Health Canada Santé Canada

SUMMARY BASIS OF DECISION (SBD)

BEXXAR™ THERAPY

Tositumomab and Iodine I 131 tositumomab, 35 and 225 mg, Solution

GlaxoSmithKline Inc.

Submission Control No. 084518

Date Issued	2006/11/08

Health Products and Food Branch

Canada

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Health Products and Food Branch

Également disponible en français sous le titre : Sommaire des motifs de décision (SMD), BEXXAR[MD] THERAPY, tositumomab et 131 I tositumomab, 35 mg et 225 mg, solution, GlaxoSmithKline Inc., N[o] de contrôle de la présentation 084518

FOREWORD

Health Canada's Summary Basis of Decision (SBD) documents outline the scientific and regulatory considerations that factor into Health Canada regulatory decisions related to drugs and medical devices. SBDs are written in technical language for stakeholders interested in product-specific Health Canada decisions, and are a direct reflection of observations detailed within reviewer reports. As such, SBDs are intended to complement and not duplicate information provided within the Product Monograph.

Readers are encouraged to consult the 'Reader's Guide to the Summary Basis of Decision - Drugs' to assist with interpretation of terms and acronyms referred to herein. In addition, a brief overview of the drug submission review process is provided in the Fact Sheet entitled 'How Drugs are Reviewed in Canada'. This Fact Sheet describes the factors considered by Health Canada during the review and authorization process of a drug submission. Readers should also consult the 'Summary Basis of Decision Initiative - Frequently Asked Questions' document. These documents are all available on the Health Canada website.

The SBD reflects the information available to Health Canada regulators at the time a decision has been rendered. Subsequent submissions reviewed for additional uses will not be captured under Phase I of the SBD implementation strategy. For up-to-date information on a particular product, readers should refer to the most recent Product Monograph for a product. For information related to post-market warnings or advisories as a result of adverse events, interested parties are advised to access the Health Canada website.

For further information on a particular product, readers may also access websites of other regulatory jurisdictions, available under 'Related Links' on the Health Canada website. The information received in support of a Canadian drug submission may not be identical to that received by other jurisdictions.

Other Drug Policies and Guidance:

Readers should consult the Health Canada website for other drug policies and guidance documents. In particular, readers may wish to refer to the 'Management of Drug Submissions Guidance'.

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1 PRODUCT AND SUBMISSION INFORMATION

Brand Name	Bexxar™ Therapy
Manufacturer/Sponsor	GlaxoSmithKline Inc.
Medicinal Ingredient	Tositumomab; Iodine I 131 tositumomab
International Non-proprietary Name	Tositumomab; Iodine I 131 tositumomab
Strengths	35 mg and 225 mg
Dosage form	Solution
Route of Administration	Intravenous
DIN	02270471
Pharmaco-therapeutic group (ATC Code)	Anti-neoplastic radioimmunotherapeutic
Non-medicinal Ingredients	Tositumomab: phosphoric acid, potassium hydroxide, maltose, sodium chloride, and water for injection Iodine I 131 tositumomab: povidone, ascorbic acid, maltose, sodium chloride, phosphoric acid, potassium hydroxide
Submission Type and Control No.	New Drug Submission, Control No. 084518
Date of Submission	2003/05/16
Date of Authorization	2005/08/18

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2 NOTICE OF DECISION

On August 18, 2005, Health Canada issued a Notice of Compliance to GlaxoSmithKline Inc. for the drug product Bexxar™ Therapy, an anti-neoplastic radioimmunotherapeutic. Bexxar™ Therapy is composed of the monoclonal antibody tositumomab, and the radiolabelled monoclonal antibody iodine I 131 tositumomab. This submission was granted Priority Review due to the unmet medical need for an innovative therapy in the treatment of follicular lymphoma.

Bexxar™ Therapy 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. Tositumomab is a murine IgG_{2a} monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B-cell lymphocytes. When administered, Bexxar™ Therapy selectively targets tumour cells with the delivery of a high radiation dose, thereby destroying them.

The issuance of marketing authorization for Bexxar™ Therapy was based on satisfactory review of quality (chemistry and manufacturing), non-clinical, and clinical data. Patients treated with Bexxar™ Therapy exhibited adequate evidence of efficacy for the authorized indication. The data submitted demonstrate that Bexxar™ Therapy can be administered safely when used under the conditions stated in the Product Monograph.

Bexxar™ Therapy is supplied as a kit with two distinct package configurations which are used in the administration of treatment involving a two-step process: the dosimetric and therapeutic steps. Each step consists of a sequential infusion of tositumomab followed by iodine I 131 tositumomab. The therapeutic step is administered seven to fourteen days after the dosimetric step. Detailed conditions for the use of Bexxar™ Therapy are available in the Product Monograph.

Bexxar™ Therapy is contraindicated in patients with known hypersensitivity to murine proteins or any component of the Bexxar™ Therapy regimen.

Based on Health Canada's review of data on quality, safety, and effectiveness, Health Canada considers that the benefit/risk profile of Bexxar™ Therapy is favourable in the treatment of patients with rituximab-relapsed or refractory CD20 positive follicular B-cell non-Hodgkin's lymphoma.

3 SCIENTIFIC AND REGULATORY BASIS FOR DECISION

3.1 Quality Basis for Decision

3.1.1 Drug Substance (Medicinal Ingredient)

Description

Tositumomab is a murine IgG_{2a} monoclonal antibody that binds to the CD20 antigen on the surface of normal and malignant B cells.

Manufacturing Process and Process Controls

The monoclonal antibody tositumomab is secreted from a murine hybridoma cell substrate. Production of tositumomab is based on a cell bank system which has been thoroughly characterized and tested for adventitious microorganisms (bacteria, mycoplasma, and viruses) and endogenous viruses, in accordance with international guidelines. Results of these tests confirmed the absence of adventitious microorganisms and the cell line identity. Genetic characterization (e.g., nucleotide sequence analysis) also demonstrated stability of the Master Cell Bank (MCB).

The manufacture of tositumomab comprises a series of steps which include fermentation, harvest and purification processes. The purification is performed via a combination of chromatography and viral inactivation /removal steps. The method of manufacture and the controls used during manufacturing are validated based on the production of three consecutive lots. Each lot met specifications for drug substance production. In-process controls performed during manufacture were reviewed and considered acceptable. The specifications for the raw materials used in manufacturing the drug substance are also considered satisfactory.

Characterization

Tositumomab is a monoclonal antibody possessing a typical antibody structure of the IgG class, composed of two heavy and two light amino acid chains.

The structures of tositumomab and I 131 tositumomab have been adequately explained and the representative spectra have been provided. Physical and chemical properties have been described and found to be satisfactory. Comparability of tositumomab lots produced by three different manufacturers, different processes, and different clones was performed and comparable physicochemical characteristics and immunoreactivity were demonstrated.

Control of Drug Substance

Validation reports are considered satisfactory for all analytical procedures used for in-process and release testing of the drug substance. Results from process validation studies indicate that the methods used during processing are adequately controlled and impurities that were reported and characterized were found to be within established limits. The drug substance specifications and the analytical methods used for the evaluation of the identity, composition, potency and purity of tositumomab are considered acceptable.

Data from the batch chosen to serve as a suitable reference standard and from three consistency batches were considered acceptable according to the specifications of the drug substance.

Stability

Based upon the real-time and accelerated stability studies, the proposed shelf-life and storage conditions for the drug substance were supported and considered to be satisfactory.

3.1.2 Drug Product

Description and Composition

Bexxar™ Therapy is composed of the monoclonal antibody tositumomab and the radiolabelled monoclonal antibody, iodine I 131 tositumomab. Tositumomab is supplied as a sterile, pyrogen-free, clear to opalescent, colourless to slightly yellow, preservative-free solution at a concentration of 14 mg/mL. Iodine I 131 tositumomab is supplied as a sterile, clear, preservative-free solution for IV administration. Bexxar™ Therapy is supplied as a kit with two single-use 225 mg vials (16.1 mL), and one single-use 35 mg vial (2.5 mL) of tositumomab for each of the dosimetric and therapeutic dosing steps. The dosimetric dosing kit also includes a single-use vial of I 131 tositumomab at 22.57 MBq/mL while the therapeutic dosing kit includes one or two single-use vials of I 131 tositumomab at 207.2 MBq/mL. The container/closure system used for tositumomab consists of Type I glass vial with a rubber stopper and aluminum flip-off cap.

All excipients found in the drug product are acceptable for use in drugs by the Canadian *Food and Drug Regulations*. The compatibility of tositumomab with the excipients and the container closure system is demonstrated by the stability data presented on the proposed commercial formulation.

Pharmaceutical Development

Pharmaceutical development data, including development of the container closure system, were considered acceptable. Data provided in this section include composition of I 131 tositumomab for both the dosimetric and therapeutic dosage form, rationale for choice of formulation, manufacturing process including packaging, information on batches used in *in vitro* studies for characterization and discussion on the effect of formulation change on the safety and/or efficacy of I 131 tositumomab. Studies which justified the type and proposed concentration of excipients to be used in the drug product were also reviewed and considered to be acceptable.

Manufacturing Process and Process Controls

Manufacturing of tositumomab drug product consists of sterile filtration of tositumomab drug substance, aseptic filling, capping, labelling, and packaging.

Manufacturing of I 131 tositumomab consists of preparation of solutions of ascorbic acid and povidone, sterile filtration, dispensing, labelling and inspection, packaging, and decontamination and cleaning.

Critical process parameters such as volumetric flow rate of reactant solutions, IODO-GEN-coated bead concentration, manufacturing source of unlabelled antibody, process hold times for bulk intermediate drug product and bulk final drug product and particle levels (viable and non-viable) during process operations, have been validated according to validation protocol.

All equipment, operating parameters, in-process tests, and detailed instructions are adequately defined in the submission. The manufacturing process is considered to be adequately controlled within justified limits.

Control of Drug Product

Bexxar™ Therapy is tested to verify its appearance, composition, identity, immunoreactivity, purity, potency, sterility, and radiochemical attributes.

Analytical testing results from different batches of tositumomab drug product (both dosimetric and therapeutic dosage form) were provided and reviewed, and were found to meet the required specifications.

Stability

Stability data provided on tositumomab drug product support a shelf-life of 36 months at 2-8ºC when stored in 2.5 mL or 16.1 mL glass vials. Additional stability data also demonstrated that diluted solutions of tositumomab (either with 0.9% NaCl or 5% dextrose) are stable for up to 24 hours at 2-8ºC and for up to 8 hours at room temperature. Stability data for the radiolabelled I 131 tositumomab support a 14-day shelf-life for the dosimetric dosage form and a 5-day shelf-life for the therapeutic dosage form when stored frozen. These test results also demonstrate that both dosage forms can be manufactured consistently to meet the required specification of $\leq$ 3.0% unbound I 131 at release.

At least one lot representative of each dosage form will be monitored annually for post-market stability.

3.1.3 Facilities and Equipment

The design, operations, and controls of the facilities and the equipment are considered suitable for the production of tositumomab and the Bexxar™ Therapy drug product. All facilities are compliant with Good Manufacturing Practices (GMP).

3.1.4 Adventitious Agents Safety Evaluation

Pre-harvest cell culture fluid from each lot of tositumomab is tested to ensure freedom of adventitious microorganisms (bioburden, mycoplasma, and viruses). Steps from the tositumomab purification process designed to remove and inactivate viruses were appropriately validated. Raw materials of animal and recombinant origin used in the manufacture of tositumomab have been adequately tested to ensure freedom of adventitious agents. There are no excipients of animal/human origin in the formulation of tositumomab drug product.

3.1.5 Summary and Conclusion

This New Drug Submission is considered to meet the requirements of Division C.08.002 of the *Food and Drug Regulations* insofar as the Quality (Chemistry and Manufacturing) information is concerned. The Chemistry and Manufacturing information submitted for Bexxar™ Therapy has demonstrated that the drug substance and drug product can be consistently manufactured to meet the specifications. Proper development and validation studies were conducted, and adequate controls are in place for the commercial processes.

3.2 Non-clinical Basis for Decision

3.2.1 Pharmacodynamics

The sponsor provided data from published literature pertaining to the anti-B1 antibody. Specifically, the following topics were presented in the submission: the nature of the anti-B1 antibody (tositumomab); its target molecule, the CD20 antigen (also known as B1 antigen); the iodine-131 (I 131) radiolabel; and known mechanisms of action of the antibody.

The sponsor presented established scientific facts supporting the molecular mechanism of action of the anti-B1 antibody against cells expressing the CD20 antigen at the surface of the cell membrane:

- the CD20 antigen is a trans-membrane protein that acts as a calcium-permeable channel and IGF-I modulator in normal B lymphocytes and malignant B cells; it is likely involved in the mechanism of B-lymphocyte proliferation;
- anti-B1 antibody binds to CD20-positive cells;
- the CD20 antigen is neither shed nor internalized upon anti-B1 antibody binding;
- anti-B1 antibody binds the CD20 antigen in primates but not in other mammals;
- I 131 anti-B1 is a murine IgG_{2a} antibody conjugated to the I 131 radioisotope;
- accretion of I 131 anti-B1 antibody into tumours expressing the CD20 antigen is increased by pre-dosing with unlabelled anti-B1 antibody;
- besides the gamma radiation used for imaging (364 keV), I 131 also generates ionizing high-energy (606 keV) beta minus radiation with a range of many cell diameters, which may allow killing of adjacent tumour cells;
- I 131 anti-B1 antibody is thought to produce its anti-tumour effects through the synergistic effects of cytotoxic ionizing radiation and direct cytotoxic effects of the antibody on CD20-positive cells; these latter cytotoxic mechanisms potentially include: apoptosis following ligation of the CD20 antigen by antibody in the presence of Fc Receptor (Fc-R) expressing cells, antibody-dependent cellular cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC).

Experiments with monkeys showed that over time, radioactivity was largely eliminated from blood and organs that did not contain B lymphocytes, whereas the I 131 anti-B1 antibody was retained in spleen and lymph nodes. It is stated that splenic and lymph node biopsies showed specific binding of I 131 anti-B1 antibody to B lymphocytes in these tissues while kidney, liver, and pancreas biopsies showed no binding of non-B cells.

In terms of scintigraphic studies conducted in an immunodefficient mouse model using human B-cell tumour xenografts, results showed that localisation of tositumomab radiolabelled with I 125 or I 131 was tumour-specific and preferential to normal tissues. It is stated that pre-dosing with unlabelled antibody substantially increased tumour uptake and transit time; it also led to an increase of antibody level in the blood pool of the animal.

As per published literature cited by the sponsor, no cross-reactivity of anti-B1 antibody is known other than with the CD20 antigen in cynomolgus and Rhesus monkeys, and baboons. It is unclear whether mouse IgG_{2a} can bind Fc-R-gamma (Fc receptor for IgG class immunoglobulins) in non-human primates as the study cited found "no staining of non-B cells" *in vivo* upon IV injection of 0.1 mg/kg of I 131 anti-B1 in Rhesus monkeys. However, it was shown elsewhere (not cited by sponsor) that mouse IgG_{2a} can bind all three types of Fc-R-gamma in humans and thus can potentially bind reticuloendothelial cells (specifically, tissue macrophages) expressing Fc-R-gamma at the surface of the cell membrane. How the IgG_{2a} interaction with Fc-R-gamma could impact on the physiology of the immune system in primates and humans is not considered in this submission beyond potential anti-tumour cytotoxic mechanisms that include apoptosis and ADCC.

It is noted that the CD20 antigen is also expressed on a minor population of T lymphocytes ($CD20^{DIM}$), which reportedly represent 2.4±1.5 % of primate B lymphocytes (PBLs). It is unclear whether the physiology of the immune system could be affected on the long term by the binding of tositumomab to CD20-expressing T lymphocytes. The $CD20^{DIM}$ T lymphocytes have been reported elsewhere to be predominantly in the memory cytotoxic class and their counts increase with age.

No potential undesirable pharmacodynamic effects on physiological functions were described in the literature or observed in experiments carried out in animals. All antibody treated animals developed a serum immunoglobulin response to the mouse antibody, which is consistent with the development of human anti-murine antibodies (HAMA) in treated patients (see section 3.3 Clinical Basis for Decision). No known drug interactions in the pre-clinical pharmacodynamic studies were reported.

Overall, data in published literature support a mechanism of action whereby I 131 tositumomab specifically binds the CD20 antigen on human and primate B lymphocytes, or human tumours expressing the CD20 antigen in immunodeficient mice. Pre-dosing with unlabelled antibody reportedly increases anti-B1 antibody binding and tumour residence *in vivo*. Potentially ensuing tumour cytotoxicity could be mediated by mechanisms involving ADCC, CDC, and/or ionizing radiation effects.

3.2.2 Pharmacokinetics

The sponsor cited published experiments performed in monkeys with radiolabelled anti-B1 antibody. The terminal half-life for serum clearance of total reactivity was 24-28 hours, while the terminal half-life value for serum clearance of protein-associated radioactivity was 27-31 hours. While at 24 hours post-infusion 90% of the radioactivity in serum was protein-associated, at 144 hours post-infusion it decreased to 53-72%. Free I 131 was excreted primarily in urine; cumulative excretion of I 131 over 7 days ranged from 28-34% depending on the dose. Less than 7% of the radioactivity in urine was protein-associated. Up to 70% of B lymphocytes in the lymph nodes bound radiolabelled anti-B1 antibody *in vivo* as determined at various time points between 40 hours and 6 days post-infusion. Other published experiments with I 131 anti-B1 antibody in immunodeficient mice carrying human B lymphocyte tumour xenografts showed that localization of the labelled antibody was tumour specific and preferential to other normal tissues, with the exception of blood.

The sponsor and affiliates conducted five pharmacokinetic/biodistribution studies in mice and cynomolgus monkeys using radiolabelled anti-B1 antibody:

Study B1-PT-019
This study was dual-label and non-GLP-compliant. Site-radiolabelled I 125 anti-B1 antibody and centrally-radiolabelled I 131 antibody preparations were co-administered intravenously to mice. Each time point analysis included six animals. Animals were either bled at 12 time points over 216 hours post-injection to determine blood clearance profiles, or sacrificed at six time points to determine the tissue-to-blood ratio of radioactivity. The results showed no meaningful difference in the blood and tissue clearance and tissue distribution of the two radiolabelled anti-B1 antibody preparations in normal mice following IV administration.

Study B1-PT-002
This study was non-GLP-compliant and similar in design to the previous study, but with the following differences: the centrally-labelled antibody was from a different lot and the dosing solution was modelled on a dosimetric rather than therapeutic patient dose. The results showed

no meaningful difference in the blood and tissue clearance and tissue distribution of the two radiolabelled anti-B1 antibody preparations in normal mice following IV administration. It is notable however, that the terminal half-life of the product was consistently almost twice that of the previous experiment.

Study B1-PT-001

This study was non-GLP-compliant and compared the tissue distribution and blood clearance profiles of I 131 anti-B1 antibody in two different dosing vehicles, 5.5% PVP and 5% HSA, both in PBS, following IV administration in mice. Blood samples were taken at 13 time points for 168 hours and tissue distribution was measured at 168 hours post-injection. The results indicated no meaningful difference between the two formulations, however the terminal half-life with PVP was more variable (240±191 hours) than with HSA (175±84 hours).

Study 3-F44

This study was GLP-compliant and compared the blood and whole body clearance of two antibody preparations labelled alternatively with I 131 and I 125 in monkeys. The purpose of this study was to provide support for a change in the manufacturing process of anti-B1 antibody. After blocking thyroid uptake of unbound radiolabelled iodine (48, 24, and 1 hour prior to treatment; continued once daily through Day 4), unlabelled antibody preparations were administered via one hour infusions to cynomolgus monkeys and were followed with thirty minute infusions of a mixture of radiolabelled antibody preparations. The tositumomab dose administered was 7.5 mg/kg unlabelled with 0.125 mCi (0.3 mg) each iodine-131 and iodine-125 labelled. Specific activity delivered was approximately 125 uCi/kg of each radiolabelled antibody. Clearance profiles were similar for both groups and the administered antibodies appeared to be located predominantly in plasma. Blood radioactivity appeared to be primarily (80%) associated with precipitable plasma proteins. Results indicated that radioactivity was eliminated almost exclusively via the kidney. The isotope recovery analysis of the two preparations were substantially equivalent.

Study 3-K06

This study was GLP-compliant and compared the clearance of two lots of anti-B1 antibody following IV administration to cynomolgus monkeys. The purpose of this study was to provide support for a change in the manufacturing process of anti-B1 antibody. The two preparations of anti-B1 antibody, labelled alternatively with I 131 and I 125 and administered via one hour infusion to monkeys, were followed with thirty minute infusions of radiolabelled antibody preparations after loading the animals with Iodine to block thyroid uptake of unbound radiolabelled iodine. The tositumomab dose administered was 7.5 mg/kg unlabelled with 0.125 mCi (0.3 mg) each of I 131 and I 125 labelled. The specific activity delivered was

approximately 125 uCi/kg of each radiolabelled antibody. Clearance profiles were similar for both groups. The administered antibodies appeared to be located predominantly in plasma. Blood radioactivity appeared to be primarily (90%) associated with precipitable plasma proteins. Results indicated that radioactivity was eliminated almost exclusively via the kidney. It is stated that the two antibody preparations were substantially equivalent for comparative clearance in cynomolgus monkeys.

No known drug interactions in the pre-clinical pharmacokinetic studies were reported.

3.2.3 Toxicology

This section includes results of non-human primate toxicology studies and *in vitro* tissue reactivity studies. No long-term animal studies have been performed to establish the carcinogenic or mutagenic potential of Bexxar™ Therapy or to determine its effects on fertility in males or females.

One repeat-dose intravenous toxicity study was conducted in monkeys to evaluate the toxicity of the tositumomab antibody. Anti-B1 antibody was given as two injections, 1 week apart, at dosages of 7.5 or 75 mg/kg to groups of male and female cynomolgus monkeys. Depletion of B lymphocytes, consistent with the pharmacologic activity of this monoclonal antibody to CD20, was evident in all drug-treated monkeys from 24 hours post-dosing through Day 10, after which they recovered up to 88-100% (males) or 62-65% (females) of baseline values over 3 months. Analysis of lymphocytes from lymph node biopsies on Day 30 found CD20+ and CD40+ B cells decreased 33%-69% for all animals. Monkeys that received 75 mg/kg anti-B1 antibody showed up to a two-fold increase in T lymphocyte proliferative response to concanavalin A (a T lymphocyte-specific activator) that returned to baseline by Day 84; the biological basis of this effect is unknown. All monkeys administered 7.5 or 75 mg/kg anti-B1 antibody developed anti-mouse IgG antibodies. Anti-mouse antibody response was generally stronger in females than in males. There was no evidence of immune system suppression during the study. Anti-B1 antibody was generally well tolerated in monkeys up to 10-fold the human therapeutic equivalent dosage, thus supporting the safety of the anti-B1 antibody for this clinical indication.

Three *in vitro* studies were conducted to investigate tissue reactivity (antibody binding). Two studies compared the tissue specificity of unlabelled anti-B1 antibody supplied by different manufacturers. Some non-specific background staining of some human tissues was apparent, but it was concluded that the anti-B1 antibodies produced by all manufacturers exhibited

indistinguishable patterns of tissue reactivity, which were also consistent with known C20 expression. The third study aimed to demonstrate that conjugation with Iodine, using the same process used for radio-iodination, did not alter tissue specificity of anti-B1 antibody. It was concluded that non-iodinated anti-B1 antibody exhibited a pattern of tissue reactivity that was indistinguishable from the same lot of anti-B1 antibody conjugated with I 127, and was consistent with known C20 expression.

3.2.4 Summary and Conclusion

The metabolism of the I 131 anti-B1 antibody results in small peptides and unbound I 131 which are eliminated mainly in urine. However, most of the I-131 in the blood of the animals receiving I 131 anti-B1 antibody remains bound to the antibody during the first few days after infusion; this means the effective half-life of I 131 is strongly dependent on the half-life of the antibody it is bound to. In non-human primates included in these pre-clinical studies, tositumomab and I 131 tositumomab had similar pharmacokinetic and biodistribution characteristics regardless of manufacturer, radiolabelling location, or formulation.

Although the pharmacokinetics studies did not specifically include toxicity experimental endpoints, no unexpected overt toxicity was noted in any of these studies that should raise safety concerns. The well-known clinical risks of I 131 exposure (i.e., myelosuppression, thyroid gland ablation, mutagenicity/carcinogenicity, and teratogenicity) were not addressed in studies performed on animals. However, *in vitro* treatment of human bone marrow cultures with anti-B1 antibody and complement did not result in toxicity to early differentiating bone marrow cells.

Tositumomab was immunogenic in all drug-treated monkeys and the immune response (HAMA) was somewhat stronger in females than in males. Blood CD20+ cell count recovery was also slower in females than in males. However, there was no evidence of immune system suppression during the study. This does not necessarily rule out the concern of whether the amount of IgG antibody administered to the animals may have impacted on the responsiveness of the reticuloendothelial system in relation to antibodies generated by immune responses developed against other foreign antigens during the time course of the study.

Based on the results of the repeat-dose intravenous toxicity study in cynomolgus monkeys, tositumomab was well tolerated, and there was no overt drug-related toxicity. Overall, the evaluation of the general preclinical data supports the safety, function, and dosing schema for I 131 tositumomab.

3.3 Clinical Basis for Decision

The stated goal of treatment with I 131 tositumomab is to selectively deliver radiotherapy to the tumour cells, thus minimizing toxicity to normal cells. Patients receiving non-myeloablative doses of I 131 tositumomab underwent a two-phase antibody administration: a dosimetric phase, which allowed for the calculation of a patient-specific whole body radiation dose, and a therapeutic phase. In each phase, unlabelled tositumomab was administered immediately prior to the labelled antibody to improve tumour targeting. Patients were administered oral Iodine (Iodide solution) prior to, during, and after the dosimetric and therapeutic doses to block uptake of unbound I 131 by the thyroid gland.

A total of seven clinical trials were conducted. Two clinical Phase I/II studies (RIT-I-000 and RIT-II-001) evaluated the optimal dose of unlabelled antibody, the maximum tolerated dose (MTD), and reproducibility of whole body dosimetry, safety, and efficacy. Five clinical trials (RIT-II-002, RIT-II-003, RIT-II-004, CP-97-012, and CP-98-020) provided additional bioavailability, pharmacokinetic, and dosimetry data, along with efficacy and safety data.

Patients underwent two treatment phases with a fixed antibody pre-dose. In the first phase, termed the 'dosimetric dose', patients received an infusion of 450 mg of unlabelled anti-B1 antibody over 70 minutes (including a 10-minute flush) followed by a 30-minute infusion (including a 10-minute flush) of 35 mg of anti-B1 antibody radiolabelled with 5 mCi of I 131. Whole body dosimetric data were then collected at selected time points over the next six or seven days. In the second phase, termed the 'therapeutic dose', patients received 450 mg of unlabelled anti-B1 antibody over 70 minutes (including a 10-minute flush) followed by a 30-minute infusion (including a 10-minute flush) of 35 mg of anti-B1 antibody radiolabelled with a patient-specific amount of I 131 calculated to deliver a specific total body dose (TBD). TBD was 75 cGy, with attenuation for obese patients and patients who underwent BMT. With this patient-specific dosing methodology, patients who cleared I 131 anti-B1 antibody more rapidly received a higher administered activity than patients who had slower clearance. This methodology allowed maximum radiation doses to tumours, while controlling the total body radiation dose (TBRD).

Competitive uptake by the thyroid gland of unbound I 131 resulting from the metabolism of I 131 tositumomab was actively prevented in patients before, during, and after therapy by administration of unlabelled iodine (iodide solution).

Radioactive counts of I 131 administered as part of the I 131 anti-B1 antibody were used to estimate the clinical pharmacokinetic parameters. Total body counts obtained from I 131 gamma emission were collected for each patient. In addition, counts from I 131 radioactivity from blood and ROIs (tumours, spleen, and other organs) were collected to analyse the blood pharmacokinetics, organ doses, and tumour doses. Studies RIT-I-000 and RIT-II-003 included components of the pharmacokinetics and dosimetry of I 131 anti-B1 antibody. Additional data on the pharmacokinetics of anti-B1 antibody based on ELISA were collected in study RIT-II-004.

3.3.1 Bioavailability and Bioequivalence

A comparison of pharmacokinetic parameters obtained with I 131 anti-B1 antibody manufactured by three different suppliers was provided. Total body dosimetry parameters, organ residence times, and organ dosimetry parameters were also compared. All data for the pharmacokinetic and dosimetric clinical comparisons were obtained by the sponsor from radioactive counts of I 131 antibody administered as part of the dosimetric dose. There were no significant differences between the respective pairs of data sets. Organ doses were similar and were below normal tissue tolerance doses. Blood pharmacokinetics were also similar. Spleen size had the greatest influence on antibody exposure parameters (AUC); patients with larger spleen sizes had a smaller AUC and the effect was similar between antibodies. Patient weight had the greatest influence on the maximum concentration of antibody (C_{max}); patients with larger mass had smaller C_{max}.

It is noted that the dose-limiting toxicity for patients receiving I 131 anti-B1 antibody is hematologic. The red marrow doses were comparable between patients receiving the three manufactured antibodies. Overall, the hematologic toxicity profiles were comparable between the two patient groups.

Qualitative, visual interpretations of the targeting and biodistribution of the radiolabelled antibody were performed by one of the study investigators at the University of Michigan. The data indicated that antibodies behaved comparably in these patients, with no visually apparent differences in organ distribution and tumour targeting.

Overall, the clinical pharmacokinetic, hematologic, total body dosimetric, organ dosimetric and biodistribution data from patients who received I 131 anti-B1 antibody from any of the three manufacturers were comparable and considered bioequivalent.

3.3.2 Pharmacodynamics

Dose-dependent anti-tumour activity was noted with increasing TBD in study RIT-I-000 (in subsequent studies patients were dosed at MTD). With regard to anti-tumour activity, antibody dose and absorbed radiation dose were confounding variables in that study. The response rate varied from 33% (1 of 3) for 0 cGy TBD to 67% (2 of 3) for 85 cGy TBD. Tumour responses of shorter duration than those seen with higher TBD have been noted without a therapeutic dose of I 131 anti-B1 antibody in study RIT-I-000 and in Arm B of study RIT-II-002. The median duration of response was 7.4 months for patients receiving a 75 cGy TBD and 8.9 months for patients receiving a 65 cGy TBD.

B-cell pharmacodynamics were collected in studies RIT-I-000 and RIT-II-003. The absolute CD20+ cell counts per mm^3 were calculated from flow cytometry and complete blood counts. Eighty-six of 110 (78%) patients with baseline and follow-up B-cell counts had a post-treatment B-cell count that was below the normal range, including some patients that had no B-cells. Subsequently, 66 of the 86 (77%) patients had their B-cells return to the normal range. The median time to B-cell recovery was 167 days following the dosimetric dose. Due to limited follow-up, the other 20 patients' B-cell counts were below the normal range at the time of their last B-cell count (range: 6-271 days) following the dosimetric dose. Protein dose-dependent B-cell recovery was observed, with patients who received a lower protein dose having more rapid B-cell recovery.

Given the observed clinical effects (tumour shrinkage, in some patients detectable already at the dosimetric dose stage; the dramatic decrease in CD20+ cell counts) a pharmacodynamic effect of the I 131 anti-B1 antibody was clearly manifest in treated patients. It is unclear though what percentage of the tumour cell population is affected by the cytotoxic effects; based on pre-clinical data, it is safe to assume that this therapy can only induce temporary remissions by diminishing the pool of neoplastic cells and reducing the normal B lymphocyte population. The question remains as to how many times can the therapy be repeated in each patient, given the generalized HAMA response.

The mechanisms of action of I 131 anti-B1 antibody *in viv*o were apparently not investigated in the context of a clinical trial. Radiation generated by I 131 can most likely account for the observed hematologic toxicity; however, it is not clear what the relative contribution is to the global cytotoxic effect on the B-cell population of the I 131 moiety and the tositumomab moiety. In particular, it is not clear whether or not a similar cytotoxic effect could be induced by larger amounts of tositumomab alone.

The potential saturating effect of the mouse IgG on human Fc-R-gamma bearing cells was not evaluated.

Overall, the clinical pharmacology data is regarded as supportive with respect to the objective of the trials conducted with I 131 anti-B1 antibody.

3.3.3 Pharmacokinetics

An integrated summary found that the median AUC of anti-B1 antibody was 1.47 % ID hr/ml and ranged from 0.38 to 3.32 % ID hr/ml. The median maximum concentration was 0.019 % ID/mL and ranged from 0.011 to 0.036 % ID/mL. The median terminal half-life was 66.4 hours and ranged from 26.3 to 196.7 hours. Antibody dose-dependent pharmacokinetics were observed, with slower clearance and a longer terminal half-life following larger pre-doses of unlabelled anti-B1 antibody. The total body half-life (TBHL) was correlated with blood AUC and the blood terminal half-life. While no significant differences were noted in the means across studies, gender, and manufacturer of anti-B1 antibody, there were significant differences based on the same factors that were noted to affect the blood pharmacokinetics (see below).

Blood concentrations of anti-B1 antibody and HPLC analyses of the I 131 distribution in blood were collected and demonstrated that the blood concentrations and pharmacokinetics of anti-B1 antibody and I 131 anti-B1 antibody are similar and that the I 131 in blood is predominantly (more than 90%) antibody-bound, with a small component of I 131 products.

Blood pharmacokinetics followed a two-compartment model, variable but independent from the manufacturer of the antibody. Patients with high tumour burden, splenomegaly, or bone marrow involvement were noted to have more rapid clearance, shorter half-life, and larger volume of distribution. The blood pharmacokinetics following the dosimetric and therapeutic doses were correlated. Since dosing was patient-specific and designed so that all patients received the same TBD, the variability seen in pharmacokinetics following the fixed dose of 5 mCi administration of I 131 anti-B1 antibody was accounted for by patient-specific mCi administration in the therapeutic dose.

The main route of excretion was renal. In spite of the variability of total body clearance across individual patients, the elimination appeared to be nearly constant and was correlated with blood pharmacokinetics.

There were apparently no differences in the pharmacokinetics between patients who became HAMA-positive and those who remained HAMA-negative following the dosimetric or the therapeutic doses.

No drug-drug interactions were identified. Theoretically, however, there may be a drug-drug interaction with rituximab, or other CD20-binding radioimmunotherapeutic antibodies, as they bind to the same antigen. Caution should be taken with the concomitant administration of tositumomab with other myelopsuppressive agents as these agents could increase the degree of myelosuppression.

3.3.4 Radiation Dosimetry

Residence times of I 131 anti-B1 antibody were calculated for the kidney, liver, lung, spleen, bone marrow, blood, and total body. These values were used with the MIRDOSE 3.1 software to estimate doses to normal organs. Doses to normal organs were below normal tissue tolerated doses based on external beam radiation. Tumour doses based on a 75 cGy TBD were on average greater than 10 times the TBD. With a TBD of 75 cGy, no significant radiation-induced toxicity to organs was seen other than toxicity to bone marrow. No apparent differences in organ doses based on HAMA status were noted within or across clinical studies.

The radiation doses delivered to tumours provided evidence of the anti-tumour activity. The overall tumour dose was 895 cGy/75 cGy TBD. Tumour doses were consistent across subgroups, including by study, gender, and tumour grade.

It is noted that the dose-limiting toxicity for patients receiving I 131 anti-B1 antibody is hematologic. Of the patients receiving a 75 cGy TBD, 8 of 20 (40%) developed Grade IV thrombocytopenia, 6 of 20 (30%) developed Grade IV neutropenia, and 1 of 20 (5%) developed Grade IV anaemia. Of the patients receiving a 65 cGy TBD, 11 of 38 (29%) developed Grade IV thrombocytopenia, 10 of 38 (26%) developed Grade IV neutropenia, and 1 of 38 (3%) developed Grade IV anemia. Symptoms that might have been due to potential hematologic toxicity of the product in treated patients were in some cases difficult to distinguish from pathophysiologic effects of the disease (myelosuppression, neutropenia, thrombocytopenia, etc.) or pre-existing medical conditions (thyroid dysfunction).

In Non-Hodgkin's Lymphoma (NHL) patients who had previously received treatment with rituximab, a mouse-human chimeric monoclonal antibody directed against the CD20 antigen, nineteen patients (48%) experienced one or more Grade III/IV hematologic adverse events. The three most common hematologic Grade III/IV adverse events were ANC < 1000 cells/mm^3 (38%), WBC < 2000 cells/mm^3 (33%), and platelets < 50,000 cells/mm^3 (25%). Of the 32 thyroid stimulating hormone (TSH)-evaluable patients, 3 patients (9%) had an elevated TSH level or initiated thyroid medication following I 131 tositumomab antibody. Two of the 40

evaluable patients (5%) became HAMA positive. The median time to HAMA positivity was 9 days. One of 40 patients (3%) was diagnosed with myelodysplasia (MDS) after receiving I 131 tositumomab antibody. This patient had received prior fludarabine/cyclophosphamide and rituximab before enrolling in this study, received I 131 tositumomab antibody 2.2 years after NHL diagnosis, and was diagnosed with MDS 2.1 years after receiving the dosimetric dose. The annual incidence rate of MDS for patients in this study was 2.0% per year. It is concluded that treatment with I 131 tositumomab antibody was well tolerated and had substantial anti-tumour activity in patients who failed to respond to, or who relapsed/progressed following rituximab.

Overall, the clinical radiation dosimetry data is regarded as supportive with respect to the objective of the trials conducted with I 131 anti-B1 antibody.

3.3.5 Clinical Efficacy

The integrated analysis of submitted clinical studies provided a database of 250 patients with chemotherapy relapse or refractory indolent low grade and low grade transformed NHL. The group as a whole had several poor prognostic features with patients having advanced and bulky disease, in the majority of cases greater than 3-4 regimens to which they had become refractory, bone marrow involvement, and elevated levels of LDH. The overall efficacy analysis demonstrated a 45-68% general response rate and a complete response rate of 20-43% for I 131 tositumomab. More striking is the independent validation of long-term responders as shown in 78 patients.

Primary efficacy was compared to patients' previous response to therapy. This demonstrated a significantly greater number of patients achieving a response to I 131 tositumomab compared to their last chemotherapy. This is meaningful as it demonstrated a reversal of trends where refractory patients usually have less meaningful responses with subsequent therapy. Of interest is the efficacy in patients who have failed on prior rituximab therapy and the fact that prior response to rituximab might be a possible predictor to complete response but not overall response. This will need further evaluation in a post-marketing phase as it may allow for selection of those patients with the best chance to benefit from I 131 tositumomab.

The efficacy demonstrated in transformed low grade lymphomas is also noteworthy. Transformed low grade lymphomas are associated with a significant worsening of prognosis. They tend to be more resistant to therapy and are associated with poor median survival (<12 months). Treatment with I 131 tositumomab has demonstrated meaningful and durable efficacy and offers a useful therapeutic option in this group of patients.

3.3.6 Clinical Safety

The integrated safety review was based on a detailed analysis of a vast database. It included a total of 995 patients: 230 enrolled in the core clinical trials, and 765 enrolled in an expanded Access Study designed to provide wider access and experience with I 131 tositumomab.

As anticipated with radioimmunotherapy, hematological toxicity was dose limiting and was more prolonged than that observed following a single cycle of traditional chemotherapy. Regular monitoring has allowed better characterization of the duration and recovery of myelosuppression. This toxicity was manageable and required a low rate of supportive measures such as transfusions or administration of hematological growth stimulating factors. Of particular interest is the relatively low incidence of infections with neutropenia; this is likely due to the fact that toxicity of I 131 tositumomab was rarely associated with GI toxicity such as mucositis, as it is with chemotherapy toxicity. Non-hematological toxicity was generally uncommon and mild. HAMA conversion was also low, occurring in <10% of cases over a period of 15 months and the cumulative incidence of hypothyroidism was 12.5% over a four-year follow-up period.

A significant long-term concern associated with radioimmunotherapy is the development of myelodysplasia/leukemia. Long-term development of leukemia and myelodysplasia are known complications of radiation or alkylating-based chemotherapy in lymphomas. Following close monitoring of patients across the studies, the integrated safety analysis demonstrated an annualized incidence of myelodysplasia/leukemia of 1.6% per year (1.1% based on an independent review). Several cases of myelodysplasia pre-dated treatment with I 131 tositumomab therapy. Patients with myelodysplasia had typical characteristics of multiple exposures to alkylating agents, topoisomerase II inhibitors, fludarabine, and/or ionizing radiation, as well as distinctive chromosomal abnormalities usually associated with such prior therapies. Of interest is the lack of documentation of such a complication in the study of patients receiving I 131 tositumomab in previously untreated patients. It is not possible, with the experience to date, to determine the extent to which I 131 tositumomab may contribute to the incidence of myelodysplasia and acute leukemia in this patient population, and further follow-up and monitoring in a post-arketed phase is warranted.

3.4 Benefit/risk Assessment and Recommendation

3.4.1 Benefit/risk assessment

The efficacy results reported with tositumomab and I 131 tositumomab for treatment of CD20 positive relapsed or refractory, low grade, follicular, or transformed non-Hodgkin's lymphoma, including patients with rituximab-refractory non-Hodgkin's lymphoma, along with good safety and tolerability provide substantial support for Bexxar™ Therapy. This submission was also granted Priority Review due to the unmet medical need for an innovative therapy in the treatment of follicular lymphoma and it is determined that the benefits of Bexxar™ Therapy outweigh the risks associated with the use of this drug.

3.4.2 Recommendation

Based on the Health Canada review of data on quality, safety and efficacy, Health Canada considers that the benefit/risk profile of Bexxar™ Therapy is favourable in 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. The New Drug Submission complies with the requirements of sections C.08.002 and C.08.005.1 and therefore Health Canada has granted the Notice of Compliance pursuant to section C.08.004 of the *Food and Drug Regulations*.

4 SUBMISSION MILESTONES

Submission Milestone	Date
Pre-submission meeting	2003/03/07
Request for priority status	
Filed	2003/03/18
Approval issued by Director, Bureau of Radiopharmaceuticals and Evaluation Centre	2003/04/14
Submission filed	2003/05/21
Screening	
Screening Deficiency Notice issued	2003/07/14
Response filed	2003/07/30
Screening Acceptance Letter issued	2003/07/31
Update Notice issued	2004/01/29
Response filed	2004/03/01
Review	
Quality Evaluation complete	2005/08/10
Clinical Evaluation complete	2005/07/18
Labelling Review complete	2005/08/09
NOC issued by Director General	2005/08/18