PRODUCT MONOGRAPH

BEXXAR® therapy

(tositumomab and iodine I 131 tositumomab)

Intravenous 35 mg and 225 mg tositumomab

444-666 MBq (12 -18 mCi) and 4144-6216 MBq (112 - 168 mCi) iodine I 131 tositumomab

Anti-Neoplastic Radioimmunotherapeutic

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BEXXAR® therapy

(tositumomab and iodine I 131 tositumomab)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	Intravenous / 35 mg / 2.5 mL 225 mg /16.1 mL	Not applicable. *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

Physical Characteristics

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 an energy of 364.5 keV.[22]

External Radiation

The specific gamma ray constant for iodine-131 is 2.2 R/millicurie hour at 1 cm. The first half-value layer is 0.24 cm lead (Pb) shielding. A range of values is shown in Table 1 for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of Pb. To facilitate control of the radiation exposure from this radionuclide, the use of a 2.55 cm thickness of Pb will attenuate the radiation emitted by a factor of about 1,000.

Table 1
Radiation Attenuation by Lead Shielding

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

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

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

Physical decay is presented in Table 2.

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

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

*(Calibration day)

INDICATIONS AND CLINICAL USE

BEXXAR® therapy (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.

This product should be administered under the supervision of a qualified health professional who is appropriately qualified in the use of radioimmunotherapy and the management of patients with non-Hodgkin's lymphoma (NHL). Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

CONTRAINDICATIONS

BEXXAR® therapy (tositumomab and iodine I 131 tositumomab) is contraindicated in patients with known hypersensitivity to murine proteins or any component of BEXXAR®.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Special requirements: BEXXAR® therapy (tositumomab and iodine I 131 tositumomab) contains a radioactive component and should be administered only by physicians and other health care professionals qualified by training in the safe use and handling of therapeutic radionuclides.

Thyroid-blocking therapy must be initiated at least 24 hour before receiving the dosimetric dose and continued for 14 days after the therapeutic dose of BEXXAR® to decrease the risk of hypothyroidism (See WARNINGS AND PRECAUTIONS, Endocrine and Metabolism and DOSAGE AND ADMINISTRATION).

Hypersensitivity reactions, including anaphylaxis: Serious hypersensitivity reactions, including some with fatal outcome, have been reported with BEXXAR®. Medications for the treatment of severe hypersensitivity reactions should be available for immediate use. Patients who develop severe hypersensitivity reactions should have infusions of BEXXAR® discontinued and receive medical attention (see ADVERSE REACTIONS, Infusional Toxicity and WARNINGS AND PRECAUTIONS, Immune).

Prolonged and severe cytopenias: The majority of patients who received BEXXAR® experienced severe thrombocytopenia and neutropenia. BEXXAR® should not be administered to patients with > 25% lymphoma marrow involvement, platelet count < 100 x 10^9/L or neutrophil count < 1.5 x 10^9/L, and/or impaired bone marrow reserve (see WARNINGS AND PRECAUTIONS, Hematologic and ADVERSE REACTIONS).

Pregnancy: BEXXAR® can cause fetal harm when administered to a pregnant woman.

General

BEXXAR® therapy (tositumomab and iodine I 131 tositumomab) is a biologic product with a radioactive component and should be administered only under the supervision of a health professional who is experienced in the use of radionuclides. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

Radionuclide Precautions: Iodine I 131 tositumomab is radioactive. It may be received, used and administered only by authorized personnel. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of local competent official organizations. As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

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.

Contamination

The following measures should be taken by the patient for up to 2 weeks after receiving the radiopharmaceutical.

Therapeutic dose:

Avoidance of contact with infants, young children and pregnant women. Sleeping in a separate bed (separated by a distance of at least 2 to 3 meters). Maintain an appropriate distance of 2 meters from others. Travel alone in a private automobile if possible, otherwise maintain as great a distance as possible between patient and driver. Toilet should be used instead of urinal. Male patients should sit to use the toilet. Toilet should be flushed several times after use. Separate laundry and eating utensils and wash items separately.

Carcinogenesis, Mutagenesis and Impairment of Fertility

No long-term animal studies have been performed to establish the carcinogenic or mutagenic potential of BEXXAR® or to determine its effects on fertility in males or females. However, radiation is a potential carcinogen and mutagen. Administration of BEXXAR® results in delivery of a significant radiation dose to the testes. The radiation dose to the ovaries has not been established. There have been no studies to evaluate whether administration of BEXXAR® causes hypogonadism, premature menopause, azoospermia, and/or mutagenic alterations to germ cells. There is a potential risk that BEXXAR® may cause toxic effects on the male and female gonads. Effective contraceptive methods should be used during treatment and for 12 months following administration of BEXXAR®.

Secondary Malignancies: Although there were 995 patients in the investigator assessment, 10 patients were determined to have MDS/AML prior to BEXXAR® and were then excluded from the independent, masked pathology review. Based on an independent, masked pathology review, myelodysplastic syndrome (MDS) and/or acute leukemia developed in 32/985 (3.2%) patients after receiving BEXXAR®. This analysis yields an annualised incidence of 1.3% per year (95% CI: 0.9% - 1.8% per year).

Most patients had extensive exposure to common alkylating agents and/or to topoisomerase II inhibiting agents, which have all been documented as risk factors for the development of MDS and leukemia.[9,11,13] It is unknown to what extent BEXXAR® plays a role in the development of MDS and/or leukemia in patients with NHL. (See ADVERSE REACTIONS, Secondary Leukemias and Myelodysplastic Syndrome (MDS))

Endocrine and Metabolism

Hypothyroidism: Use of BEXXAR® may result in hypothyroidism. Thyroid-blocking therapy must be initiated at least 24 hours before receiving the dosimetric dose and continue for 14 days after the therapeutic dose of BEXXAR® to decrease the risk of hypothyroidism. TSH levels should be monitored before and after BEXXAR®. After treatment, patients should be monitored for elevation of TSH and/or signs or symptoms of hypothyroidism every 6 months for the first 2 years, and annually thereafter.

Hematologic

Prolonged and Severe Cytopenias (See Serious Warnings and Precautions and ADVERSE REACTIONS, Hematologic Events): The most common adverse reactions associated with BEXXAR® were grade 3 or grade 4 cytopenias. These consisted primarily of grade 3 or 4 thrombocytopenia (53%) and grade 3 or 4 neutropenia (63%). The time to nadir was 4 to 7 weeks and the duration of cytopenias was approximately 30 days. Thrombocytopenia, neutropenia, and anemia persisted for more than 90 days following administration of BEXXAR® in 16 (7%), 15 (7%), and 12 (5%) patients respectively (this includes patients with transient recovery followed by recurrent cytopenia). Due to the variable nature in the onset of cytopenias, complete blood counts should be obtained weekly following BEXXAR® and should continue until levels recover.

The safety of BEXXAR® has not been established in patients with > 25% lymphoma marrow involvement, platelet count < 100 x 10^9/L or neutrophil count < 1.5 x 10^9/L, therefore it should not be administered to these patients.

Immune

Hypersensitivity Reactions Including Anaphylaxis (see ADVERSE REACTIONS: Immunogenicity)**:** Severe hypersensitivity reactions may result in fatal outcomes during and following administration of BEXXAR®. Emergency supplies including medications for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines, and corticosteroids, should be available for immediate use in the event of an allergic reaction during administration of BEXXAR®. Signs and symptoms of severe allergic reactions may include fever, rigors or chills, sweating, hypotension, dyspnea, bronchospasm, and nausea and have been reported during or within 48 hours of infusion. Patients who have received murine proteins should be screened for human anti-murine antibodies (HAMA). Patients who are positive for HAMA may be at increased risk of anaphylaxis and serious hypersensitivity reactions during administration of BEXXAR®.

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

Renal

Renal Function: Iodine I 131 tositumomab and iodine-131 are excreted primarily by the kidneys. Impaired renal function may decrease the rate of excretion of the radiolabelled iodine and increase patient exposure to the radioactive component of BEXXAR®. There are no data regarding the safety of administration of BEXXAR® in patients with impaired renal function.

Special Populations

Pregnant Women: Ideally examinations and treatments using radiopharmaceuticals, in women of childbearing capability should be performed during the first ten days following the onset of menses. Limited data suggest an increased risk of miscarriage up to a year following I-131 treatment. While there are no adequate and well-controlled studies of BEXXAR® in pregnant animals or humans, use of BEXXAR® in women of childbearing age should be deferred until the possibility of pregnancy has been ruled out. If the patient becomes pregnant while being treated with BEXXAR®, the patient should be apprised of the potential hazard to the fetus.

Males and females of reproductive potential should use effective contraceptive methods during treatment and for 12 months following administration of BEXXAR®.

Embryo-fetal Toxicity: Use of BEXXAR® may cause fetal harm when administered to a pregnant woman. Iodine-131 may cause harm to the fetal thyroid gland when administered to pregnant women. Review of the literature has shown that transplacental passage of radioiodide may cause severe, and possibly irreversible, hypothyroidism in neonates. Evaluate infants born to mothers treated with BEXXAR® during pregnancy for hypothyroidism at time of delivery and during the neaonatal period

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

Pediatrics (< 18 years of age): The safety and effectiveness of BEXXAR® in pediatric patients has not been evaluated.

Geriatrics (> 65 years of age): Clinical studies of BEXXAR® did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In clinical studies, 230 patients received BEXXAR® at the recommended dose. Of these, 27% (61 patients) were age 65 or older and 4% (10 patients) were age 75 or older. While the incidence of severe hematologic toxicity was lower, the duration of severe hematologic toxicity was longer in those age 65 or older as compared to patients less than 65 years of age. Due to the limited experience, greater sensitivity of some older individuals cannot be ruled out.

Monitoring and Laboratory Tests

A complete blood count (CBC) with differential and platelet count should be obtained prior to, and at least weekly following, administration of BEXXAR® and should continue until levels recover. More frequent monitoring is indicated in patients with evidence of moderate or more severe cytopenias (see WARNINGS AND PRECAUTIONS). Thyroid stimulating hormone (TSH) levels should be monitored before treatment with BEXXAR®, and then every 6 months for the first 2 years, and annually thereafter. Serum creatinine levels should be measured prior to administration of BEXXAR®.

Administration of BEXXAR® may result in the development of human anti-murine antibodies (HAMA). The presence of HAMA may affect the accuracy of the results of *in vitro* and *in vivo* diagnostic tests and may affect the toxicity profile and efficacy of therapeutic agents that rely on murine antibody technology. Patients who are HAMA positive may be at increased risk for serious allergic reactions and other side effects if they undergo *in vivo* diagnostic testing or treatment with murine monoclonal antibodies.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

The most serious adverse reactions observed in the clinical trials were prolonged and severe cytopenias, which were generally reversible, and the sequelae of cytopenias, which included infections (sepsis) and hemorrhage in thrombocytopenic patients, allergic reactions (bronchospasm and angioedema), secondary leukemia, and myelodysplasia (see WARNINGS AND PRECAUTIONS section).

The most common adverse reactions occurring in the clinical trials included neutropenia, thromobocytopenia, and anemia. Less common but severe adverse reactions included pneumonia, pleural effusion, and dehydration.

Data regarding adverse events were primarily obtained in 230 patients with non-Hodgkin's lymphoma enrolled in five clinical trials using the recommended dose and schedule. Patients had a median follow-up of 39 months and 79% of the patients were followed at least 12 months for survival and selected adverse events. Patients had a median of 3 prior chemotherapy regimens, a median age of 55 years, 60% were male, 27% had transformation to a higher grade histology, 29% were intermediate grade and 2% high grade histology (IWF), and 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 red marrow. In the expanded access program, which included 765 patients, data regarding clinical serious adverse events and HAMA and TSH levels were used to supplement the characterization of

delayed adverse events (see ADVERSE REACTIONS, Hypothyroidism, Secondary Leukemia and Myelodysplastic Syndrome, Immunogenicity).

Table 3 lists adverse events that occurred in ≥ 1% of patients in clinical trials.

Table 3
Incidence of Adverse Experiences Regardless of Relationship to Study Drug Occurring in ≥ 1% of the Patients Treated with BEXXAR® therapy (N = 230)

Body System Preferred Term	All Grades[a]	Grade III/IV
Total	**n = 224 (97%)**	**n = 180 (78%)**
Non-Hematologic AEs		
Body as a Whole	**81%**	**12%**
Asthenia	46%	2%
Fever	37%	2%
Infection[b]	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%
Malaise	4%	<1%
Sepsis	4%	3%
Injection site reaction	3%	0%
Face oedema	2%	0%
Pelvic pain	2%	0%
Cellulitis	2%	0%
Injection site hypersensitivity	1%	0%
Flu syndrome	1%	0%
Cardiovascular System	**26%**	**3%**
Hypotension	7%	1%
Vasodilation	5%	0%
Tachycardia	5%	0%
Cardiovascular disorder	3%	0%
Deep thrombophlebitis	2%	<1%
Palpitation	2%	0%
Syncope	2%	<1%
Postural hypotension	1%	0%
Digestive System	**56%**	**9%**
Nausea	36%	3%
Vomiting	15%	1%
Anorexia	14%	0%
Diarrhea	12%	0%
Constipation	6%	1%
Dyspepsia	6%	<1%
Dysphagia	2%	<1%
Stomatitis	2%	<1%
Flatulence	2%	0%
Gastrointestinal Carcinoma[c]	2%	2%
Rectal disorder	2%	0%
Gastritis	1%	0%
Melena	1%	0%
Mouth ulceration	1%	0%
Ulcerative stomatitis	1%	0%
Endocrine System	**7%**	**0%**
Hypothyroidism[c]	7%	0%
Hemic and lymphatic system	66%	65%
Myeloproliferative disorder	10%	10%
Ecchymosis	4%	<1%
Acute myeloblastic leukemia[c]	3%	3%
Lymphadenopathy	2%	0%

Lymphoma like reaction	2%	1%
Petechia	2%	0%
Metabolic and Nutritional Disorders	**21%**	**3%**
Peripheral edema	9%	0%
Weight loss	6%	<1%
Oedema	3%	<1%
Dehydration	3%	<1%
Hypercalcaemia	2%	<1%
Musculoskeletal System	**23%**	**3%**
Myalgia	13%	<1%
Arthralgia	10%	1%
Pathological fracture	2%	<1%
Arthritis	1%	<1%
Myasthenia	1%	0%
Nervous System	**26%**	**3%**
Dizziness	5%	0%
Somnolence	5%	0%
Insomnia	4%	0%
Anxiety	3%	0%
Confusion	2%	1%
Paresthesia	2%	0%
Peripheral Neuritis	1%	0%
Depression	1%	0%
Respiratory System	**44%**	**8%**
Cough increased	21%	1%
Pharyngitis	12%	0%
Dyspnea	11%	3%
Rhinitis	10%	0%
Pneumonia	6%	3%
Epistaxis	4%	0%
Bronchitis	4%	<1%
Sinusitis	3%	0%
Lung disorder	3%	<1%
Pleural effusion	3%	2%
Asthma	2%	0%
Skin and Appendages	**44%**	**5%**
Rash	17%	<1%
Pruritus	10%	0%
Sweating	8%	<1%
Skin carcinoma[c]	7%	3%
Urticaria	4%	0%
Herpes zoster	4%	0%
Skin disorder	3%	0%
Skin ulcer	3%	1%
Herpes simplex	2%	0%
Special Senses	8%	<1%
Conjunctivitis	2%	0%
Ear disorder	2%	0%
Urogenital System	14%	3%
Urinary tract infection	4%	<1%
Urinary frequency	2%	0%
Dysuria	1%	0%
Bladder carcinoma[c]	1%	<1%

[a] AEs for ANC, platelets, and hemoglobin derived from laboratory data. Only Grade 3/4 hematologic AEs are reported from laboratory data.

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

[c] Please refer to the Delayed Adverse Reactions section for details.

Hematologic Events: Hematologic toxicity was the most frequently observed adverse event in clinical trials with BEXXAR® therapy (tositumomab and iodine I 131 tositumomab) (see Table 4). Sixty-three (27%) of 230 patients received one or more hematologic supportive care measures following the therapeutic dose (see WARNINGS AND PRECAUTIONS) 12% received filgrastim, 7% received Epoetin alfa, 15% received platelet transfusions, and 16% received packed red blood cell transfusions. Twenty-eight (12%) patients experienced hemorrhagic events; the majority were mild to moderate. Table 4 provides a detailed description of the hematologic toxicity.

Table 4
Hematologic Toxicity[a] (N=230)

Endpoint	Values
Platelets	
Median nadir (x 10^9/L)	43
Per patient incidence[a] platelets < 50 x 10^9/L	53% (n=123)
Median[b] duration of platelets < 50 x 10^9/L (days)	32
Grade 3/4 without recovery to Grade 2, N (%)	16 (7%)
Per patient incidence[c] platelets < 25 x 10^9/L	21% (n=47)
ANC	
Median nadir (x 10^9/L)	0.69
Per patient incidence[a] ANC < 1 x 10^9/L	63% (n=145)
Median[b] duration of ANC < 1 x 10^9/L (days)	31
Grade 3/4 without recovery to Grade 2, N (%)	15 (7%)
Per patient incidence[c] ANC < 0.5 x 10^9/L	25% (n=57)
Hemoglobin	
Median nadir (gm/L)	100
Per patient incidence[a] < 80 gm/L	29% (n=66)
Median[b] duration of hemoglobin < 80 gm/L (days)	23
Grade 3/4 without recovery to Grade 2, N (%)	12 (5%)
Per patient incidence[c] hemoglobin < 65 gm/L	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 1000+ 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.

Infectious Events: One hundred and thirty of 230 (57%) patients developed one or more adverse events possibly related to infection. The majority of these were viral (rhinitis, pharyngitis, flu symptoms, or herpes) or other minor infections. Twenty of 230 (9%) patients experienced 24 infections that were considered to be serious, because the patient was hospitalized for management of the infection. Documented infections included pneumonia, bacteremia, septicemia, bronchitis, and skin infections.

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

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

Infusional Toxicity: A constellation of symptoms, including fever, rigors or chills, sweating, hypotension, dyspnea, bronchospasm, and nausea have been reported during or within 48 hours of infusion. Sixty-seven patients (29%) reported fever, rigors/chills, or sweating within 14 days following the dosimetric dose. Adjustment of the rate of infusion to control adverse reactions occurred in 16 patients (7%); seven patients required adjustments for only the dosimetric infusion, two required adjustments for only the therapeutic infusion, and seven required adjustments for both the dosimetric and the therapeutic infusions. Adjustments included reduction in the rate of infusion by 50%, temporary interruption of the infusion, and in 2 patients, infusion was permanently discontinued.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following list the adverse experiences regardless of relationship to study drug occurring in <1% of the patients treated with BEXXAR® therapy.

Body as a Whole: abdomen enlarged, accidental injury, allergic reaction, anaphylactoid reaction, ascites, carcinoma, chest pain substernal, chills and fever, cyst, hernia, injection site edema, injection site pain, neck rigidity, and serum sickness.

Cardiovascular system: aortic stenosis, arrhythmia, atrial flutter, cardiomegaly, cerebral hemorrhage, hemorrhage, migraine, peripheral vascular disorder, pulmonary embolus, shock, thrombophlebitis and thrombosis.

Digestive system: abnormal stools, carcinoma of mouth, cholecystitis, colitis, dry mouth, eructation, gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, gingivitis, glossitis, gum hemorrhage, hepatitis, increased appetite, intestinal obstruction, jaundice, liver function tests abnormal, nausea and vomiting, oral moniliasis, periodontal abscess, tenesmus and ulcerative colitis.

Hemic and Lymphatic system: chronic leukemia, leukemia, lymphedema.

Metabolic and Nutritional Disorders: generalized edema, hyperuricemia, hypoglycemia, hypokalemia, hyponatremia, hypovolemia and weight gain.

Musculoskeletal system: arthrosis, bone disorder, bone pain, muscle atrophy, tendon disorder and tenosynovitis.

Nervous system: abnormal gait, agitation, amnesia, ataxia, depersonalization, encephalopathy, foot drop, hypertonia, hypokinesia, nervousness, neuralgia, neuropathy, paralysis, subdural hematoma, thinking abnormal and tremor.

Respiratory system: aspiration pneumonia, atelectasis, carcinoma of lung, hemoptysis, hyperventilation, hypoxia, laryngismus, lung hemorrhage, pneumothorax and voice alteration.

Skin and Appendages: acne, erythema nodosum, fungal dermatitis, hair disorder, maculopapular rash, pustular rash, skin benign neoplasm, skin discoloration, skin melanoma, skin nodule and vesiculobullous rash.

Special Senses: abnormal vision, amblyopia, diplopia, dry eyes, ear pain, lacrimation disorder, parosmia, taste loss, taste perversion, tinnitus and vestibular disorder.

Urogenital system: breast carcinoma, breast pain, genital edema, hydronephrosis, kidney failure, kidney function abnormal, nocturia, oliguria, prostatic carcinoma, urinary incontinence, urinary retention, urinary tract disorder, urinary urgency and urination impaired.

Delayed Adverse Reactions

Delayed adverse reactions, including hypothyroidism, HAMA, and myelodysplasia/leukemia, were assessed in 230 patients included in clinical studies and 765 patients included in expanded access programs. The entry characteristics of patients included from the expanded access programs were similar to the characteristics of patients enrolled in the clinical studies, except that the median number of prior chemotherapy regimens was fewer (2 vs. 3) and the proportion with low-grade histology was higher (77% vs. 70%) in patients from the expanded access programs.

Hypothyroidism: Twelve percent (27/230) of the patients included from the clinical studies had an elevated TSH level (8%) or no TSH level obtained (4%) prior to treatment. Of the 203 patients documented to be euthyroid at entry, 137 (67%) patients had at least one follow-up TSH value. The overall incidence of hypothyroidism in the clinical study patients was 18% with cumulative incidences of 11% and 19% at 2 and 5 years respectively. New events have been observed up to 90 months post-treatment. Of the 765 patients in the expanded access programs, 670 patients did not have elevated TSH upon study entry. Of these, 455 patients had at least one post-treatment TSH value available and were not taking thyroid hormonal treatment upon study entry. With a median follow-up period of 33 months, the incidence of hypothyroidism based on elevated TSH or initiation of thyroid replacement therapy in these 455 patients was 13% with a median time to development of hypothyroidism of 15 months. The cumulative incidences of hypothyroidism at 2 and 5 years in these patients were 9% and 17% respectively.

Immunogenicity: Immune response to murine antibody may be masked in patients after administration of BEXXAR®. Eighty of the 788 patients (10%) with a negative baseline HAMA and follow-up converted to a positive HAMA. The median time to a positive HAMA was 167 days (range: 5 - 3400 days). After administration of BEXXAR®, the 1-, 2-, and 5-year cumulative incidences of testing positive for HAMA were 9% (95% CI: 7% - 11%), 9% (95% CI: 8% - 12%), and 10% (95% CI: 8% - 12%), respectively. There was an apparent plateau in the cumulative incidence between 1 and 2 years.

The data reflect the percentage of patients whose test results were considered positive for HAMA in an ELISA assay that detects antibodies to the Fc portion of IgG_1 murine immunoglobulin and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of HAMA in patients treated with BEXXAR® with the incidence of HAMA in patients treated with other products may be misleading.

Secondary Leukemia and Myelodysplastic Syndrome (MDS): There were 34 new cases of MDS/secondary leukemia reported among 995 (3.4%) patients included in clinical studies and expanded access programs, with a median follow-up of 2.4 years. The overall 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 MDS of 34 months. The cumulative incidence of MDS/secondary leukemia was 4.7% at 2 years and 15% at 5 years. Among the 765 patients included in the expanded access program, where the median duration of follow-up was shorter (27 months), the overall incidence of MDS/secondary leukemia was 3% (20/765) and the median time to development of MDS was 31 months. In the expanded access population, the cumulative incidence of MDS/secondary leukemia was 1.6% at 2 years and 6% at 5 years.

In a study of 76 previously untreated patients with low-grade non-Hodgkin's lymphoma who received BEXXAR®, no patients developed MDS with a median follow-up of 5.1 years.

Secondary Malignancies: There were 65 reports of second malignancies, excluding secondary leukemia. The most common included non-melanomatous skin cancers, breast, lung, bladder, and head and neck cancers. Some of these events included recurrence of an earlier diagnosis of cancer.

Postmarketing Reactions

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.

DRUG INTERACTIONS

Drug-Drug Interactions

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

DOSAGE AND ADMINISTRATION

BEXXAR® therapy (tositumomab and iodine I 131 tositumomab) is suitable for administration on an outpatient basis with appropriate license conditions as granted by the Canadian Nuclear Safety Commission (CNSC). BEXXAR® is intended as a single course of treatment. The safety of multiple courses of BEXXAR® therapy, or combination of this regimen with other forms of irradiation or chemotherapy, has not been evaluated.

Dosing Considerations

The safety of BEXXAR® was established only in the setting of patients receiving thyroid blocking agents and premedication to ameliorate/prevent infusion reactions (see Concomitant Medications).

Concomitant Medications: The safety of BEXXAR® was established in studies in which all patients received the following concurrent medications:

- Thyroid protective agents: Saturated solution of potassium iodide (SSKI) 4 drops orally three times daily; Lugol's solution 20 drops orally three times daily; or potassium iodide tablets 130 mg orally daily. Thyroid protective agents should be initiated at least 24 hours prior to administration of the iodine I 131 tositumomab dosimetric dose and continued until 2 weeks after administration of the iodine I

131 tositumomab therapeutic dose.

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

- Acetaminophen 650 mg orally and diphenhydramine 50 mg orally 30 minutes prior to administration of tositumomab in the dosimetric and therapeutic steps.

Dosage

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

Dosimetric step

- Tositumomab 450 mg intravenously in 50 mL 0.9% sodium chloride over 60 minutes. Reduce the rate of infusion by 50% for mild to moderate infusional toxicity; interrupt infusion for severe infusional toxicity. After complete resolution of severe infusional toxicity, infusion may be resumed with a 50% reduction in the rate of infusion.

- Iodine I 131 tositumomab (containing 185 MBq (5.0 mCi) iodine-131 and 35 mg tositumomab) intravenously in 30 mL 0.9% Sodium Chloride over 20 minutes. Reduce the rate of infusion by 50% for mild to moderate infusional toxicity; interrupt infusion for severe infusional toxicity. After complete resolution of severe infusional toxicity, infusion may be resumed with a 50% reduction in the rate of infusion.

Therapeutic step

Note: Do not administer the therapeutic step if biodistribution is altered (see Assessment of Biodistribution of iodine I 131 tositumomab).

- Tositumomab 450 mg intravenously in 50 mL 0.9% Sodium Chloride over 60 minutes. Reduce the rate of infusion by 50% for mild to moderate infusional toxicity; interrupt infusion for severe infusional toxicity. After complete resolution of severe infusional toxicity, infusion may be resumed with a 50% reduction in the rate of infusion.

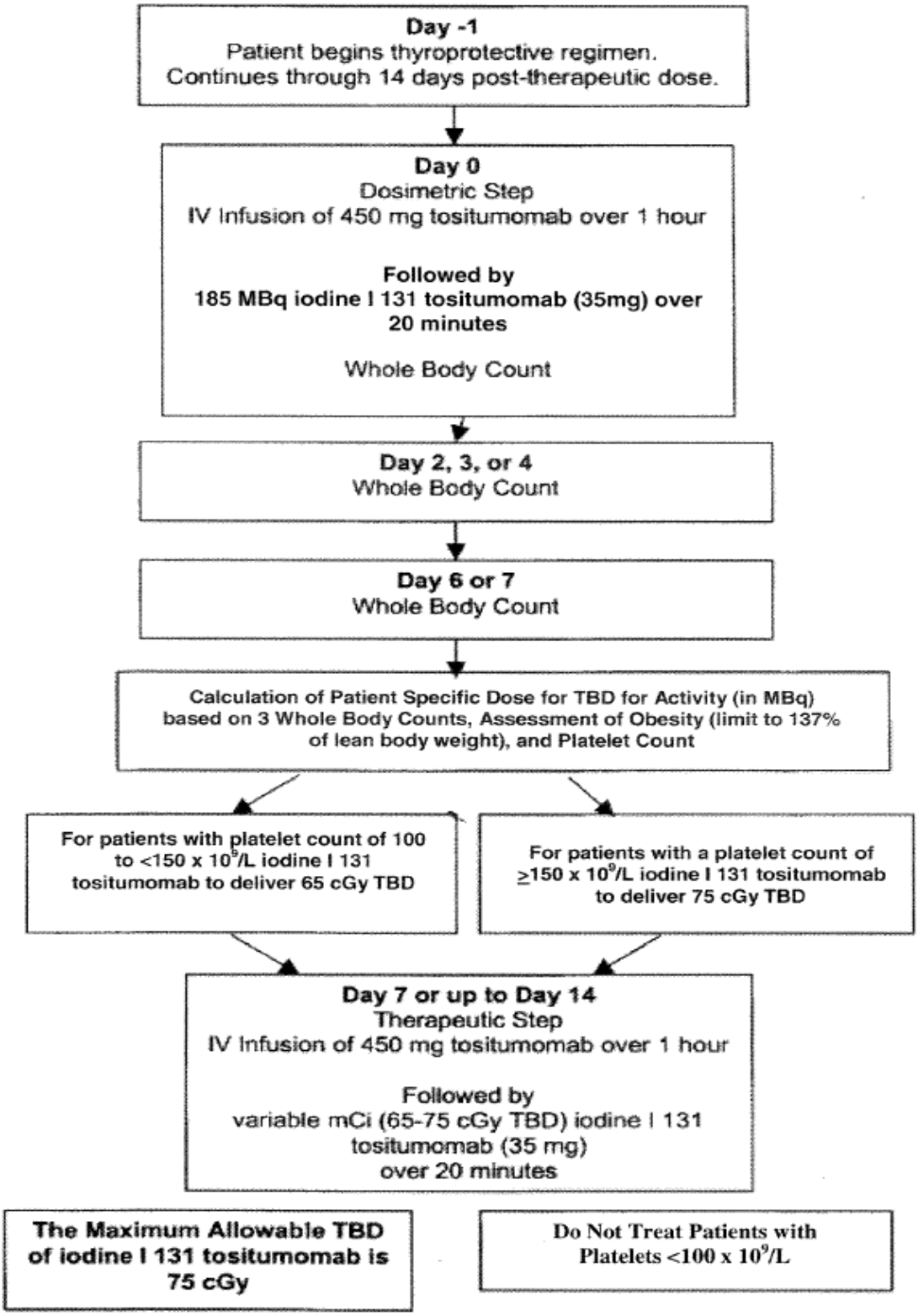
- Iodine I 131 tositumomab (see calculation of iodine-131 activity for the therapeutic dose). Reduce the rate of infusion by 50% for mild to moderate infusional toxicity; interrupt infusion for severe infusional toxicity. After complete resolution of severe infusional toxicity, infusion may be resumed with a 50% reduction in the rate of infusion.

- Patients with platelet counts $\geq 150 \times 10^9$/L: The recommended dose is the activity of iodine-131 calculated to deliver 75 cGy total body irradiation and 35 mg tositumomab, administered intravenously over 20 minutes.

- Patients with NCI Grade 1 thrombocytopenia (platelet counts ≥ 100 x 10^9/L but < 150 x 10^9/L): The recommended dose is the activity of iodine-131 calculated to deliver 65 cGy total body irradiation and 35 mg tositumomab, administered intravenously over 20 minutes.

Figure 1 shows an overview of the dosing schedule.

Figure 1: Effective Recommended Dose - Dosing Schedule



Dosimetry

The following section describes the procedures for image acquisition for collection of dosimetry data, interpretation of biodistribution images, calculation of residence time, and calculation of activity hours. Please read all sections carefully.

Image Acquisition and Interpretation

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

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

Each imaging day, 3 separate anterior whole body scans are acquired, one each for the source, background, and patient. The source, background and patient scans are acquired in whole body mode using the exact same scanning parameters for all 3 scans. The source and background counts are obtained first and the camera sensitivity (i.e., constant counting efficiency) is established prior to obtaining the patient count.

The total counts from each scan are separately recorded. Please note that some equipment may require drawing a Region of Interest (ROI) around the whole body field of view to obtain total counts from the whole body scan. Use whatever procedure is necessary for the type of camera used.

Gamma Camera Set-Up

The same camera, collimator, scanning speed, energy window, and setup must be used for all studies.

The gamma camera must be capable of whole body imaging and have a large or extra large field of view with a digital interface.

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

- High-energy or medium-energy parallel hole collimator
- 20-25% symmetric window centred on the 364-keV photo peak of iodine
- Matrix: appropriate whole body matrix
- Scanning speed: 30-100 cm/minute as appropriate for collimator (314-414 keV)

Counts from Calibrated Source for Quality Control
Camera sensitivity for iodine-131 must be determined each day. Determination of the gamma camera's sensitivity is obtained by scanning a calibrated activity of iodine-131 (e.g., 7400 - 9250 kBq (200 - 250 μCi) in at least 20 mL of saline within a sealed pharmaceutical vial). The radioactivity of the iodine-131 source is first determined using a NIST-traceable-calibrated clinical dose calibrator at the iodine-131 setting.

Background Counts
The background count is obtained from a scan with no radioactive source. This should be obtained following the count of the calibrated source just prior to obtaining the patient count.

If abnormally high background counts are measured, the source should be identified and, if possible, removed. If abnormally low background counts are measured, the camera energy window setting and collimator should be verified before repeating the background counts.

The counts per kBq (μCi) are obtained by dividing the background-corrected source count by the calibrated activity for that day. For a specific camera and collimator, the counts per kBq (μCi) should be relatively constant. When values vary more than 10% from the established ratio, the reason for the discrepancy should be ascertained and corrected and the source count repeated.

Patient Total Body Counts
Acquire anterior whole body images for gamma camera counts. For any particular patient, the same gamma camera must be used for all scans. To obtain proper counts, extremities must be included in the images, and arms should not cross over the body. The scans should be centred on the midline of the patient. Record the time of the start of the radiolabelled dosimetric infusion and the time of the start of each count acquisition.

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

Count 1: Within an hour of end of the infusion of the iodine I 131 tositumomab dosimetric dose prior to patient voiding.

Count 2: Two to 4 days after administration of the iodine I 131 tositumomab dosimetric dose and immediately following patient voiding.

Count 3: Six to 7 days after the administration of the iodine I 131 tositumomab dosimetric dose and immediately following patient voiding.

Tumour or organ imaging is not required.

Assessment of Biodistribution of iodine I 131 tositumomab
The biodistribution of iodine I 131 tositumomab should be assessed by either evaluation of the total body residence time or visual examination of whole body gamma camera images from the first image taken at the time of Count 1 (within an hour of the end of the infusion) and from the second image taken at the time of Count 2 (at 2 to 4 days after administration). To resolve ambiguities, an evaluation of the third image at the time of Count 3 (6 to 7 days after administration) may be necessary. Biodistribution should not be evaluated on the third image. If either of these methods indicate that the biodistribution is altered when compared to expected biodistribution as described below, the tositumomab iodine I 131 therapeutic dose should not be administered. A Nuclear Medicine Physician and/or Radiation Oncologist (as appropriate) should be consulted to determine whether the gamma scans indicate that the biodistribution is altered when compared to expected biodistribution as described below.

Anterior images obtained using a high energy or medium energy collimator used at 30-100 cm/min (as appropriate) are adequate for evaluation.

Expected Biodistribution

Total Body Residence Time: The median total body residence time is 90 hours with an expected range of 50 to 150 hours.

Whole Body Camera Imaging: On the first image, obtained shortly after the dosimetric dose injection, most of the activity is in the blood pool (heart and major blood vessels) and the uptake in normal liver and spleen is generally less than in the heart. On the second image, obtained 2-4 days after administration of the dosimetric dose, the activity in the blood pool decreases significantly and is generally moderately decreased in liver and spleen. Images may show uptake by thyroid, kidneys, stomach, and urinary bladder, and minimal uptake in the lungs. Tumour uptake in soft tissues and in normal organs may be seen as areas of increased intensity in the later images. If tumour is present in the spleen, focal or moderately intense splenic uptake is an expected pattern. Visualization of tumours is desirable, but not required for the expected biodistribution pattern.

Altered Biodistribution

Total Body Residence Time: Total body residence times outside the range of 50 to 150 hours are considered altered. (Note: If the results are outside the range, first verify the camera acquisition and the calculations of the total body residence time).

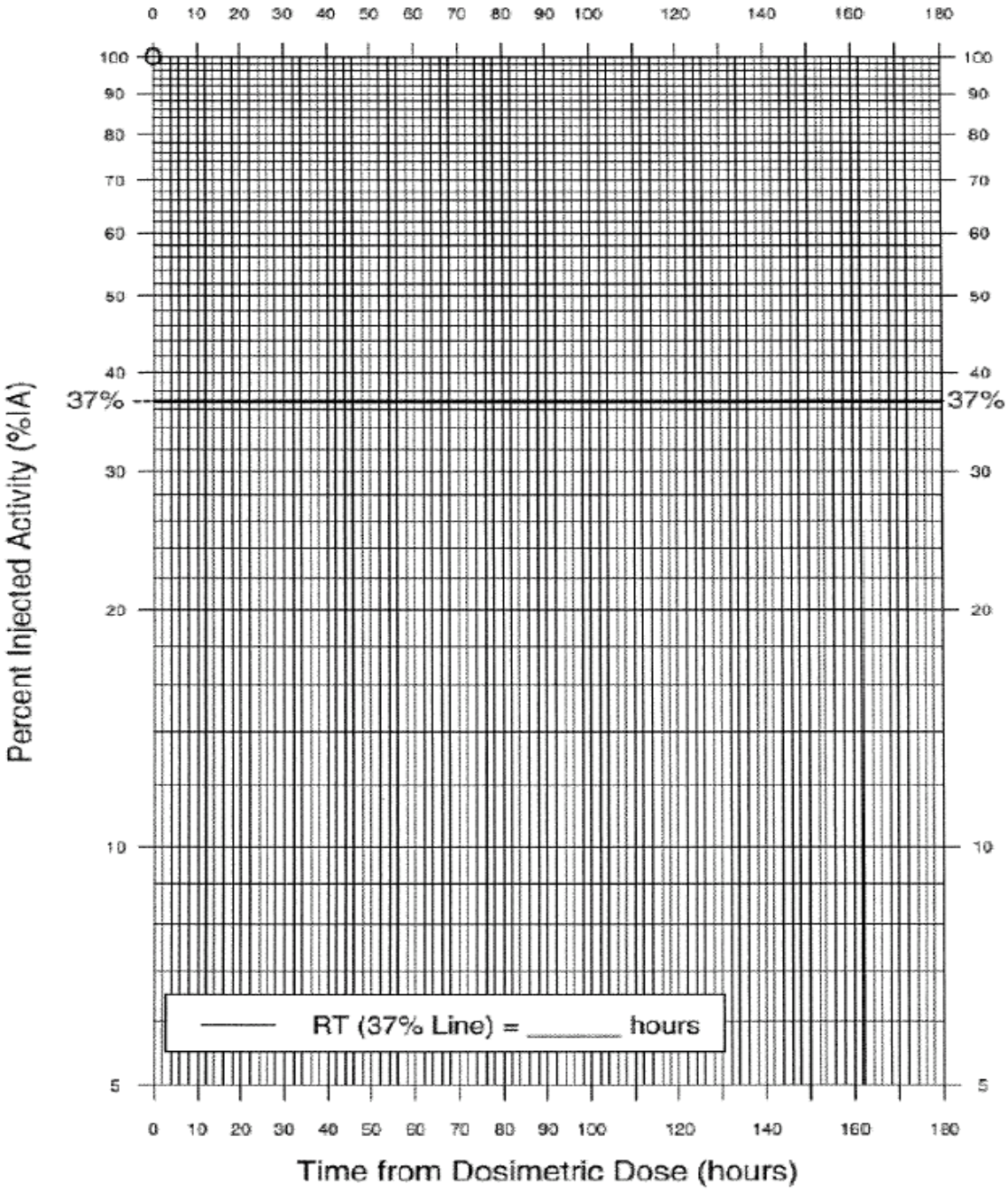
Whole Body Camera Imaging: On the first day, if the blood pool is not visualized on the first imaging study or if there is diffuse intense tracer uptake in the liver and/or spleen or uptake suggestive of urinary obstruction the biodistribution is altered. Diffuse lung uptake greater than that of blood pool on the first day would not be expected unless there was pulmonary involvement with tumour.

Calculation of iodine-131 Activity for Therapeutic Dose
There are two options for calculation of the lodine-131 activity for the therapeutic dose. The derived values and calculation of the therapeutic dose may be determined manually [see "The Dosimetry Workbook"] or calculated automatically using the BEXXAR® Dosimetry Software.

The methods for determining the activity hours (MBq hr or mCi hr), residence time (hr), and desired total body dose (cGy) are described below:

Residence Time (hr)
For each timepoint, calculate the background corrected total body count by subtracting the background count from the patient's anterior total body count. The percent of injected activity remaining at each timepoint is calculated by dividing the background-corrected total body count from that timepoint by the background-corrected total body count from Day 0 and multiplying by 100. The time from the start of the dosimetric dose of iodine I 131 tositumomab to the acquisition of each total body count should be calculated in hours. The residence time (hr) is determined by plotting the time from the start of the infusion and the percent injected activity values for the last two patient count acquisition timepoints on Graph 1.

Graph 1
Graph to Estimate Total Body Residence Time



A best-fit line is then drawn from 100% (the pre-plotted day 0 value) through the two plotted points (if the line does not intersect the two points, one point must lie above the best-fit line and one point must lie the same distance below the best-fit line). The residence time (hr) is read from the x axis of the graph at the point where the fitted line intersects the horizontal 37% injected activity line.

Activity Hours (MBq hr)

In order to determine the activity hours (MBq hr), look up the patient's maximum effective mass derived from the patient's sex and height in Table 5. If the patient's actual weight is less than the maximum effective mass, the actual weight should be used in the activity hours table (see Table 6). If the patient's actual weight is greater than the maximum effective mass, the maximum effective mass from Table 5 should be used.

Table 5
Dosimetry - Maximum Effective Mass

Men			Women		
Height (ft'-in")	Height (cm)	Maximum Effective Mass (kg)	Height (ft'-in")	Height (cm)	Maximum Effective Mass (kg)
4'-5"	134.5	40.5	4'-5"	134.5	40.7
4'-6"	137.0	44.2	4'-6"	137.0	43.8
4'-7"	140.0	47.9	4'-7"	140.0	47.0
4'-8"	142.0	51.6	4'-8"	142.0	50.2
4'-9"	145.0	55.3	4'-9"	145.0	53.3
4'-10"	147.5	59.0	4'-10"	147.5	56.5
4'-11"	150.0	62.7	4'-11"	150.0	59.7
5'-0"	152.5	66.3	5'-0"	152.5	62.8
5'-1"	155.0	70.0	5'-1"	155.0	66.0
5'-2"	157.5	73.7	5'-2"	157.5	69.2
5'-3"	160.0	77.4	5'-3"	160.0	72.3
5'-4"	162.5	81.1	5'-4"	162.5	75.5
5'-5"	165.0	84.8	5'-5"	165.0	78.7
5'-6"	167.5	88.5	5'-6"	167.5	81.8
5'-7"	170.0	92.2	5'-7"	170.0	85.0
5'-8"	172.5	95.8	5'-8"	172.5	88.2
5'-9"	175.5	99.5	5'-9"	175.5	91.3
5'-10"	178.0	103.2	5'-10"	178.0	94.5
5'-11"	180.5	106.9	5'-11"	180.5	97.7
6'-0"	183.0	110.6	6'-0"	183.0	100.8
6'-1"	185.5	114.3	6'-1"	185.5	104.0
6'-2"	188.0	118.0	6'-2"	188.0	107.2
6'-3"	190.5	121.7	6'-3"	190.5	110.3
6'-4"	193.0	125.4	6'-4"	193.0	113.5
6'-5"	195.5	129.0	6'-5"	195.5	116.7
6'-6"	198.0	132.7	6'-6"	198.0	119.8
6'-7"	200.5	136.4	6'-7"	200.5	123.0
6'-8"	203.0	140.0	6'-8"	203.0	126.2
6'-9"	205.5	143.8	6'-9"	205.5	129.3
6'-10"	208.5	147.5	6'-10"	208.5	132.5
6'-11"	211.0	151.2	6'-11"	211.0	135.7
7'-0"	213.5	154.9	7'-0"	213.5	138.8

Multiply pounds by 0.454 to obtain kilograms. To calculate the maximum effective mass for patient heights not included in above table, use the following formulas:

Males: Maximum effective mass (kg) = 65.76 + 1.452 (height in cm – 152)

Females: Maximum effective mass (kg) = 62.34 + 1.247 (height in cm – 152)

Adapted from: Zasadny KR *et al* [23]

Table 6
Dosimetry: Activity Hours

Mass [a] (kg)	Activity Hours (MBqh)	Mass [a] (kg)	Activity Hours (MBqh)	Mass [a] (kg)	Activity Hours (MBqh)	Mass [a] (kg)	Activity Hours (MBqh)	Mass [a] (kg)	Activity Hours (MBqh)
40.0	171606	60.0	247382	80.0	320790	100.0	392015	120.0	461131
40.5	173530	60.5	249269	80.5	322566	100.5	393791	120.5	462833
41.0	175491	61.0	251119	81.0	324379	101.0	395530	121.0	464572
41.5	177452	61.5	253006	81.5	326192	101.5	397306	121.5	466274
42.0	179376	62.0	254856	82.0	327968	102.0	399045	122.0	467976
42.5	181337	62.5	256706	82.5	329781	102.5	400821	122.5	469678
43.0	183261	63.0	258593	83.0	331557	103.0	402560	123.0	471417
43.5	185185	63.5	260443	83.5	333370	103.5	404299	123.5	473119
44.0	187109	64.0	262293	84.0	335146	104.0	406075	124.0	474821
44.5	189033	64.5	264143	84.5	336922	104.5	407814	124.5	476523
45.0	190920	65.0	265993	85.0	338698	105.0	409553	125.0	478225
45.5	192844	65.5	267806	85.5	340474	105.5	411292	125.5	479927
46.0	194768	66.0	269656	86.0	342287	106.0	413031	126.0	481629
46.5	196655	66.5	271506	86.5	344063	106.5	414770	126.5	483331
47.0	198542	67.0	273319	87.0	345839	107.0	416509	127.0	485033
47.5	200466	67.5	275169	87.5	347578	107.5	418248	127.5	486735
48.0	202353	68.0	276982	88.0	349354	108.0	419987	128.0	488400
48.5	204240	68.5	278832	88.5	351130	108.5	421726	128.5	490102
49.0	206127	69.0	280645	89.0	352906	109.0	423465	129.0	491804
49.5	207977	69.5	282458	89.5	354645	109.5	425204	129.5	493469
50.0	209864	70.0	284271	90.0	356421	110.0	426906	130.0	495171
50.5	211788	70.5	286121	90.5	358234	110.5	428645	130.5	496873
51.0	213675	71.0	287971	91.0	360010	111.0	430384	131.0	498538
51.5	215562	71.5	298821	91.5	361823	111.5	432086	131.5	500240
52.0	217486	72.0	291671	92.0	363599	112.0	433825	132.0	501905
52.5	219373	72.5	293484	92.5	365375	112.5	435527	132.5	503607
53.0	221260	73.0	295334	93.0	367188	113.0	437266	133.0	505272
53.5	223147	73.5	297147	93.5	368964	113.5	438968	133.5	506937
54.0	225034	74.0	298997	94.0	370740	114.0	440670	134.0	508639
54.5	226921	74.5	300810	94.5	372516	114.5	442409	134.5	510304
55.0	228808	75.0	302660	95.0	374329	115.0	444111	135.0	511969
55.5	230658	75.5	304473	95.5	376105	115.5	445813	135.5	513634
56.0	232545	76.0	306286	96.0	377881	116.0	447515	136.0	515336
56.5	234395	76.5	308099	96.5	379657	116.5	449217	136.5	517001
57.0	236282	77.0	309912	97.0	381433	117.0	450919	137.0	518666
57.5	238132	77.5	311725	97.5	383209	117.5	452621	137.5	520331
58.0	239982	78.0	313538	98.0	384948	118.0	454323	138.0	521996
58.5	241832	78.5	315351	98.5	386724	118.5	456025	138.5	523661
59.0	243682	79.0	317164	99.0	388500	119.0	457727	139.0	525326
59.5	245532	79.5	318977	99.5	390276	119.5	459429	139.5	526954

[a] The minimum of the patient's actual weight (kg) or maximum effective mass (kg) from Table 5. For values between 140 kg and 160 kg, use the following formula:

Activity Hours (MBqh) = 14287 + (88.74) (Wt in kg – 140)

Calculation of iodine-131 Activity for the iodine I 131 tositumomab Therapeutic Dose

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

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

*1 mCi = 37 MBq

Instructions for Preparation and Use

PREPARATION OF BEXXAR®

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

The iodine I 131 tositumomab dosimetric and therapeutic doses should be measured by a suitable radioactivity calibration system immediately prior to administration. The dose calibrator must be operated in accordance with the manufacturer's specifications and quality control for the measurement of iodine-131.

All supplies used for preparation and administration of BEXXAR® therapy should be sterile. Use appropriate aseptic technique and radiation precautions for the preparation of the components for BEXXAR®.

Gloves (i.e., latex, vinyl, etc.) should be utilized in the preparation and administration of the product. Iodine I 131 tositumomab doses should be prepared, assayed, and administered by personnel who are licensed to handle and/or administer radionuclides. Appropriate shielding should be used during preparation and administration of the product.

Restrictions on patient contact with others and release from the hospital must follow all applicable regulations and/or appropriate licenses of local competent official organizations.

Preparation for the Dosimetric Step

Tositumomab Dose

Method:

1. Using an aseptic needle, withdraw and dispose of 32 mL of saline from a 50 mL bag of sterile 0.9% sodium chloride for injection, USP.

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

3. Gently mix the solution by inverting/rotating the bag. **Do not shake.**

4. The diluted tositumomab may be stored for up to 24 hours when stored refrigerated at 2°C-8°C (36°F-46°F) and for up to 8 hours at room temperature.

Note: tositumomab solution may contain particulates that are generally white in nature. The product should appear clear to opalescent, colourless to slightly yellow.

Preparation of iodine I 131 tositumomab Dosimetric Dose

Method:

1. Allow minimum 60 minutes (may require up to 120 minutes) for thawing (at ambient temperature) of the iodine I 131 tositumomab dosimetric vial with appropriate lead shielding.

2. Based on the activity concentration of the vial (see actual product specification sheet for the vial supplied in the dosimetric package), calculate the volume required for an iodine I 131 tositumomab activity of 185 MBq (5.0 mCi)

3. Withdraw the calculated volume from the iodine I 131 tositumomab vial.

4. Transfer this volume to the shielded preparation vial.

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

    a. If the assayed dose is 185 MBq (5.0 mCi) (+/- 10%) proceed with step 6.

b. If the assayed dose does not contain 185 MBq (5.0 mCi) (+/- 10%) recalculate the activity concentration of the iodine I 131 tositumomab at this time, based on the volume and the activity in the preparation vial. Recalculate the volume required for an iodine I 131 tositumomab activity of 185 MBq (5.0 mCi). Using the same 30 mL syringe, add or subtract the appropriate volume from the iodine I 131 tositumomab vial so that the preparation vial contains the volume required for an iodine I 131 tositumomab activity of 185 MBq (5.0 mCi) (+/- 10%). Re-assay the preparation vial and proceed with step 6.

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

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

8. 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 the solutions.

9. Withdraw the entire contents from the preparation vial into a 30 mL or larger syringe with a large bore needle (18 - 20 gauge).

10. Assay and record the activity.

Administration

Administration of the Dosimetric Step
BEXXAR® is administered via an IV tubing set with an in-line 0.22 micron filter. **The same IV tubing set and filter must be throughout the entire dosimetric or therapeutic step. A change in filter can result in loss of drug.** If a new IV line without an in-line filter is connected to the patient's intravenous access, prime the IV line with 0.9% sodium chloride prior to the iodine I 131 tositumomab infusion.

Tositumomab Infusion:
A 0.22 micron in-line filter should be attached to the primary IV infusion set and the bag of sterile 0.9% Sodium Chloride for Injection. Prime lines. Attach tositumomab bags and infuse tositumomab over 60 minutes. After completion of the tositumomab infusion, inject 50 mL saline into empty tositumomab bag and mix. Flush primary IV infusion set and the in-line IV filter set for 10 minutes. Discard the tositumomab bag.

Iodine I 131 Tositumomab Dosimetric Infusion:
Set syringe pump to deliver the entire 185 MBq (5.0 mCi) (35 mg) dose of iodine I 131 tositumomab over 20 minutes. At the end of the infusion, attach a syringe with 30 mL of 0.9% sodium chloride to the 3-way stopcock and back flush (rinse) the syringe. Infuse the 30 mL rinse into the patient over 10 minutes (infusion rate of 180 mL/hour).

Determination of Dose for the Therapeutic Step (see calculation of iodine-131 activity for therapeutic dose):
The methodology for determining and calculating the patient-specific dose of iodine-131 activity (MBq or mCi) to be administered in the therapeutic step involves the following three steps:

1. Following infusion of the iodine I 131 tositumomab dosimetric dose, obtain total body gamma camera counts and whole body images:

    - Within one hour of infusion and prior to urination;
    - 2-4 days after infusion of the dosimetric dose, following urination;
    - 6-7 days after infusion of the dosimetric dose, following urination.

2. Assess biodistribution. If biodistribution is altered, the therapeutic step should not be administered.

3. Calculate iodine-131 activity for the therapeutic dose. This step can be completed manually or calculate automatically using the BEXXAR® dosimetry software.

For more detail regarding image acquisition and therapeutic dose calculations see **Dosimetry section.**

Preparation for the Therapeutic Step (7 to 14 days following dosimetric dose)

Tositumomab Dose

Refer to **Preparation for the Dosimetric Step. Tositumomab Dose**
Preparation of iodine I 131 tositumomab Therapeutic Dose

Method:
1. Allow minimum 60 (may require up to 120 minutes) for thawing (at ambient temperature) of the iodine I 131 tositumomab therapeutic vial with appropriate lead shielding.

2. Calculate the dose of iodine I 131 tositumomab required (see calculation of iodine-131 activity for therapeutic dose).

3. Based on the activity concentration of the vial (see actual product specification sheet for each vial supplied in the therapeutic package), calculate the volume required for the iodine I 131 tositumomab activity required for the therapeutic dose.

4. Using one or more 30 mL syringe withdraw the calculated volume from the iodine I 131 tositumomab vials.

5. Transfer this volume to the shielded preparation vial.

6. Assay the dose to ensure that the appropriate activity (MBq or mCi) has been prepared.

    a. If the assayed dose is the calculated dose (+/- 10%) needed for the therapeutic step, proceed with step 7.

    b. If the assayed dose does not contain the desired dose (+/- 10%), re-calculate the activity concentration of the iodine I 131 tositumomab at this time, based on the volume and the activity in the preparation vial. Re-calculate the volume required for an iodine I 131 tositumomab activity for the therapeutic dose. Using the same syringe, add or subtract the appropriate volume from the iodine I 131 tositumomab vial so that the preparation vial contains the volume required for the iodine I 131 tositumomab activity required for the therapeutic dose. Re-assay the preparation vial. Proceed to step 7.

7. Calculate the amount of tositumomab protein contained in the solution of iodine I 131 tositumomab in the shielded preparation vial, based on the volume and protein concentration (see product specification sheet).

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

    Note: If the dose of iodine I 131 tositumomab requires the use of 2 vials of iodine I 131 tositumomab or the entire contents of a single vial of iodine I 131 tositumomab, there may be no need to add protein from the 35 mg vial of tositumomab.

9. 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 the solutions.

10. Withdraw the entire volume from the preparation vial into a sterile 30 mL or 60 mL syringe using a large bore needle.

11. Assay and record the activity.

Administration of the Therapeutic Step
Note: Release from the hospital must follow all applicable federal and institutional regulations.

BEXXAR® therapy can be administered on an outpatient basis with specific instructions to minimize radiation dose to others.

Tositumomab Infusion:

Refer to **Administration of the Dosimetric Step: Tositumomab Infusion**

Iodine I 131 Tositumomab Therapeutic Infusion:
Set syringe pump to deliver the entire therapeutic dose of iodine I 131 Tositumomab over 20 minutes.

After completion of the infusion of iodine I 131 tositumomab, close the stopcock to the syringe. Flush the secondary IV infusion set and the extension set with 0.9% sodium chloride from the 50 mL bag of sterile, 0.9% sodium chloride for injection, USP.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Some patients have received more than 75 cGy total body dose of radiation. The maximum dose of BEXXAR® therapy (tositumomab and iodine I 131 tositumomab) that was administered in clinical trials was 88 cGy. Three patients were treated with a total body dose of 85 cGy of iodine I 131 tositumomab in a dose escalation study. Two of the 3 patients developed Grade 4 toxicity of 5 weeks duration with subsequent recovery. In addition, accidental overdose of BEXXAR® occurred in one patient at a total body dose of 88 cGy. The patient developed Grade 3 hematologic toxicity of 18 days duration. Patients who receive an accidental overdose of iodine I 131 tositumomab should be monitored closely for cytopenias and radiation-related toxicity. The effectiveness of hematopoietic stem cell transplantation as a supportive care measure for marrow injury has not been studied; however, the timing of such support should take into account the pharmacokinetics of BEXXAR® and decay rate of the iodine-131 in order to minimize the possibility of irradiation of infused hematopoietic stem cells.

ACTION AND CLINICAL PHARMACOLOGY

BEXXAR® therapy (tositumomab and iodine I 131 tositumomab) is an anti-neoplastic radioimmunotherapeutic monoclonal antibody-based regimen composed of the monoclonal antibody, tositumomab, and the radiolabeled monoclonal antibody, iodine I 131 tositumomab.

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 high-energy beta particles emitted by I-131 are cytotoxic over distances of approximately 1-2 mm (the average path length is 0.8 mm and the maximum path length is 2.4 mm), thus permitting eradication of antigen-negative tumour cells by crossfire from neighbouring antibody-coated cells.[20] In addition to cell death associated with ionizing radiation from the radioisotope, possible mechanisms of action of BEXXAR® include induction of apoptosis[16], complement-dependent cytotoxicity (CDC)[5], and antibody-dependent cellular cytotoxicity (ADCC)[3] mediated by the antibody.

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. 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.

Pharmacokinetics

Table 7 Summary of Pharmacokinetic Parameters of Iodine I131 Tositumumab in Patients with Non-Hodgkin's Lymphoma [Median (range)]

	C_{max} (%ID/mL)	$t_{½}$ (h)	$AUC_{0-\infty}$ (%ID.h/mL)	CL (mL/h)	Vss (L)
≥450 mg TST + I131-TST	0.0188 (0.0108-0.0356)	66.4 (26.3-197)	1.47 (0.38-3.32)	68.2 (30.2-261)	6.69 (3.73-12.7)

TST = tositumomab; %ID = percentage of injected dose

Absorption: BEXXAR therapy is administered by intravenous infusion. The median values of C_{max} and $AUC_{0-\infty}$ after administration of 485 mg protein (450 mg tositumumab and 35 mg iodine I131 tositumomab) in 110 patients with non-Hodgkin's lymphoma (NHL) were 0.0188 %ID/mL and 1.47 %ID.h/mL.

Distribution: Tositumumab/I131-tositumomab had a small volume of distribution, with a median value of 6.7 L in 110 patients with NHL after adminstration of 485 mg protein

(450 mg tositumomab and 35 mg iodine I131 tositumomab).

Metabolism/Excretion:
Tositumomab is a protein for which the expected metabolic pathway is degradation to small peptides and individual amino acids by ubiquitous proteolytic enzymes.

The median blood clearance following administration of 485 mg of protein (450 mg dose of tositumomab followed by a 35 mg dose of tositumomab containing the appropriate MBq (mCi) of iodine I 131 tositumomab) in 110 patients with NHL was 68.2 mL/hr. Patients with high tumour burden, splenomegaly, or bone marrow involvement were noted to have a faster clearance, shorter terminal half-life, and larger volume of distribution. The total body clearance, as measured by total body gamma camera counts, was mono-exponential and dependent on the same factors noted for blood clearance. The effective half-life was 65 hours.[19]

Elimination of iodine-131 occurs by decay (see Table 2) and excretion in the urine. Urine was collected for 49 dosimetric doses. After 5 days, the whole body excretion was 67% of the injected dose. Ninety-eight percent (98%) of the excretion was accounted for in the urine.

Special Populations and Conditions
Pharmacokinetic parameter values in 110 patients with NHL were summarized by patient characteristics, and the median values were compared. Patient-specific dosing using dosimetry, based on total body clearance, provided a consistent total body radiation dose, despite variable pharmacokinetics, by allowing each patient's administered activity to be adjusted for individual patient variables.

Pediatrics: No pharmacokinetic data are available in pediatric patients.

Geriatrics: There were insufficient pharmacokinetic data in geriatric patients to assess the influence of age.

Gender: Female patients had 29% smaller median clearance, 30% higher median Cmax, and 29% smaller median volume of distribution than male patients. Patient-specific dosing adjusts for individual patient variables.

Race: Most (95%) patients were Caucasian; thus, the effect of race on pharmacokinetics could not be assessed.

Hepatic Insufficiency: No pharmacokinetic data are available in patients with hepatic insufficiency.

Renal Insufficiency: No assessment was made of the effect of impaired renal function on pharmacokinetics.

Genetic Polymorphism: No genetic polymorphism data are available.

RADIATION DOSIMETRY

Estimations of radiation-absorbed doses for iodine I 131 tositumomab were performed using sequential whole body images and the MIRDOSE 3 software program. The estimated radiation-absorbed doses to organs and marrow from a course of the BEXXAR® therapy (tositumomab and iodine I 131 tositumomab) are presented in Table 8. The average tumour dose was 12 times the total body dose and higher than any of the average organ doses.

Table 8
Estimated Radiation-Absorbed Organ Doses

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

STORAGE AND STABILITY

Tositumomab

Vials of tositumomab (35 mg and 225 mg) should be stored refrigerated at 2-8°C (36-

46°F) prior to dilution. Do not use beyond expiration date. Protect from strong light. **Do not shake.** Do not freeze. Discard any unused portions left in the vial.

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

Iodine I 131 Tositumomab
Store frozen in the original lead pots. Do not use beyond the expiration date on the label of the lead pot. The dosimetric dose has a 16 day shelf life and the therapeutic dose has a shelf life of 5 days when stored frozen.

Thawed dosimetric and therapeutic doses of iodine I 131 tositumomab should be stored in the upright position. Thawed doses are stable up to 8 hours at 2-8°C (36-46°F) or at room temperature. Because solutions of iodine I 131 tositumomab diluted for infusion contain no preservatives, it is recommended that the diluted solution be stored refrigerated at 2-8°C (36-46°F) prior to administration (do not freeze). Any unused portion must be discarded according to federal regulations.

SPECIAL HANDLING INSTRUCTIONS

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers. See DOSAGE AND ADMINISTRATION section.

DOSAGE FORMS, COMPOSITION AND PACKAGING

BEXXAR® therapy
The components of the BEXXAR® therapy (tositumomab, iodine I 131 tositumomab) for the dosimetric or therapeutic step are scheduled to arrive on the same day. These components include :

Tositumomab therapy Kit.
Two single - use 225 mg vials (16.1 mL) and one single-use 35 mg vial (2.5mL) of tositumomab supplied by GlaxoSmithKline Inc. One kit is supplied for **each** of the dosimetric and therapeutic doses.

Iodine I 131 Tositumomab Dosimetric Dose Vial
Each lead pot for preparation of the iodine I 131 tositumomab dosimetric dose contains one single-use vial with not less than 20 mL of iodine I 131 tositumomab at nominal protein and activity concentrations of 0.1 mg/mL and 22.57 MBq/mL (0.61 mCi/mL) (at calibration), respectively supplied by MDS Nordion.

Iodine I 131 Tositumomab Therapeutic Dose Vial
Each lead pot for preparation of the iodine I 131 tositumomab therapeutic dose contains one single-use vial with not less than 20 mL of iodine I 131 tositumomab at nominal protein and activity concentrations of 1.1 mg/mL and 207.2 MBq/mL (5.6 mCi/mL) (at calibration), respectively, supplied by MDS Nordion.

BEXXAR® therapy

BEXXAR® is supplied in two discrete steps as follows:

BEXXAR® Dosimetric Step

- A carton containing two single-use 225 mg vials and one single-use 35 mg vial of tositumomab supplied by GlaxoSmithKline Inc. and
- A package containing a single-use vial of iodine I 131 tositumomab (22.57 MBq/mL (0.61 mCi/mL) at calibration), supplied by MDS Nordion.

BEXXAR® Therapeutic Step

- A carton containing two single-use 225 mg vials and one single-use 35 mg vial of tositumomab, supplied by GlaxoSmithKline Inc. and
- A package containing one or two single-use vials of iodine I 131 tositumomab (207.2 MBq/mL (5.6 mCi/mL) at calibration), supplied by MDS Nordion.

Composition
BEXXAR® is an anti-neoplastic radioimmunotherapeutic monoclonal antibody-based regimen composed of the monoclonal antibody, tositumomab, and the radiolabelled monoclonal antibody, iodine I 131 tositumomab.

Iodine I 131 tositumomab is produced by oxidative radioiodination of the base monoclonal antibody to form stable covalent bonds with iodine-131. The radiolabelled antibody is purified by ion exchange chromatography to remove unbound iodine.

Tositumomab
Tositumomab is a murine IgG_{2a} lambda monoclonal antibody directed against the CD20 antigen, which is found on the surface of normal and malignant B lymphocytes. Tositumomab is produced in an antibiotic-free culture of mammalian cells and the manufacturing process includes specific steps for viral inactivation and viral removal. The antibody is composed of two murine gamma 2a heavy chains of 451 amino acids each and two lambda light chains of 220 amino acids each. The approximate molecular weight of tositumomab is 150 kD.

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

17.5 mM potassium hydroxide, and Water for Injection, USP. The pH is approximately 7.2.

Iodine I 131 Tositumomab

Iodine I 131 tositumomab is a radioiodinated derivative of tositumomab that has been covalently linked to iodine-131. Unbound radioiodine and other reactants have been removed by chromatographic purification steps. Iodine I 131 tositumomab is supplied as a sterile, clear, preservative-free liquid for IV administration. The dosimetric dosage form is supplied at nominal protein and activity concentrations of 0.1 mg/mL and 22.57 MBq/mL (0.61 mCi/mL) (at date of calibration), respectively. The therapeutic dosage form is supplied at nominal protein and activity concentrations of 1.1 mg/mL and 207.2 MBq/mL (5.6 mCi/mL) (at date of calibration), respectively. The formulation for the dosimetric and the therapeutic dosage forms contains 4.4%-6.6% (w/v) povidone, 1-2 mg/mL maltose (dosimetric dose) or 9-15 mg/mL maltose (therapeutic dose), 8.5 - 9.5 mg/mL sodium chloride, 1.22 mg/mL phosphoric acid, 1.05- 6.57 mg/mL potassium hydroxide and 0.9-1.3 mg/mL ascorbic acid. The pH is approximately 7.0.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

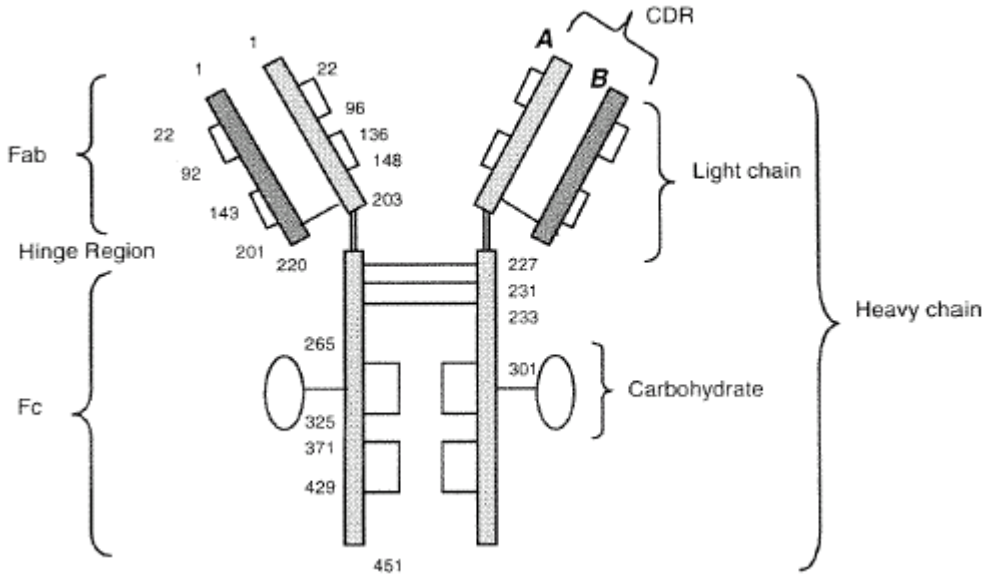
Drug Substance

Proper name: Base monoclonal antibody: tositumomab,
Radiolabeled monoclonal antibody: iodine I 131 tositumomab

Molecular formula: $C_{6542}\ H_{10156}\ N_{1724}\ O_{2026}\ S_{60,}$

Molecular mass: The calculated molecular masses (monoisotopic mass) for the heavy and light chain amino acid sequences are: heavy chain 49,764.6 Da and light chain 23,837.7 Da, resulting in a theoretical mass of 147,204.6 Da.
Glycosylation of the heavy chain, with the core N-linked oligosaccharide HexNAc4 Hex3 dHex1, results in a mass of 150,095.5 Da (monoisotopic mass).

Structural formula:



Product Characteristics

Physical Characteristics

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 an energy of 364.5 keV.[22]

External Radiation

The specific gamma ray constant for iodine-131 is 2.2 R/millicurie hour at 1 cm. The first half-value layer is 0.24 cm lead (Pb) shielding. A range of values is shown in Table 1 for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of Pb. To facilitate control of the radiation exposure from this radionuclide, the use of a 2.55 cm thickness of Pb will attenuate the radiation emitted by a factor of about 1,000.

CLINICAL TRIALS

The efficacy of the BEXXAR® therapy (tositumomab, iodine I 131 tositumomab) was evaluated in 2 pivotal studies and 3 supportive studies of patients with low-grade, follicular, or transformed low-grade; or follicular large-cell lymphoma whose disease had not responded to or had progressed after chemotherapy and rituximab therapy (Study 1) or chemotherapy alone (Studies 2 - 5).

Determination of clinical benefit of the was based on evidence of durable responses without evidence of an effect on survival. All patients in the studies had received prior treatment without an objective response, or had progression of disease following treatment.

Patients were also required to have a granulocyte count > 1.5 x 10^9/L, a platelet count > 100 x 10^9/L, an average of < 25% of the intratrabecular marrow space involved by lymphoma, and no evidence of progressive disease arising in a field irradiated with > 3500 cGy within 1 year of completion of irradiation.

Study 1 (CP-97-012): This was a multicenter, single arm study of forty patients whose disease had not responded to or had progressed after at least four doses of rituximab therapy.

The median age was 57 (range: 35-78); the median time from diagnosis to protocol entry was 50 months (range: 11-70); and the median number of prior chemotherapy regimens was 4 (range: 1-11). Twenty-four patients had disease that did not respond to their last treatment with rituximab, 11 patients had disease that responded to rituximab for less than 6 months, and five patients had disease that responded to rituximab, with a duration of response of 6 months or greater. The median duration of response to the most recent rituximab therapy was 4.7 months. Overall, 35 of the 40 patients met the definition of "rituximab refractory", defined as no response or a response of less than 6 months duration. Table 9 summarizes efficacy outcome data from study 1, as determined by an independent panel that reviewed patient records and radiologic studies. The median duration of follow-up was 26 months for all patients and 26 months for the rituximab-refractory subset.

Table 9
Efficacy Outcomes in Rituximab-Relapsed/Refractory Patients

	Objective Responses to BEXXAR® therapy in Patients Refractory to rituximab N=35		**Objective Responses to BEXXAR® therapy in All Patients N=40**	
	Response Rate (%) (95% CI[a])	**Median Duration of Response (Mos, Range)**	**Response Rate (%) (95% CI[a])**	**Median Duration of Response (Mos, Range)**
Overall Response	63% (45%, 79%)	25 (4+, 35+)	68% (51%, 81%)	16 (1+, 35+)
Complete Response [c]	29% (15%, 46%)	NR[b] (4, 35+)	33% (19%, 49%)	NR (4, 35+)

[a]CI = Confidence Interval
[b]NR = Not reached
[c]Complete response rate = Pathologic and clinical complete response

Durable responses to BEXXAR® defined as responses with a time to progression of greater than 1 year) were observed in 17 of 40 (43%) patients. The median time to progression for these 17 patients was 31.5 months (range:12 - 36.7+ months).

Study 2 (RIT-II-004): This was a multicenter, single arm, open-label study of 60 chemotherapy refractory patients with low-grade and transformed low grade NHL. The median age was 60 (range: 38 - 82), the median time from diagnosis to protocol entry was 53 months (range: 9 - 334), the median number of prior chemotherapy regimes was 4 (range: 2 - 13) and 38% had transformed NHL.

Fifty-three patients had not responded to prior therapy and 7 patients had responded with a duration of response < 6 months.

The primary endpoint was a comparison, as assessed by an independent panel, of the number of patients with a longer duration of response (> 30 days) following BEXXAR® to the number of patients with a longer duration of response following their last qualifying chemotherapy regimen. Twenty-six patients had a longer duration of response following BEXXAR® while only 5 had a longer duration of response on the last qualifying chemotherapy regimen ($p < 0.001$).

Secondary endpoints included response rate and duration of response are shown in Table 9. The overall response rate in this population was 47% and the complete response rate was 20%. Duration of overall response was 11.7 months and duration of complete response was 47.2 months. Fifteen of 60 (25%) patients achieved a durable response (defined as responders with time to progression greater than 1 year). Median time to progression for the durable responders was 48.7 months.

Studies 3 to 5 (RIT-II-002, RIT-I-000, RIT-II-001): Three single-arm studies enrolled 130 patients evaluable for efficacy with rituximab-naive, follicular non-Hodgkin's lymphoma with or without transformation, who had relapsed following, or were refractory to, chemotherapy. In these studies, the overall response rates ranged from 49% to 64% and the median duration of response ranged from 12.6 to 15.5 months. Results are shown in Table 10.

Table 10
Efficacy Outcomes in Chemotherapy Relapsed/Refractory Patients

	Overall Response		Complete Response	
Study Number	**Response Rate (%)**	**Median Duration of Response (months)**	**Response Rate %**	**Median Duration of Response (months)**
Primary Studies				
RIT-II-004 (N=60)	47%	11.7	20%	47.2
CP-97-012 (N=40)	68%	16.1	33%	NR
Supportive Studies				
RIT-I-000[b] (N=22)	64%[c]	15.5	41%	36.5
RIT-II-001 (N=47)	49%[c]	12.6	26%	58.4
RIT-II-002 (N=61[a])	59%	13.2	36%	NR

[a]Patients receiving iodine I 131 tositumomab (Arm A and Arm B Crossover). Excludes patients who only received tositumomab (Arm B).

[b]Excludes 17 patients with intermediate- or high-grade lymphoma.

[c]MIRROR Panel-assessed when available (i.e., all patients with transformed low-grade NHL and those patients with low-grade NHL who had available radiographs and medical notes and Investigator-assessed TTP of a least 12 months).
TTP=Time to progression; NR=Not reached. MIRROR=Masked Independent Randomized Radiology and Oncology Review.

DETAILED PHARMACOLOGY

Tositumomab has been shown to bind with high affinity and unique specificity to the CD20 antigen.[2,10,16] This antigen is a transmembrane phosphoprotein expressed on pre-B lymphocytes and at higher density on mature B lymphocytes.[17] The antigen is also expressed on >90% of B-cell non-Hodgkin's lymphomas (NHL).[1] CD20 is not expressed on hematopoietic stem cells, normal plasma cells, or other normal tissues.[1,6,16] CD20 is expressed at low levels on a minor population of T-lymphocytes. The recognition epitope for tositumomab is found within the extracellular domain of the CD20 antigen. CD20 does not shed from the cell surface and does not internalize following antibody binding.[12]

Mechanism of Action

The high-energy beta particles emitted by I-131 are cytotoxic over distances of approximately 1-2 mm (the average path length is 0.8 mm and the maximum path length is 2.4 mm), thus permitting eradication of antigen-negative tumour cells by crossfire from neighbouring antibody-coated cells.[20] In addition to cell death associated with ionizing radiation from the radioisotope, possible mechanisms of action of BEXXAR® therapy (tositumomab, iodine I 131 tositumomab) include induction of apoptosis[16], complement-dependent cytotoxicity (CDC)[5], and antibody-dependent cellular cytotoxicity (ADCC)[3] mediated by the antibody.

Pharmacokinetics/Pharmacodynamics

The unlabelled antibody (tositumomab) is given prior to the radiolabelled dose to exert immune-related cytotoxicity and to saturate non-tumour B-cells in the circulation and organs (live and spleen) leading to increased tumour uptake of radiolabelled tositumomab.[14] Administration of tositumomab prior to radiolabelled tositumomab resulted in an increased tumour uptake of radiolabelled tositumomab in a mouse xenograft tumour model.[4] Dose-dependent blood pharmacokinetics of the antibody were observed with increasing amounts of tositumomab prior to administration of iodine I 131 tositumomab. A total protein dose of 485 mg (450-mg dose of tositumomab followed by a 35-mg dose of tositumomab containing the appropriate MBq (mCi) of iodine I 131 tositumomab) was selected for the dosimetric and therapeutic doses based on or high tumour burden, a higher response rate, and reduced pharmacokinetic variability. The median blood clearance following administration of 485 mg of protein in 110 patients with NHL was 68.2 mg/hr (range: 30.2 - 260.8 mg/hr). Patients with high tumour burden, splenomegaly, or bone marrow involvement were noted to have a faster clearance, shorter terminal half-life, and larger volume of distribution. The total body clearance, as measured by total body gamma camera counts, was mono-exponential and dependent on the same factors noted for blood clearance. The effective half-life was 65 hours.[19] Patient-specific dosing using dosimetry, based on total body clearance, provided a consistent total body radiation dose, despite variable pharmacokinetics, by allowing each patient's administered activity to be adjusted for individual patient variables.

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

Administration of BEXXAR® results in sustained depletion of circulating CD20 positive cells. The impact of administration of BEXXAR® on circulating CD20 positive cells was assessed in two clinical studies, one conducted in chemotherapy-naïve patients and one in heavily pretreated patients. The assessment of circulating lymphocytes did not distinguish normal from malignant cells. Consequently, assessment of recovery of normal B cell function was not directly assessed. At seven weeks, the median number of circulating CD20 positive cells was zero (range: 0 - 0.49 x 10^9/L). Lymphocyte recovery began at approximately 12 weeks following treatment. Among patients who had CD20 positive cell counts recorded at baseline and at 6 months, 8 of 58 (14%) chemotherapy-naïve patients had CD20 positive cell counts below normal limits at six months and 6 of 19 (32%) heavily pretreated patients had CD20 positive cell counts below normal limits at six months. There was no consistent effect of BEXXAR® on post-treatment serum IgG, IgA, or IgM levels.

TOXICOLOGY

No long-term animal studies have been performed to evaluate carcinogenic or mutagenic potential or whether BEXXAR® therapy (tositumomab and iodine I 131 tositumomab) affects fertility in males and females.

As with other radiopharmaceuticals which distribute intracellularly, there may be increased risk of chromosome damage from Auger electrons if nuclear uptake occurs.

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PART III: CONSUMER INFORMATION
BEXXAR® therapy
(tositumomab and iodine I 131 tositumomab)
Intravenous

This leaflet is part III of a three-part "Product Monograph" published for BEXXAR® therapy approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about BEXXAR® therapy. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
BEXXAR® therapy (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.

This product should be administered under the supervision of a qualified health professional who is appropriately qualified in the use of radioimmunotherapy and the management of patients with non-Hodgkin's lymphoma (NHL). Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

What it does:
BEXXAR® therapy is considered a dual action treatment for non-Hodgkin's lymphoma because it attacks cancer cells in two ways, providing both radiation therapy and immunotherapy in a single treatment. That's why BEXXAR® is called radioimmunotherapy.

The immunotherapy action of BEXXAR® is provided by a monoclonal antibody called tositumomab. Tositumomab seeks out and attaches to the CD20 antigen on the surface of non-Hodgkin's lymphoma cells. The radiation therapy action of BEXXAR® comes from a radioactive substance, called an isotope (a form of an element that is often radioactive), which is attached to the monoclonal antibody. The isotope in BEXXAR® is iodine-131. When tositumomab binds to the cancer cells, iodine-131 releases radiation that kills the attached cells. Radiation may also reach tumor cells that the monoclonal antibody cannot attach to. This is called crossfire effect. Other cells may also receive beams of radiation from the isotope. Some of the normal cells nearby may be affected as well.

When it should not be used:
Do not take BEXXAR® therapy if :

- you have a known hypersensitivity (serious allergic reaction) to "murine proteins" (proteins that come from mice)
- if you are allergic to any component of BEXXAR®.
- if you have > 25% lymphoma involvement in your bone marrow, platelet count < 100 x 10^9/L or neutrophil count < 1.5 x 10^9/L.
- if you have impaired bone marrow.
- if you are pregnant.

What the medicinal ingredient is:
BEXXAR® therapy is composed of a monoclonal antibody, tositumomab, and a radiolabeled monoclonal antibody, iodine I 131 tositumomab. The radiation component of BEXXAR®, iodine-131, leaves your body through urine over about a week, so radiation does not build up and stay in your body.

What the important nonmedicinal ingredients are:
The tositumomab formulation contains 10% (w/v) maltose, 145 mM sodium chloride, 10 mM phosphate, 17.5 mM potassium hydroxide, and Water for Injection, USP.

The iodine I 131 tositumomab formulation for dosimetric and therapeutic dosage forms contains 4.4%-6.6% (w/v) povidone, 1-2 mg/mL maltose (dosimetric dose) or 9-15 mg/mL maltose (therapeutic dose), 8.5-9.5 mg/mL sodium chloride, 1.22 mg/mL phosphoric acid, 1.05- 6.57 mg/mL potassium hydroxide, and 0.9-1.3 mg/mL ascorbic acid. The pH is approximately 7.0.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Special requirements: BEXXAR® therapy contains a radioactive component and should be administered only by physicians and other health care professionals qualified by training in the safe use and handling of therapeutic radionuclides.

Thyroid-blocking therapy must be started at least 24 hours before receiving the first (dosimetric) dose and continued for 14 days after the treatment (therapeutic) dose of BEXXAR® to decrease the risk of hypothyroidism (when your thyroid loses some function). Your doctor should provide you with a prescription for medication. Make sure you take your prescription as directed by your doctor.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Hypersensitivity Reactions (serious allergic reactions), including Anaphylaxis (a severe allergic reaction, that may be life threatening): Serious hypersensitivity reactions, including some with fatal outcome, have been reported with BEXXAR®. Medications for the treatment of severe hypersensitivity reactions should be available for immediate use. Signs and symptoms of severe allergic reactions may include fever, chills, sweating, low blood pressure, shortness of breath, bronchospasm, and nausea and have been reported during or within 48 hours of infusion. Patients who develop severe hypersensitivity reactions should have infusions of BEXXAR® discontinued and receive medical attention.

Prolonged and Severe Cytopenias (a reduction in the number of blood cells): The majority of patients who received BEXXAR® experienced severe thrombocytopenia (a disorder in which the number of platelets (a type of blood cell) is abnormally low, sometimes associated with abnormal bleeding) and neutropenia (an abnormally low level of neutrophils (white blood cells) in the blood). BEXXAR® should not be administered to patients with > 25% lymphoma marrow involvement, platelet count < 100 x 10^9/L or neutrophil count < 1.5 x 10^9/L and/or impaired bone marrow reserve.

Pregnancy: BEXXAR® can cause fetal harm when administered to a pregnant woman.

BEFORE you receive BEXXAR® talk to your doctor if:

- you are allergic to tositumomab, murine proteins (proteins that come from mice) or any other ingredient in BEXXAR® (see What the important nonmedicinal ingredients are).
- you are having or planning to have any vaccinations.
- you are pregnant or could be pregnant.
- you are breast-feeding. You must not receive BEXXAR® if you are breast-feeding.

Pregnancy

- Use a reliable method of contraception to avoid becoming pregnant while you're being treated with BEXXAR®, and for 12 months after your last treatment. There may be an increased risk of miscarriage up to a year following treatment with BEXXAR®.
- Use of BEXXAR® while pregnant can cause fetal harm. Severe and possibly irreversible hypothyroidism in infants may occur.

Prolonged low blood cell counts

BEXXAR® may result in low blood cell counts that may last for an extended period of time (see SIDE EFFECTS AND WHAT TO DO ABOUT THEM). Patients with ≥ 25% of their bone marrow cells affected by lymphoma and/or patients whose bone marrow may have difficulty recovery from therapy should not receive BEXXAR®.

Hypothyroidism

Patients who receive BEXXAR® are at risk of losing some function of their thyroid (hypothyroidism). Your doctor will test how well your thyroid is working before you are given BEXXAR®, as well as afterwards (every 6 months for the first 2 years and each year thereafter). Symptoms of hypothyroidism include: weakness, weight gain, brittle fingernails and/or hair, pale skin.

In order to minimize your risk of hypothyroidism, remember to take your thyroid blocking medicine as directed.

Secondary cancers

A small percentage of cancer patients (approximately 3 in 100) participating in BEXXAR® studies developed a second type of cancer involving blood cells. Most of these patients, however, had already received other cancer drugs, such as alkylating agents and/or topoisomerase inhibitors, that have already been shown to potentially cause secondary cancers. Therefore it is difficult to know whether BEXXAR® itself contributes to the risk of developing a secondary cancer.

Children

The safety and effectiveness of BEXXAR® in children have not been evaluated.

Safety precautions after receiving BEXXAR®

The following measures should be taken by the patient for up to 2 weeks after receiving the radiopharmaceutical.

Therapeutic dose:

Avoidance of contact with infants, young children, and pregnant women. Sleeping in a separate bed (separated by a distance of at least 2 to 3 meters). Maintain an appropriate distance of 2 meters from others. Travel alone in a private automobile if possible, otherwise maintain as great a distance as possible between patient and driver. Toilet should be used instead of urinal. Toilet should be flushed several times after use. Separate laundry and eating utensils and wash items separately. Ask your Nuclear Medicine physician for more specific information.

INTERACTIONS WITH THIS MEDICATION

Make sure your doctor knows about other medications you

are taking, including those you can buy without a prescription as well as herbal and alternative medicines.

No formal drug-drug interaction studies have been performed. If you are taking blood thinners or other medications that interfere with blood clotting, your doctor will need to monitor your blood counts carefully during and after treatment with BEXXAR®.

PROPER USE OF THIS MEDICATION

BEXXAR® therapy is not self administered by an individual. It should be administered under the supervision of a health professional who is experienced in the use of biologics and radiopharmaceuticals.

Preparation before receiving treatment with BEXXAR®
You must start your thyroid protective agent at least 24 hours before your first dose (Day 0) and continue until 2 weeks after your last dose of BEXXAR®.

BEXXAR® therapy
BEXXAR® therapy consists of 4 components given in 2 discrete steps: the dosimetric step, followed 7-14 days later by a therapeutic step.

Step 1 – Dosimetric step
During your first visit (Day 0), you will:
- receive tositumomab (the monoclonal antibody) by intravenous infusion over 1 hour, then
- receive an intravenous infusion of iodine I 131 tositumomab (radiolabeled monoclonal antibody) over 20 minutes
- have a whole body scan within an hour of the end of the intravenous infusion. You MUST NOT go to the bathroom (urinating) until AFTER this scan is done.

On your second visit (Day 2, 3 or 4), you will have a second whole body scan right after urinating.

On your third visit (Day 6 or 7), you will have another whole body scan right after urinating. These scans will help your doctor to determine your personalized dosing.

Step 2 – Therapeutic step
During your fourth visit (Day 7 or up to Day 14), you will:
- receive tositumomab by intravenous infusion over 1 hour, then
- receive an intravenous infusion of your personalized dose of iodine I 131 tositumomab over 20 minutes.

Follow-up after receiving BEXXAR® therapy
Your blood cell counts will continue to be monitored every week after completion of BEXXAR® therapy until your blood counts have recovered (at least 8 weeks). Talk to your doctor for more details regarding your follow-up.

Overdose:

In case of overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The premedications you are given before receiving BEXXAR® may help control the most common side effects that some patients may experience, like fever, chills, and flu-like symptoms.

During infusions, your treatment team will monitor your blood pressure, heart rate, breathing, and temperature. If changes occur, your treatment team may decide to slow down or stop the infusion.

Most patients who receive BEXXAR®, experience decreased blood counts. This decrease may last a number of weeks. During this time, you may be susceptible to serious infections. You may need to receive blood transfusions or medications that will help your counts recover faster. Please see the table for information on low white blood cells, platelets and red blood cells.

BEXXAR® may cause reactions because it contains proteins not usually found in your body.

After you complete treatment and go home, be sure to call your oncologist or hematologist if any side effects get worse, or if you have any new side effects from the BEXXAR® treatment.

Possible side effects with BEXXAR® therapy are outlined in the table below.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Abdominal pain		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and**
	Nausea		✓	
	Vomitting		✓	
	Shortness of breath		✓	
	Fever		✓	
	General weakness		✓	
	Pain, incl. muscle pain, back pain, neck pain, joint pain		✓	
	Chills		✓	
	Constipation		✓	
	Cough increased		✓	
Uncommon	Indigestion		✓	
	Infection		✓	
	Rash		✓	
	Sweating		✓	
	Weight loss		✓	

This is not a complete list of side effects. For any unexpected effects while taking BEXXAR®, contact your doctor or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.gsk.com
or by contacting the sponsor, GlaxoSmithKline Inc at:

7333 Mississauga Road
Mississauga, Ontario
L5N 6L4
1-800-387-7374.

Visit
The Health Canada
Biologics and Genetics Therapies Directorate at :
http://www.hc-sc.gc.ca/dhp-mps/brgtherap/index_e.html
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