic reactions; interrupt for severe infusion reactions. If severe infusion reaction completely resolves, the infusion may be continued at 50% of the previous infusion rate.

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

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

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

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

2.5 Assessment of Dosimetry and Biodistribution

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

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

(1) Count 1 (Day 0): Within 1 hour following the end of the I-131 tositumomab infusion and prior to urination, obtain total body gamma camera count and whole body images

(2) Count 2 (Day 2, 3, or 4): Obtain total body gamma camera counts and whole body images, immediately following urination.

(3) Count 3 (Day 6 or 7): Obtain total body gamma camera counts and whole body images, immediately following urination.

Verify that the expected biodistribution is present.

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

Expected biodistribution characteristics:

Count 1 (day of dosimetric dose)

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

Count 2 (day 2, 3, or 4) and Count 3 (day 6 or 7)

- Activity in the blood pool decreases significantly. Decreased accumulation of activity in normal liver and spleen. Possible uptake present in thyroid, kidney, and urinary bladder with minimal uptake in the lungs. Possible increased intensity at known lymphoma sites. Biodistribution is altered if any of the following is present:

Count 1*:*

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

Count 2 and Count 3*:*

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

2.6 Calculation of I-131 Therapeutic Dose

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

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

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

2.7 Preparation of Therapeutic Dose

Tositumomab

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

I-131 tositumomab

Required materials (not supplied):

Lead shielding for preparation vial and syringe pump

One sterile 50-mL preparation vial

Two lead pots at room temperature.

Method

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

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

(1) Calculate the volume (see activity concentration on the product specification sheet provided with the therapeutic vial) of I-131 tositumomab activity required to deliver either 75cGy or 65cGy total body irradiation *[*see *Dosage and Administration (2.6)]*.

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

(3) Assay preparation vial to confirm calculated activity using a suitable radioactivity calibration system operated in accordance with the manufacturer's specifications and quality control for the measurement of Iodine-131.

- If the assayed dose in the preparation vial contains the calculated activity (±10%), proceed to step 5.
- If the assayed dose in the preparation vial does not contain the calculated activity (±10%), determine the activity concentration of I-131 tositumomab based on the volume and the activity in the preparation vial. Add or subtract the appropriate volume of I-131 tositumomab to the preparation vial to achieve the required I-131 tositumomab activity. Re-assay the preparation vial contents to confirm.

(4) Calculate the amount of tositumomab in the shielded preparation vial, based on the volume and protein concentration of I-131 tositumomab (refer to product specification sheet for the vial in the therapeutic carton). If the amount of tositumomab in the preparation vial is less than 35 mg, add additional tositumomab from the non-radioactive 35-mg vial to the shielded preparation vial to yield a total of 35 mg tositumomab in the shielded vial.

(5) Add a sufficient quantity of 0.9% Sodium Chloride for Injection, USP to the shielded preparation vial to yield a final volume of 30 mL. Gently mix contents.

(6) Withdraw the entire contents from the shielded preparation vial into a 60-mL syringe using a large bore needle (18-gauge) and shield contents of syringe and syringe pump.

(7) Assay and record activity.

2.8 Administration of Therapeutic Dose

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

Tositumomab

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

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

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

I-131 Tositumomab

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

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

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

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

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

2.9 Radiation Dosimetry

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

Table 1. Estimated Radiation-Absorbed Organ Doses

	The BEXXAR therapeutic regimen mGy/MBq Median	The BEXXAR therapeutic regimen mGy/MBq Range
Organ Regions of Interest (ROIs)		
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
Whole Body ROIs		
Urine bladder wall	0.64	0.6 - 0.9
Bone surfaces	0.41	0.4 - 0.6
Pancreas	0.31	0.2 - 0.4
Gall bladder wall	0.29	0.2 - 0.3
Adrenals	0.28	0.2 - 0.3
Ovaries	0.25	0.2 - 0.3
Small intestine	0.23	0.2 - 0.3
Thymus	0.22	0.1 - 0.3
Uterus	0.20	0.2 - 0.2
Muscle	0.18	0.1 - 0.2
Breasts	0.16	0.1 - 0.2
Skin	0.13	0.1 - 0.2
Brain	0.13	0.1 - 0.2
Total body	0.24	0.2 - 0.3

3 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

I-131 tositumomab solution containing 12-18 mCi Iodine-131 per vial (not less than 20 mL containing 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 protein concentration), single-use vial

I-131 tositumomab solution containing 112-168 mCi Iodine-131 per vial (not less than 20 mL containing 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 protein concentration), single-use vial

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Serious Allergic Reactions, Including Anaphylaxis

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

5.2 Prolonged and Severe Cytopenias

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

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

5.3 Radiation Exposure

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

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

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

5.4 Secondary Malignancies

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

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

5.5 Hypothyroidism

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

5.6 Embryo-fetal Toxicity

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

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

5.7 Excessive Radiation Exposure in Patients With Impaired Renal Function

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

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

5.8 Immunization

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

6 ADVERSE REACTIONS

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

- Serious Allergic Reactions, Including Anaphylaxis *[see Boxed Warning, Warnings and Precautions (5.1)*
- Prolonged and Severe Cytopenias *[see Warnings and Precautions (5.2)]*
- Secondary malignancies *[see Warnings and Precautions (5.4)]*
- Hypothyroidism *[*see *Warnings and Precautions (5.5)]*

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

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

6.1 Clinical Trials Experience

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

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

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

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

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

Body System Preferred Term	All Grades	Grade ¾
Total	96%	48%
Body as a Whole	81%	12%
Asthenia	46%	2%
Fever	37%	2%
Infection[a]	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%
Cardiovascular System	26%	3%
Hypotension	7%	1%
Vasodilatation	5%	0%
Digestive System	56%	9%
Nausea	36%	3%
Vomiting	15%	1%
Anorexia	14%	0%
Diarrhea	12%	0%
Constipation	6%	1%
Dyspepsia	6%	<1%
Endocrine System	7%	0%
Hypothyroidism	7%	0%
Metabolic and Nutritional Disorders	21%	3%
Peripheral edema	9%	0%
Weight loss	6%	<1%
Musculoskeletal System	23%	3%

Myalgia	13%	<1%
Arthralgia	10%	1%
Nervous System	26%	3%
Dizziness	5%	0%
Somnolence	5%	0%
Respiratory System	44%	8%
Cough increased	21%	1%
Pharyngitis	12%	0%
Dyspnea	11%	3%
Rhinitis	10%	0%
Pneumonia	6%	0%
Skin and Appendages	44%	5%
Rash	17%	<1%
Pruritus	10%	0%
Sweating	8%	<1%

[a] The COSTART term for infection includes a subset of infections (e.g., upper respiratory infection). Other types of infections are mapped to preferred terms (e.g., pneumonia and sepsis).

Table 3. Hematologic Toxicity[a] (N = 230)

Parameter	Values
Platelets	
Median nadir (cells/mm^3)	43,000
Per patient incidence[a] platelets <50,000/mm^3	53% (n = 123)
Median[b] duration of platelets <50,000/mm^3	32 days
Grade 3/4 without recovery to Grade 2, N (%)	16 (7%)
Per patient incidence[c] platelets <25,000/mm^3	21% (n = 47)
Absolute Neutrophil Count (ANC)	
Median nadir (cells/mm^3)	690
Per patient incidence[a] ANC <1,000 cells/mm^3	63% (n = 145)
Median[b] duration of ANC <1,000 cells/mm^3	31 days
Grade 3/4 without recovery to Grade 2, N (%)	15 (7%)
Per patient incidence[c] ANC <500 cells/mm^3	25% (n = 57)
Hemoglobin	
Median nadir (gm/dL)	10
Per patient incidence[a] <8 gm/dL	29% (n = 66)
Median[b] duration of hemoglobin <8.0 gm/dL	23 days
Grade 3/4 without recovery to Grade 2, N (%)	12 (5%)
Per patient incidence[c] hemoglobin <6.5 gm/dL	5% (n = 11)

[a] Grade 3/4 toxicity was assumed if patient was missing 2 or more weeks of hematology data between Week 5 and Week 9.

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

[c] 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.

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

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

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

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

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

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

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

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

6.2 Immunogenicity

There is a potential for immunogenicity with therapeutic proteins such as tositumomab. Serum samples from 989 chemotherapy-relapsed or refractory patients included in the clinical studies or the expanded access program were tested by an enzyme-linked immunosorbent assay (ELISA) that detects antibodies to the Fc portion of IgG_1 murine immunoglobulin. One percent of the patients (11/989) had a positive serology for HAMA prior to treatment. The post-treatment incidence of HAMA seropositivity is summarized in Table 4.

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

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

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

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

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

6.3 Postmarketing Experience

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

Immune system disorders: Hypersensitivity reactions including fatal anaphylaxis.

Nervous system disorders: Axonal neuropathy leading to quadriparesis.

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

8.3 Nursing Mothers

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

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Renal Impairment

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

8.7 Females and Males of Reproductive Potential

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

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

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

10 OVERDOSAGE

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

11 DESCRIPTION

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

Tositumomab is a murine IgG_{2a} lambda monoclonal antibody directed against the CD20 antigen, produced in mammalian cells. The approximate molecular weight of tositumomab is 150 kD.

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

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

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

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

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

Physical decay is presented in Table 5.

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

Days	Fraction Remaining
0[a]	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

[a] Calibration day.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

14 CLINICAL STUDIES

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

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

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

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

Table 6. Efficacy Outcomes for the BEXXAR Therapeutic Regimen

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

[a] CI = confidence interval

[b] NR = not reached, median duration of follow-up: Study 1 = 26 months, Study 2 = 30 months

[c] Complete response rate = pathologic and clinical complete responses

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

16 HOW SUPPLIED/STORAGE AND HANDLING

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

16.1 Dosimetric Dose Components

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

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

16.2 Therapeutic Dose Components

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

16.3 Storage

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

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

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

17 PATIENT COUNSELING INFORMATION

Advise patients:

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

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

BEXXAR is a registered trademark of GlaxoSmithKline.
LUER-LOK is a trademark of Becton, Dickinson and Company.

GlaxoSmithKline
Research Triangle Park, NC 27709
U.S. Lic. 1727

Month Year
BXX:XPI