CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125011

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **July 2, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Approved Labeling

Participants: **FDA/CBER/OTRR**: Karen D. Jones
Corixa: Jill Henrich

DISCUSSION:

I called Jill Henrich of Corixa in response to the 6-30-03 and 7-1-03 telephone calls held with Jill Henrich of Corixa regarding mistakes in the final draft labeling that was approved for the BLA:

- The povidone specification (5%-6%) was not correct; it should have been [redacted]). I stated that the CMC reviewer had confirmed that the data supporting the [redacted] % range for the povidone specification had indeed been reviewed and has been documented in the BLA CMC review (and is acceptable). FDA requests that Corixa implement the corrections in the final printed labeling and submit the changes in the first annual report for the product. b(4)
- The correct name of the contract manufacturer, McKesson Bioservices should be included in the final printed labeling and submitted as a change in the annual report.
- The correct dates for clinical PMCs #1 and #3 will be listed in the PMC tracking database maintained by FDA and will be the dates for which Corixa will be responsible.

Ms. Henrich agreed to implement the labeling changes in the first printing of the final printed labeling and to submit the changes in the annual report for the product.

Ms. Henrich also asked that I contact the product reviewer about storage conditions and expiration dating for the PBDS. She stated that all stability protocols and data for storage at 2-8°C for 12 months had been submitted to the BLA and that there were also data to support storage at -20°. She stated that once the lots produced in March, stored at 2-8°C have expired, all of the PBDS would then be stored frozen. I responded that I would bring this to the attention of the CMC reviewer who will then follow-up with Corixa on this topic.

The call concluded.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **July 1, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Approval Letter

Participants: **FDA/CBER/OTRR**: Karen D. Jones
Corixa: Jill Henrich

DISCUSSION:

Jill Henrich of Corixa called regarding the June 30, 2003 approval letter for Tositumomab and Iodine I 131 Tositumomab and in follow-up to the June 30, 2003 teleconference regarding the specification for povidone. She stated that Amendment 055 of the BLA contained the validation data for an additional release test method that has the relaxed povidone specification. She also stated that the name of one of the contract manufacturers was not correct in the labeling; the firm is called McKesson Bioservices, not McKesson Biosciences. In addition, the dates for 2 PMCs are not correct in the approval letter (the numbers are transposed): clinical PMC # 1 in the letter is listed as having a study completion date of September 7, 2003, whereas the correct date is September 3, 2007, and clinical PMC #3 should list the study completion date as March 31, 2008. I stated that I would bring all of these items to the attention of the appropriate FDA staff and would respond to Corixa as soon as possible.

The call concluded.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **June 30, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Approved Labeling

Participants: **FDA/CBER/OTRR**: Karen D. Jones
Corixa: Jill Henrich

DISCUSSION:

Jill Henrich of Corixa called to inform FDA that Corixa had noted a mistake in the final draft labeling that was approved for the BLA. The povidone specification (5%-6%) was not correct; it should have been 4.4%-6.6%. The revised specification has been reviewed and found acceptable by the FDA CMC reviewer. Ms. Henrich indicated that this information is located on the dose pot labels and in the description section of the package insert label. I responded that I would have to discuss this with the CMC reviewer to confirm that the revised specification was reviewed and was determined to be acceptable and also with management to determine how to handle the correction in the labeling. The call concluded.

Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: Establishment Inspection File (EIF)
STN Number 125011/0

From: Deborah Trout, Biologist, Inspector, DMPQ, HFM-675

Subject: Recommendation for licensure of Corxica's facility located in South San Francisco, California for the primary responsibility of final release and disposition of all Anti-B1 Antibody and Iodine-131 Anti-B1 Antibody Bulk Drug Substance, Packaged Bulk Drug Substance, and Drug Product based on the pre-approval inspection.

Date: June 23, 2003

I have reviewed and evaluated the April 29, 2003, responses which were in reply to the FDA-483 List of Observations dated April 11, 2003. The corrective actions, which have been taken to correct the deficiencies noted during the pre-approval inspection, appear to be adequate. Follow-up on all observations should be considered during the next facility inspections.

Therefore, I recommend that the product be considered for licensure on the basis of the pre-approval inspection, provided that all other considerations are in compliance with applicable regulations.

Deborah Trout, CBER, DMPQ HFM-675

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

DATE: June 27, 2003

FROM: Karen D. Jones and LCDR Craig Doty, Pharm.D.
Regulatory Project Managers
Division of Application Review and Policy, HFM-588
Office of Therapeutics Research and Review

TO: STN BL 125011/0

SUBJECT: SBA Equivalent for

- Product: Tositumomab and Iodine I 131 Tositumomab (BEXXAR®)
- Manufacturer: Corixa Corporation
- License Number: 1614

Indications and Usage

Tositumomab and Iodine I 131 Tositumomab are indicated for the treatment of patients with CD20 positive, follicular, non-Hodgkin's lymphoma, with and without transformation, whose disease is refractory to Rituximab and has relapsed following chemotherapy.

Dosage Form, Route of Administration, and Recommended Dosage

BEXXAR® is marketed as two separate components administered in two discrete steps: 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 7-14 days after the dosimetric step.

Dosimetric Component:

- Tositumomab: One 35 mg single-use and two 225 mg single-use vials containing 14 mg/mL Tositumomab, 10% (w/v) maltose, 145 mM sodium chloride, 10mM phosphate and Water for Injection, USP and
- Iodine I 131 Tositumomab: A single-use vial containing not less than 20 mL Iodine I 131 Tositumomab with nominal protein and activity concentrations of 0.1 mg/mL and 0.61 mCi/mL at calibration, respectively. The formulation contains 5.0%-6.0% (w/v) povidone, 1-2 mg/mL maltose, 0.85-0.95 mg/mL sodium chloride, and 0.9-1.3mg/mL ascorbic acid. The pH is approximately 7.0.

Therapeutic Component:

- Tositumomab: One single-use 35 mg vial and two single-use 225 mg vials containing 14 mg/mL Tositumomab, 10% (w/v) maltose, 145 mM sodium chloride, 10mM phosphate and Water for Injection, USP and
- Iodine I 131 Tositumomab: A single-use vial containing not less than 20 mL Iodine I 131 Tositumomab at nominal protein and activity concentrations of 1.1 mg/mL and 5.6 mCi/mL at calibration, respectively. The formulation contains 5.0%-6.0% (w/v) povidone, 9-15 mg/mL maltose, 0.85-0.95 mg/mL sodium chloride, and 0.9-1.3mg/mL ascorbic acid. The pH is approximately 7.0.

- Contains no preservatives.
- For intravenous use.

Basis for Approval

The following reviews, filed in the CBER correspondence section of the license file for STN 125011/0, comprise the SBA equivalent for this application:

Discipline	Reviewer Name	Date
CMC (Product, Facility, etc.)	Terrye Zaremba, Ph.D.	June 27, 2003
	Walter Lange	February 20, 2001
	Deborah Trout	June 23, 2003
	Leon Epps	March 6, 2001
		February 28, 2002
		November 8, 2002
Clinical (Safety and Efficacy)	Kaushik Shastri, M.D.	June 26, 2003
Non-clinical Pharm/Tox	Martin Green, Ph.D.	June 25, 2003
Clinical Pharmacology	Martin Green, Ph.D.	June 25, 2003
Statistical	Satish Misra, Ph.D.	June 27, 2003
Bioresearch Monitoring	Mary Andrich, M.D.	June 20, 2003

S:\Doty\Tositumomab\SBA Equivalent Memo.doc

Jones, Karen

From: Henrich, Jill [Jill_Henrich@corixa.com]
Sent: Friday, June 27, 2003 5:58 PM
To: Karen Jones (E-mail)
Cc: Henrich, Jill
Subject: Draft layout of PI

BEXXAR layout.pdf
(100 KB)

Karen,

Attached please find a first draft of our PI layout. As noted in the fax cover sheet - this is draft, but gives you an idea of the layout. We expect that the layout will be on ~18-3/4" X 9-1/2" paper, with 6 columns of information on the front and on the back. Each page in the pdf provides 2 colums worth of data - 6 pages total.

Let me know if you have any questions.
Jill
<<BEXXAR layout.pdf>>

6 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 3

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **June 26, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

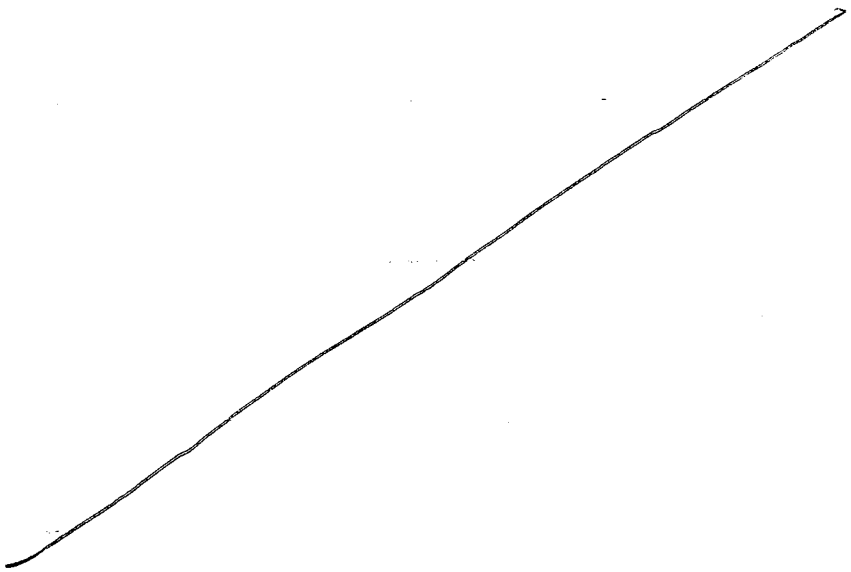
Subject: Labeling

Participants: FDA/CBER/OTRR: Karen D. Jones,

Corixa Corporation: J. Henrich, P. Stewart, M. Krieger,
Glaxo, Smith, Kline: R. Frankovick

DISCUSSION:

The purpose of the call was to discuss issues with the package insert and other labels. The following items were discussed:
Package Insert:



b(4)

9 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 4

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **June 26, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Labeling

Participants: FDA/CBER/OTRR: Karen D. Jones, Karen D. Weiss

Corixa Corporation Representatives: C. Jacobs and Monica Krieger

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DISCUSSION:

The purpose of the call initiated by Corixa was to obtain clarification on some of the requested labeling revisions discussed in a teleconference earlier this same date between Corixa representatives and Karen Jones, RPM.

- Secondary Leukemia/MDS subsection: Corixa did not understand FDA proposals. Dr. Weiss indicated that the way the section is currently written is confusing (i.e., are the numbers the actual observed incidence or are they Kaplan-Meier estimates of the projected rate if everyone lives); therefore FDA has proposed clarifying revisions. Corixa agreed to try to rewrite this section.

The call concluded.

Jones, Karen

From: Krieger, Monica [krieger@corixa.com]
Sent: Thursday, June 26, 2003 3:55 PM
To: 'jonesk@cber.fda.gov'; 'weissk@cber.fda.gov'; 'keegan@cber.fda.gov'
Cc: Henrich, Jill; Rich Francovitch (E-mail)
Subject: Bexxar Package Insert

CorixaPI6-26-03rev .doc (337 KB...

<<CorixaPI6-26-03rev.doc>> Attached please find another revision to the package insert. I accepted the changes discussed earlier today that we agreed on. I have marked changes that were made based on our discussion.

We are ready to finalize as soon as we receive your comments on the following

1. A revised section on B-cells (lines 142-160)
2. Your comments on our changes to the MDS section (lines 544-559) based on the discussion with Dr. Weiss. Note we have paralled this change by revising lines 565-571.
3. We have revised in the infusion section based on this morning's discussion. Jill will be sending you the Workbook. We have added references to the figures in the workbook.

Thank you.
Regards,
Monica

48 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 5

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **June 25, 2003 email communication**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Revised PMCs, Training Manual, QA Plan

Participants: FDA/CBER/OTRR: George Mills, M.D.

Corixa Corporation: Monica Krieger, Ph.D.

DISCUSSION:

Please see attached email communication between Dr. George Mills of FDA and Monica Krieger of Corixa Corporation regarding revised PMCs, Training Manual, and QA Plan.

Attachment: Email response from Dr. Krieger of Corixa Corporation, June 25, 2003

Jones, Karen

From: Krieger, Monica [krieger@corixa.com]
ent: Wednesday, June 25, 2003 8:45 PM
To: George Mills (E-mail); 'jonesk@cber.fda.gov'; 'keeganp@cber.fda.gov'
Cc: Henrich, Jill


commitment letter6-25-03.pdf


SiteTrainingManualforBexxarThe...


Corixa PMC ompliance Plan 25J.

Attached please find the following documents:

1. Training Manual: Changes have been made so that the training manual is consistent with the revision to the package sent to FDA today, 25 June 2003. Please note that we have not included the changes to the appendices based on the agreement between Dr. Mills and Jill Henrich. The appendices will be revised to be consistent with the insert.
2. QA Plan: Suggestions and comments from our conference call with Dr. Mills have been incorporated in this draft plan.
3. Post-marketing Commitments: We have attached a letter with the post-marketing commitments including a table of protocol names and numbers.

In our phone call today, Dr. Mills requested that we provide further information on our rationale for including the term "drug" or "biologic" in the insert. b(4)

Including the descriptive term in the package insert for BEXXAR will help reduce any confusion or ambiguity in the minds of payers and physicians. Many products with a radioactivity component are diagnostics. BEXXAR is an unusual product: it is a therapy with numerous components delivered separately over a 14-day period. Physicians and payers may be confused about the appropriate characterization of BEXXAR as a single drug regimen. In an effort to ensure that patient access to the BEXXAR therapeutic regimen is not impeded by reimbursement issues, we request that the description section of the package insert include "the BEXXAR therapeutic regiment (Tositumomab and Iodine I 131 Tositumomab) is an _____ " <<commitment letter6-25-03.pdf>> <<SiteTrainingManualforBexxarTherapy_v16-25-03.doc>> <<Corixa PMC Compliance Plan 25JUN03.doc>>

Sorry this took longer than we thought. Thanks for all your help. I will try to be in early in the morning; but if you have any questions, please feel free to call my house anytime after 8:30 AM Eastern (5:30 AM PST)

Monica S. Krieger, Ph.D.
Vice President, Regulatory Affairs
Corixa Corporation
1124 Columbia St.
Seattle, WA. 98104
krieger@corixa.com
206-754-5729

addressee you should not disseminate, distribute or copy this message. Thank you.

Corixa

Corporate Headquarters
1124 Columbia Street, Suite 200
Seattle, WA 98104 USA
Telephone: 206.754.5711
Facsimile: 206.754.5715
Website: www.corixa.com
E-mail: info@corixa.com

25 June 2003

Glenn Jones (HFM-585)
Division of Applications Review and Policy
Office of Therapeutics Research and Review
Center of Biologics Evaluation and Research
Food and Drug Administration
c/o Document Control Center (HFM-99)
1401 Rockville, Pike Suite 200N
Rockville, MD 20852-1448

RE: BLA Submission Tracking No. 125011/0
BEXXAR® Therapeutic Regimen (Tositumomab, Iodine I 131 Tositumomab)
Chemistry Manufacturing and Controls (CMC) Post Marketing Commitments

Dear Dr. Jones:

The following are Corixa Corporation's Clinical Post Marketing commitments.

1) We have agreed to conduct an open-label efficacy trial of Rituximab versus BEXXAR therapeutic regimen in patients with lymphoma who have received at least one and no more than two prior chemotherapy regimens, and who are appropriate candidates for systemic therapy (Study CCBX001-049). The primary objective of this study is demonstration of a longer event free-survival in patients treated with Tositumomab and Iodine I 131 Tositumomab as compared to those receiving Rituximab.

   We have committed to submission of the final protocol (Study CCBX001-049) for SPA review by 15 August 2003; initiation of patient accrual by 02 January 2004; and submission of final study report by 09 May 2008.

2) We have agreed to conduct an open-label trial of Zevalin versus the BEXXAR therapeutic regimen in patients with lymphoma who have failed at least 3 regimens, one of which was Rituximab (Study CCBX001-053). The primary endpoint of the trial is overall safety. The trial will be designed to demonstrate non-inferiority with regard to efficacy.

   We have committed to submission of the final protocol (CCBX001-053) for SPA review by 15 September 2003; initiation of patient accrual by 01 January 2004; and submission of final study report by 01 February 2007.

3) We have agreed to conduct a single arm, open label, multicenter, Phase 2 trial (Study CCBX001-054) evaluating the pharmacokinetics, safety, and efficacy of retreatment with the BEXXAR therapeutic regimen in patients who have had a duration of response of at least 6 months in Studies CCBX001-049 and CCBX001-053. The primary objective of the study is to compare the pharmacokinetics associated with retreatment and with initial treatment. In

addition, the study will assess the safety and efficacy of retreatment with the BEXXAR therapeutic regimen.

We have committed to submission of the final protocol (CCBX001-054) by 16 October 2003; initiation of patient accrual by 29 March 2004; and submission of a final study report by 29 September 2008.

4) We have agreed to conduct a companion study (Study CCBX001-055) to evaluate the use of prophylactic vaccines in patients with relapsed, follicular, B- cell non- Hodgkin's lymphoma receiving BEXXAR or Rituximab while participating in the Study CCBX001-049. This companion study will assess the impact of the anti-lymphoma therapies on development of protective antibody titers to recall and new antigens.

   We have committed to submission of the final companion protocol (CCBX001-055) for review by 29 August 2003 and to the same major milestones as for Study CCBX001-049: initiation of patient accrual by 02 January 2004 and submission of a final study report by 09 May 2008.

5) We have agreed to collect information on patients who become seropositive for HAMA after treatment on studies CCBX001-049 and CCBX001-053. The impact of HAMA on the following will be evaluated: ability of patients to receive subsequent therapy in which a component of the therapy was a murine or partially murine protein; alteration in the safety and/ or efficacy of subsequent therapy; interference with in vivo or in vitro diagnostic assays that utilize murine monoclonal antibodies; and ability of patients to undergo in vivo diagnostic procedures.

   Data will be integrated from the two studies and submitted to the Agency as a separate stand-alone report (CCBX001-56). We have committed to filing this report by 09 September 2008.

6) We have agreed to conduct a retrospective study (Study CCBX001-057), and a prospective sub-study (Study CCBX001-058) to determine the prevalence of interference of HAMA with diagnostic in vitro assays and the relationship, if any, between interference and level of HAMA.

   In the retrospective study (Study CCBX001-057), stored sera samples will be assayed from patients who became HAMA seropositive following BEXXAR as initial therapy. We have committed to the following dates for the retrospective study: submission of final protocol to the FDA by 30 September 2003; assay development completed by 31 December 2003; assay sera by 28 February 2004; complete data analysis by 31 March 2004; and submission of the final study report by 03 June 2004.

   The prospective sub-study (CCBX001-058) will be conducted on sera from patients in studies CCBX001-049 and CCBX001-053 who become HAMA seropositive following treatment. We have agreed to the following dates for the prospective sub-study: submission of the final prospective sub-study protocol (CCBX001-058) to the FDA by 30 October 2003; and; submission of the final study report by 01 January 2006.

7) We have agreed to collect information regarding the occurrence of myelodysplasia/acute leukemia in studies involving BEXXAR, including studies in BLA 125011.0; other studies not contained in the BLA; and those studies that are being designed to address post-marketing commitments or other regulatory requirements. We will submit this information as an integrated analysis designated as CCBX001-059.

   The integrated analysis plan (CCBX001-059) for the annual progress report will be submitted by 30 September 2003. We will provide analyses of the incidence of MDS/ AML across all studies based on this plan (CCBX001-059) annually.

8) We have developed policies and procedures, such that the Corixa/GSK will accept orders for the BEXXAR therapeutic regimen only from sites where both the site and the authorized physician have successfully completed the on-site training for qualification or have completed the certification program. We have agreed to conduct a quality assurance (QA) assessment after approval to evaluate the effectiveness of the training program for clinical sites and compliance of the BEXXAR Service Center with required procedures.

   A complete plan (CCQA001-01) for the quality assurance program will be submitted by 30 September 2003 and a report will be provided at the time of the annual update on post-marketing commitments.

We have also attached a table summarizing the commitments which includes the names of the protocols and the dates.

Sincerely,

Monica S. Krieger

Monica Krieger, Ph.D.
Vice President
Regulatory Affairs

PMC	Number	Protocol Name	Commitment	Date
1	CCBX001-049	A Multi-center, Randomized, Phase III Study of Rituximab versus Iodine I 131 Tositumomab Therapy for Patients with Relapsed Follicular non-Hodgkin's Lymphoma	o final protocol for SPA review o initiation of patient accrual o submit final study report	o 15 August 2003 o 02 January 2004 o 09 May 2008
2	CCBX001-053	A Multi-center, Randomized, Phase III Study of Iodine I 131 Tositumomab Therapy versus Ibritumomab Tiuxetan Therapy for Patients with Relapsed or Transformed Follicular non-Hodgkin's Lymphoma	o final protocol for SPA review o initiation of patient accrual o submit final study report	o 15 September 2003 o 01 January 2004 o 01 February 2007
3	CCBX001-054	A Multi-center Phase II Study of Retreatment with Iodine I 131 Tositumomab in Patients with Relapsed Follicular or Transformed Follicular non-Hodgkin's Lymphoma who Responded for at least Six Months to Initial Iodine I 131 Tositumomab Therapy	o final protocol for SPA review o initiation of patient accrual o submit final study report	o 16 October 2003 o 29 March 2004 o 29 September 2008
4	CCBX001-055	A Companion Study to Study CCBX001-049 to Evaluate Prophylactic Vaccines in Patients with Relapsed Follicular non-Hodgkin's Lymphoma	o final protocol for SPA review o submit final study report	o 29 August 2003 o 09 May 2008
5	CCBX001-056	A Report Evaluating the Impact of HAMA on Subsequent Therapy and Diagnostic Assays in Patients Following Iodine I 131 Tositumomab in Studies CCBX001-049 and CCBX001-053	o submit final report	o 08 September 2008
6	CCBX001-057	A Retrospective Study to Determine the Prevalence of Interference of HAMA with Diagnostic *In Vitro* Assays in Samples from Patients with HAMA Following Iodine I 131 Tositumomab	o final protocol for SPA review o complete assay development o completion of data analysis o submit final study report	o 30 September 2003 o 31 December 2003 o 31 March 2004 o 03 June 2004
6	CCBX001-058	A Prospective Report Determining the Prevalence of Interference of HAMA with Diagnostic *In Vitro* Assays in Patients with HAMA Following Iodine I 131 Tositumomab in Studies CCBX001-049 and CCBX001-053	o final protocol for SPA review o submit final study report	o 30 October 2003 o 01 January 2006
7	CCBX001-059	An Integrated Analysis of Myelodysplasia/Acute Leukemia in Patients Following Administration of the BEXXAR Therapeutic Regimen	o submit analysis plan o annual updates	o 30 September 2003 o yearly
8	CCQA001-01	A Corixa/GSK Compliance Plan of the Administration of the BEXXAR Therapeutic Regimen	o submit QA plan o submit report	o 30 September 2003 o As part of PMC update

5 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 6

Jones, Karen

From: Thurber, Steven on behalf of CBER Complicheck
Sent: Wednesday, June 25, 2003 11:50 AM
To: Trout, Deborah
Cc: CBER Complicheck; Kelley, Cynthia; Lange, Walter; Jones, Karen; Harley, Patricia
Subject: Compliance Check

Firms:
1) Corixa Corporation
600 Gateway Blvd.,
South San Francisco, CA 94080-7014

STN 125011/0 for Bexxar™ (tositumomab, iodine I 131 tositumomab) used in the treatment of patients with relapsed or refractory low-grade or transformed low-grade CD-20-positive, B-cell non-Hodgkin's lymphoma. Primary responsibility for the final release and disposition of all Anti-B1 Antibody and Iodine-131 Anti-B1 Antibody Bulk Drug Substance (BDS), Packaged Bulk Drug Substance (PBDS), and Drug Product (DP).

A PreLicense Inspection of Corixa Corp., for the above application was conducted from 4/10-11/03 and the inspection was classified Voluntary Action Indicated (VAI). In addition, the close out memo for this inspection was dated 6/23/03.

2) Boehringer Ingelheim Pharma KG.
Birkendorfer Strasse 65
Biberach, Germany
FEI Number: 3002806518
CFN: 9610551
Summary: Manufacture of Anti-B1 Antibody BDS, PBDS, and [redacted]

b(4)

A memo waiving the Prelicense Inspection for Boehringer Ingelheim Pharma KG was signed per SOPP 8410 on 1/30/03. Previously, Team Biologics conducted an inspection of the facility from 6/10-20/02 and the inspection was classified VAI.

3) MDS Nordion, Inc.
447 March Road
Kanata, Ontario
Canada K2K 1X8
FEI Number: 3001092088
CFN: 9617842
Summary: [redacted], manufacture, [redacted], packaging, and [redacted] of Iodine-131 Anti-B1 Antibody DP dosimetric dosage form and therapeutic dosage form.

A PreLicense Inspection of MDS Nordion, Inc., for the above application was conducted from 3/17-19/03 and the inspection was classified VAI. In addition, the close out memo for this inspection was dated 6/6/03.

4) McKesson BioServices
Pharmaceutical Services Division
14665 Rothgeb Drive
Rockville, MD 20850
Summary: [redacted] Anti-B1 Antibody PBDS and BDS; [redacted] packaging, [redacted], and [redacted] of Anti-B1 [redacted]

A PreLicense Inspection of McKesson BioServices for the above application was conducted on 3/12/03. The inspection was classified No Action Indicated (NAI). In addition, the close out memo for this inspection was dated 6/17/03.

Therefore, the Office of Compliance and Biologics Quality, Division of Case Management does not object to the approval of this application.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **June 25, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Package Insert Labeling; Training Manual; Clinical PMCs ; QA Program

Participants: FDA/CBER/OTRR: George Mills, MD, Karen D. Jones, Patricia Keegan. MD

Corixa Corporation: M. Krieger and Jill Henrich

DISCUSSION:

A telecon was held today in follow-up to the June 24, 2005 telecon between Dr. George Mills of FDA and Corixa. Changes to the package insert, training manual and PMCs were discussed. Corixa agreed to submit a revised package insert containing agreed-upon revisions, updated PMCs, updated training manual and QA program.

Addendum: Afternoon of June 25, 2003- email submission from Corixa in response to FDA request: revised package insert (see attachment-June 25, 2003 email from Monica Krieger)

Jones, Karen

From: Mills, George
Sent: Wednesday, June 25, 2003 2:45 PM
To: 'Krieger, Monica'
Cc: Henrich, Jill; Keegan, Patricia; Jones, Karen
Subject: RE: Bexxar Package Insert

Monica,

When will you be able to provide the updated PMCs, Training Manual, and QA program?

Thanks,

George

-----Original Message-----
From: Krieger, Monica [mailto:krieger@corixa.com]
Sent: Wednesday, June 25, 2003 2:10 PM
To: George Mills (E-mail); 'keegan@cber.fda.gov'; 'jonesk@cber.fda.gov'
Cc: Henrich, Jill
Subject: Bexxar Package Insert

<<CorixaPI6-25-03rev.doc>>
Karen/George/Pat

Attached is the revised package insert. We accepted changes that were agreed on during our telecon. Revisions based on our discussions are noted in revision tools. Please note the following:

The word drug is still in the insert. We will be providing information from GSK later today as requested during our telecon with Dr. Mills this morning.

2. We have not revised the wording regarding B lymphocytes. It was our understanding that you would make this change (lines 142-159).

3. We still need to agree on the wording regarding "[redacted] on lines 551 and 557. b(4)

4. We have removed the word [redacted] when determining residual activity.

5. Some minor changes were made for consistency (i.e. capitalization in titles)

Thanks.
Monica

Jones, Karen

From: Krieger, Monica [krieger@corixa.com]
nt: Wednesday, June 25, 2003 2:10 PM
o: George Mills (E-mail); 'keegan@cber.fda.gov'; 'jonesk@cber.fda.gov'
Cc: Henrich, Jill
Subject: Bexxar Package Insert

CorixaPI6-25-03rev .doc (335 KB...

<<CorixaPI6-25-03rev.doc>>

Karen/George/Pat

Attached is the revised package insert. We accepted changes that were agreed on during our telecon. Revisions based on our discussions are noted in revision tools. Please note the following:

1. The word drug is still in the insert. We will be providing information from GSK later today as requested during our telecon with Dr. Mills this morning.

2. We have not revised the wording regarding B lymphocytes. It was our understanding that you would make this change (lines 142-159).

3. We still need to agree on the wording regarding " ———— on lines 551 and 557. b(4)

4. We have removed the word ———— when determining residual activity.

. Some minor changes were made for consistency (i.e. capitalization in titles)

Thanks.
Monica

32 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 7

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **June 25, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Package Insert Labeling-Layout

Participants: FDA/CBER/OTRR: Karen D. Jones

Corixa Corporation: Jill Henrich

DISCUSSION:

On June 25, 2005, I contacted Jill Henrich to request a mock up package insert in order to see how the sections will be laid out and to assess the font size. Ms. Henrich responded that she has a draft concept of the layout (with an early version of the package insert) and she noted that Corixa is going to refrain from providing the draft labeling to their printer until FDA indicates that it is acceptable.

This same date, Ms. Henrich sent the mock up label via email (see attachment).

Follow-up: On June 27, 2005, Ms. Henrich followed up with a first draft of the proposed package insert layout. It is included here as an attachment.

Jones, Karen

From: Henrich, Jill [Jill_Henrich@corixa.com]
Sent: Wednesday, June 25, 2003 7:53 PM
To: Karen Jones (E-mail)
Cc: Henrich, Jill
Subject: PI layout

PI layout.pdf

Karen,

Attached is a pdf file that I created from a VERY old PI (so don't review for content) that we had sent to a printer to get ideas regarding layout/printing, etc... I believe this is what you are requesting to review. I think it may give you an idea of what the PI may look like - realize that we are not bound to this as we have not sent anything to our printers as of yet. Obviously - feedback at this point would be appreciated.

Jill
<<PI layout.pdf>>

1 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓
_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 8

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **June 24, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Labeling

Participants: FDA/CBER/OTRR: Karen D. Jones,

Corixa Corporation: J. Henrich

DISCUSSION:

Jill Henrich of Corixa called about the labeling for the Corixa Tositumomab product in follow-up to the June 23, 2003 telephone conversation. She stated that the colored bar on the therapeutic labels that when emailed appeared to be very dark, thus making font difficult to read, is actually light pink. The font on the colored bar will be black and will be easy to read. In addition, the words, "Bexxar" and "Corixa" will also be in black font.

Ms. Henrich also noted that Corixa will submit revised PMCs by both facsimile and hard (electronic) copy for the file.

The call concluded.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **June 24, 2003 email communication**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Stability Data for PBDS and DP; CMC PMCs

Participants: FDA/CBER/OTRR: Terrye Zaremba, Ph.D.

Corixa Corporation: J. Henrich

DISCUSSION:

Please see attached email communication between Dr. Terrye Zaremba of FDA and Jill Henrich of Corixa Corporation regarding stability data for packaged bulk drug substance and drug product and CMC PMCs.

Jones, Karen

From: Zaremba, Terrye
Sent: Wednesday, June 25, 2003 5:21 PM
To: Jones, Karen
Subject: FW: Stability Data for DP, PBDS

Importance: High

Corixa post
ipp.rev.doc (25 KB..

Karen see attachment at the bottom

-----Original Message-----
From: Zaremba, Terrye
Sent: Tuesday, June 24, 2003 5:48 PM
To: 'Henrich, Jill'
Subject: RE: Stability Data for DP, PBDS
Importance: High

Jill, everything looks OK. When you FAX the tables, please indicate in the cover letter that the specs were revised & indicate the new ones. I have attached the revised committments. Hopefully these will be OK with the bureaucrats.

-Terrye

----Original Message-----
From: Henrich, Jill [mailto:Jill_Henrich@corixa.com]
Sent: Tuesday, June 24, 2003 3:33 PM
To: Terrye Zaremba (E-mail); Karen Jones (E-mail)
Cc: Henrich, Jill
Subject: Stability Data for DP, PBDS

Terrye,

Attached are 2 tables of stability data - the PBDS and DP data requested yesterday. Please note that the tables do not reflect the revised EOSL specs- but the spec that was in use when the study was started.

Jill
<<stab tables DP - BIP.doc>> <<stab tables, PBDS - BIP.doc>>

9 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 9

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **June 24, 2003 communication**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Specifications

Participants: FDA/CBER/OTRR: Terrye Zaremba, Ph.D.

Corixa Corporation: J. Henrich

DISCUSSION:

Please see attached email communication dated 6/24/03 between Jill Henrich of Corixa Corporation and Dr. Terrye Zaremba of FDA containing information requested 6/23/04 by Dr. Zaremba regarding specifications for BDS and DP and proposed CMC postmarketing commitments.

Jones, Karen

From: Henrich, Jill [Jill_Henrich@corixa.com]
Sent: Tuesday, June 24, 2003 1:05 AM
To: Terrye Zaremba (E-mail); Karen Jones (E-mail)
Cc: Henrich, Jill
Subject: CMC issues


CMC PMC.doc


specifications.doc

Hi Terrye/Karen,

Attached please find a table of specifications. I have started to write in the serial numbers of the BLA where we made the change - but at least you can work off of this file to let you know what all of the current specifications are (for all of the products). I am also providing you an initial draft of the CMC PMC commitments so that you can comment and I can continue working on them, revising with your feedback (or let me know if this is adequate).

We have requested the data and information on the PBDS and BDS lots. I will let you know in the morning what their response was. I'll give Karen a call later on - we'll continue moving forward today (Tuesday).

Jill
<<CMC PMC.doc>> <<specifications.doc>>

7 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 10

Jones, Karen

From: Trout, Deborah
Sent: Tuesday, June 24, 2003 7:45 AM
To: CBER Complicheck
Cc: Sausville, Robert; Jones, Karen; Lange, Walter
Subject: requesting complicheck

Importance: High

I would like to get a compliance check for the following (Action Due 6/27/03):

Summary: Corixa has submitted to the Center for Biologics Evaluation and Research (CBER) a biologics license application (BLA), STN 125011/0 for Bexxar™ (tositumomab, iodine I 131 tositumomab) used in the treatment of patients with relapsed or refractory low-grade or transformed low-grade CD-20-positive, B-cell non-Hodgkin's lymphoma.

Corixa Corporation
600 Gateway Blvd.,
South San Francisco, CA 94080-7014

- Primary responsibility for the final release and disposition of all Anti-B1 Antibody and Iodine-131 Anti-B1 Antibody Bulk Drug Substance (BDS), Packaged Bulk Drug Substance (PBDS), and Drug Product (DP).

A prelicense inspection of Corixa Corp., for the above application was conducted from 4/10-11/03. All issues were resolved and the inspection was closed on 6/23/03. EIR and signed inspection closeout memo has been forwarded to PIB.

closeoutinspeccorixa.doc

Boehringer Ingelheim Pharma KG. b(4)
Birkendorfer Strasse 65
Biberach, Germany
FEI Number: 3002806518
CFN Number: 9610551

- Manufacture of Anti-B1 Antibody BDS, PBDS, and [redacted]

A memo waiving the Prelicense Inspection for Boehringer Ingelheim Pharma KG was signed per SOPP 8410 on 1/30/03 (see attached signed waiver memo).

BIpharmaWaiverMemosigned.doc

MDS Nordion, Inc.
447 March Road
Kanata, Ontario
Canada K2K 1X8
FEI Number: 3001092088
CFN Number: 9617842

- [redacted] of Anti-B1 Antibody PBDS; manufacture, [redacted], packaging, and [redacted] of Iodine-131

Anti-B1 Antibody DP dosimetric dosage form and therapeutic dosage form.
A prelicense inspection of MDS Nordion, Inc., for the above application was conducted from 3/17-19/03. All issues were resolved and the inspection was closed on 6/06/03.

lange memo 6-6
Nordion.doc

McKesson BioServices
Pharmaceutical Services Division
14665 Rothgeb Drive
Rockville, MD 20850
No FEI or CFN Number

- [redacted] and [redacted] of Anti-B1 Antibody PBDS and BDS; [redacted], packaging, [redacted], and [redacted] of Anti-B1 Antibody DP.

lange memo 6-17
mckesson.doc

b(4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **June 24, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Plan for QA Assessment of Training; Ordering; PMC Summary

Participants: FDA/CBER/OTRR: George Mills, M.D.

Corixa Corporation: M. Krieger and Jill Henrich

DISCUSSION:

A telecon was held today to discuss the information sent to FDA via email on June 23, 2003, by Dr. Monica Krieger of Corixa Corporation (see attached email). Dr. Mills requested the following:

- changes to the training manual consistent with the revisions to the package insert; the appendices will also be revised
- revisions to the QA plan
- PMCs including a listing of the protocol names and numbers

Jones, Karen

From: Krieger, Monica [krieger@corixa.com]
Sent: Monday, June 23, 2003 8:28 PM
To: George Mills (E-mail); 'jonesk@cber.fda.gov'
Cc: Henrich, Jill
Subject: Corixa information


PMC Compliance Plan 23JUN03.do...


Comment _finalrev.doc (189 K


PMC -summary.doc (35 KB)

Attached please find copies of the folowing

<<PMC Compliance Plan 23JUN03.doc>> <<Comment 2a_finalrev.doc>> <<PMC -summary.doc>>

1. Plan for QA assessment of training
2. Revision of comment 2a re: centralized ordering
3. Summary of Post-marketing committments

Regards,

Monica .

15 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 11

Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

Date: June 23, 2003

To: Terrye Zaremba, BLA Committee Chair, HFM-594

From: Deborah Trout, BLA Committee Member, HFM-675

Through: Cynthia L. Kelley, Branch 1 Chief, HFM-675

Subject: Recommend approval of Biologics License Application (BLA) from Corixa Corporation, STN 125011/0 for Bexxar™ (tositumomab, iodine I 131 tositumomab) used in the treatment of patients with relapsed or refractory low-grade or transformed low-grade CD-20-positive, B-cell non-Hodgkin's lymphoma.

I have completed my review of the following responses relating to STN number 125011/0: October 30, 2002, response to the Complete Review Letter dated March 12, 2002; and April 03, 2003, response to the Discipline Review Letter dated March 03, 2003, and have found the information submitted to be adequate to determine that this application be approved at this time. In addition, I'm recommending approval based on my review of responses submitted to the FDA Forms 483 for the Pre-Approval Inspections of Corixa Corporation located in South San Francisco, CA (see inspection closeout memos within the inspection tab).

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **June 23, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Container, carton and other labels

Participants: FDA/CBER/OTRR: Karen D. Jones,

Corixa Corporation: J. Henrich, B. Kay

DISCUSSION:

I placed a call to Corixa to discuss FDA recommended revisions to the revised container, carton and other labels faxed and emailed by Corixa to FDA on 6-20-03. The following items were discussed:

- The license number, 1614 should be placed on all labels.
- The labeling emailed prints out with very dark magenta coloring (for therapeutic labels). This makes the black font too difficult to read. Please check the true colors. Corixa suggested using white font for text on the colored strips.
- The colors used for "Bexxar" and "Corixa" are not consistent throughout the labeling. Corixa responded that this may be a marketing tool. They will check.
- What does SN# refer to on the Iodine I 131 Tositumomab glass vial and is it of such importance that it should be located on other labels? Corixa stated that it is the serial number and is used by MDS Nordion to select every 5th vial for calibration and testing. It cannot be deleted to accommodate the license number.
- On the dosimetric and therapeutic package labels: increase text prominence of sentence that begins, "Each package contains.... Follow that sentence with a space to set it apart. Change 14 mg Tositumomab/mL to 14 mg/mL Tositumomab. Add a protect from light statement as per the PI. The location of the lot # and expiration date is acceptable.
- [redacted] b(4)

b(4) [redacted] Also check how the text lines wrap; the numbers should be associated with their respective units.

- The product specification sheet should be titled as such and the license number and address should be added to the sheet as well. If the lot number is used to match up the sheet to the associated dose pot, then please move lot up to the top of the sheet.
  Corixa: the sheet entries are generated by software, thus moving the lot number would require changing the software and revalidating it. FDA agrees that lot number may remain at the bottom of the sheet.
- The [redacted] transport package, item 4 needs to be clarified, The dose pot color is not matched to a product strength, it is matched to the color on the product specification sheet. Language was discussed.

Corixa will make the requested revisions. Ms. Henrich also noted that Corixa will submit later today, a further response to question 2a of the IR letter, PMCs including the discussion of the QA program (8 clincial and 1 CMC).
The call concluded.

RECORD OF TELEPHONE CONVERSATION, BLA 125011, CORIXA, BEXXAR

DATE: 6/23/03

PARTICIPANTS: T. Zaremba, CBER
J. Henrich & B. Keig, Corixa

CBER: I looked at your submissions of August 27, 2001 & November 14, 2001, which were indicated to contain information regarding stability (see telecon of 6/20/03). Regarding the August 27th submission, which contained data for PBDS for up to — months of storage at 2-8°C, I have the following questions on Tables 9.3 & 9.4 in your response to item 9:

b(4)

1. The legend to these tables indicates that both lots were "small scale"; what is meant by this since one was ' ——& the other . —— ? Corixa responded that they did not know the meaning of this since both were stored in the proper size container (e.g., ————,). However, they will check on this.

b(4)

2. There were no results for the SDS-PAGE (Coomassie). Furthermore, no actual data were shown for the ' — month time-point. Since you are seeking an — month dating period for the PBDS, do you know when you submitted these data? Corixa responded that they did not believe these data were submitted to the file, but that they could be obtained from BI Pharma by tomorrow.

CBER: That would be very good. Regarding the November 14th submission, I have the following questions about the stability of the DP:

1. Table 6 on p.18 showed the results for 6 product lots (3 for the 2.5mL dosage form & 3 for the 16.1 mL dosage form). I note that only one of these lots was produced from BDS stored in ———— ———— All of the others were either produced from BDS stored in ———— . How are you currently storing the BDS? Corixa responded that the BDS has been stored in ———— I asked if they had additional data for DP after 36 months of storage that was produced from BDS stored in the ' ———— sine the lots reported in Table 6 were from 1997 & 1998? Corixa responded that they should indeed have these data & will obtain them from BI Pharma by tomorrow.

b(4)

2. There did not appear to be a list of specifications for the non-radiolabled DP in this submission, although all of the results & data were shown for these lots. Have you submitted final specifications for lot release and stability for the DP? In particular, in a number of instances you have revised some

specifications in response to CBER questions. For example, in your August 27, 2001 submission, item 10(c), you agreed to revise the specifications for SDS-PAGE to ≥ [redacted]% and for HPLC to ≥ [redacted]% monomer. Corixa responded that they would check to see if the current lot release & stability specifications have been submitted and will apprise me of their location in the file. However, they can also submit these to me by tomorrow by FAX. b(4)

Jones, Karen

From: Henrich, Jill [Jill_Henrich@corixa.com]
Sent: Friday, June 20, 2003 5:22 PM
To: Karen Jones (E-mail)
Subject: Draft Labeling: containers


35mg tositumomab.doc


225mg tositumomab.doc


Dx_Tx Iodine I 131 Tositumoma...

Hi Karen,

Attached are the following documents that were faxed to you earlier today:
* 35 mg Tositumomab vial
* 225 mg Tositumomab vial
* Dx and TX Iodine I 131 Tositumomab glass vial (inkjet) - actual sample of each and mock-up of changes to be made

I will provide you with carton and "other" labeling under separate cover.

Jill
<<35mg tositumomab.doc>> <<225mg tositumomab.doc>> <<Dx_Tx Iodine I 131 Tositumomab vial.doc>>

3 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 12

Jones, Karen

om: Henrich, Jill [Jill_Henrich@corixa.com]
nt: Friday, June 20, 2003 5:31 PM
o: Karen Jones (E-mail)
Subject: Draft Labeling: cartons


dx carton label.doc

tx carton label.doc

carton_end_imprint .pdf

dx dose pot.doc

tx dose pot.doc

Karen,

Attached please find the following files that were faxed to you earlier today

* Top/Side Panel of Dosimetric Carton
* Top/Side Panel of Therapeutic Carton
* Imprint of end of Dosimetric/Therapeutic Carton (Lot number/Exp. date)
* Dosimetric Dose pot
* Therapeutic Dose pot

<<dx carton label.doc>> <<tx carton label.doc>>
<<carton_end_imprint.pdf>> <<dx dose pot.doc>> <<tx dose pot.doc>>

5 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 13

Jones, Karen

ɔm: Henrich, Jill [Jill_Henrich@corixa.com]
nt: Friday, June 20, 2003 5:36 PM
ɪo: Karen Jones (E-mail)
Subject: "Other" labeling


User's instructions.doc


DX_PSS_redline.pdf


Tx_PSS_redline.pdf

* User's Instructions ("Procedure for Opening of [redacted]")

* Dosimetric and Therapeutic Product Specification Sheets (redlined version showing changes to be made)(previously called Pharmacy Inserts)

<<User's instructions.doc>> <<DX_PSS_redline.pdf>> <<Tx_PSS_redline.pdf>>

b(4)

4 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 14

MEMORANDUM
Food and Drug Administration
Center for Biologics Evaluation and Research

Date: June 20, 2003

From: Leon Epps
Regulatory Review Officer, DMA/OTRR

Subject: Corixa Corporation's BLA (STN# 125011): BEXXAR™ (Tositumomab, Iodine I 131 Tositumomab) "Justification for Allowing Limited Information on Corixa's Package and Container Labeling for Iodine-131 Tositumomab and Allowing the Required Information to be Described on the Product Specification Sheet of the Pharmacy Insert"

To: File

CC: Wendy Aaronson
Earl Dye
Glen Jones
Karen Jones
Patrick Swann
Keith Webber
Terrye Zaremba

Wendy Aaronson and Karen Jones asked me to provide this memo for future labeling reference.

OVERVIEW:

The manufacturing processes for the two dosage forms (dosimetric and therapeutic) for Iodine-131 Tositumomab involve the same manufacturing steps with similar operating parameters. The radiolabeling, formulation, purification, dispensing, labeling of the dosimetric and therapeutic drug dosages are conducted in [redacted] at MDS Nordion. These highly

b(4)

radioactive dosage forms are [redacted] b(4)

As a result, the information describing the protein concentration, activity concentration, and total activity are provided on the Product Specification Sheet of the Pharmacy Insert after lot release testing has been completed. This information cannot be added to the labels attached to the [redacted] Under these circumstances Corixa's labeling approach is reasonable and acceptable to me.

RECORD OF TELEPHONE CONVERSATION, BLA 125011, CORIXA, BEXXAR

DATE: 6/20/03

PARTICIPANTS: T. Zaremba, CBER & J. Henrich, Corixa

CBER: I need some additional information regarding dating periods for the approval letter. There were a number of studies reported in your original submission, but I am not clear on the final dating period or storage temperature for the bulk and final products. Specifically, for BDS is it —months at 2-8°C? b(4)

Corixa: Yes

CBER: What about the PBDS?

b(4)

Corixa: ' ———— –20°C.

CBER: In the O/S you indicated you were testing storage at –20, but no data for — months was shown. Can you tell me when this was submitted to your file?

Corixa: The August 27, 2001 submission, in response to item 9.

CBER: What about the non-radiolabeled DP?

Corixa: This was submitted on November 14, 2001 and contained data for up to 36 months of storage at 2-8°C.

CBER: OK, I will review these submissions. In addition, Karen Jones indicated that for any Phase 4 commitments, you would need to submit the time frames for completion. In looking over various submissions, I have the following CMC commitments for the BALL-1 cell reagent: 1) validation of the ———— 2) validation of the ———— 3) validation of the Karl Fischer moisture determination with comparison to ———— 4) setting lot release & stability specifications for the BALL-1 reagent. b(4)

Corix: Yes we have made these commitments & will submit the time frames for completion.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **June 20, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Revised Package Insert, 6-20-03 version

Participants: FDA/CBER/OTRR: Karen D. Jones,

Corixa Corporation: J. Henrich,

DISCUSSION:

Jill Henrich requested that FDA revisions to the package insert be submitted by email (non-secure) instead of by fax. [Attempts to send the revised labeling via secure email were unsuccessful.] Corixa was asked to review the changes and respond as soon as possible. Ms. Henrich stated that Corixa would try to return revised vial carton and other labels as well as PMC proposals and the revised training manual on Monday. The call concluded.

Jones, Karen

From: Jones, Karen
Sent: Friday, June 20, 2003 6:28 PM
To: 'Henrich, Jill'
Subject: RE: "Other" labeling

Importance: High

FDA revised 6-20-03 Strikeout ...

Here is the 6-20-03 FDA revised PI as per our discussion today (since the secure email reoute did not appear to work, as per your request):

Thanks.

Karen

-----Original Message-----
From: Henrich, Jill [mailto:Jill_Henrich@corixa.com]
Sent: Friday, June 20, 2003 5:36 PM
To: Karen Jones (E-mail)
Subject: "Other" labeling

* User's Instructions ("Procedure for Opening of Type A Transport Package")
Dosimetric and Therapeutic Product Specification Sheets (redlined version showing changes to be made)(previously called Pharmacy Inserts)
<<User's instructions.doc>> <<DX_PSS_redline.pdf>> <<Tx_PSS_redline.pdf>>

51 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 15

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

DATE June 20, 2003

FROM Mary Andrich, CBER/OTRR

TO Terrye Zaremba, CBER/DMA

SUBJECT Final Report of Bioresearch Monitoring Inspection Results
BLA STN 125011
Product: Bexxar (Tositumomab and ^{131}Iodine-Tositumomab)
Sponsor: Corixa Corporation

PROTOCOL CP-98-020: EXPANDED ACCESS STUDY OF IODINE-131 ANTI-B1 ANTIBODY FOR RELAPSED / REFRACTORY LOW-GRADE AND TRANSFORMED LOW-GRADE NON-HODGKIN'S LYMPHOMA

SUMMARY STATEMENT

Inspections were conducted for three clinical investigators and the sponsor. The findings are listed below.

BACKGROUND

Clinical investigator inspection assignments were conducted at three clinical sites for which the sponsor submitted data to BLA STN 125011. An inspection of the sponsor was also performed. Data for subjects were taken from the BLA and compared to source data at the study sites. The assignment included specific questions about the studies.

Data audits were performed at three clinical trial sites.

Clinical Site	Investigator	Date	FDA Form 483	Classification
Rush-Presbyterian Medical Center	Dr. Gregory	4/01	Yes	VAI
Carolinas Medical Center	Dr. Frenette	7/01 and 4/02	Yes	OAI
University of Arkansas	Dr. Maddox	8/02	Yes	OAI

INSPECTIONAL FINDINGS—CLINICAL SITES

1. Failure to ensure that the investigation was conducted according to the protocol.

   a. Enrollment of an ineligible patient. Dr. Maddox (1 subject).

   b. Failure to calculate and administer the correct therapeutic doses of the investigational product. Dr. Gregory (4 subjects) and Dr. Maddox (3 subjects).

   c. Failure to obtain follow-up laboratory tests required by protocol. Dr. Maddox (6 subjects).

   c. Failure to ensure that the Form FDA 1572 listed all subinvestigators. Dr. Gregory.

2. Failure to assay the residual activity in the infusion set following the therapeutic dose, as required by the sponsor.

Dr. Frenette (8 subjects) and Dr. Maddox (7 subjects).

Dr. Frenette assumed a loss of 10% of the activity of the investigational product in the infusion set. However, when his staff performed the assay, the actual residual activity in the infusion set ranged from 0% to 19% of the original assayed dose. Dr. Maddox assumed a loss of 0% of the activity in the infusion set.

3. Failure to provide accurate data to the sponsor.

Reporting of estimated administered doses of the investigational product as actual administered doses. Dr. Frenette (12 subjects) and Dr. Maddox (7 subjects)

4. Failure to prepare and maintain adequate and accurate case histories.

   a. Failure to maintain source documents to support adverse events reported to the sponsor on CRFs. Dr. Gregory (2 subjects).

   b. Failure to ensure that data required on the CRFs was transcribed from the records. Dr. Maddox (4 subjects).

An inspection of the sponsor was conducted in 11/02. A Form FDA 483 was issued, and the inspection was classified as OAI.

INSPECTIONAL FINDINGS—SPONSOR

1. Failure to monitor the progress of all investigations conducted under the IND.

Failure to provide adequate monitoring for the following studies: RIT-II-000, RIT-II-001, RIT-II-002, RIT-II-003, RIT-II-004, CP-97-012, and CP-98-020.

   a. Failed to ensure that clinical investigators assayed infusion sets for residual milliCurie activity after administration of the investigational product.

b. Failure to ensure that clinical investigators documented changes of the infusion set filter between doses of the cold antibody and the radiolabeled antibody. The inspection revealed that it was not possible to determine when filters were changed during infusions of the study drug.

c. Failure to follow the sponsor's SOP for Protocol CP-98-020 entitled "Site Monitoring: Monitoring Visit." This SOP required that every active site be visited a minimum of once per year. There were no monitoring reports for 35 of 38 sites reviewed. Furthermore, the sponsor did not verify the laboratory data for this protocol.

2. Failure to ensure that the investigation was conducted according to the protocols contained in the IND.

Failure to ensure that clinical investigators performed accurate dosimetric calculations, according to the protocol, prior to administration of the therapeutic doses of the investigational product for Protocols RIT-II-004 and CP-98-020.

BIMO ADMINISTRATIVE FOLLOW-UP

A Warning Letter was issued to Dr. Frenette. Untitled letters were issued to Dr. Gregory, Dr. Maddox, and the sponsor.

PREVIOUS BLA INSPECTIONS

In support of BLA 99-0813, inspections of five clinical sites were performed for Protocol RIT-II-004, entitled "Multicenter, Pivotal Phase III Study of Iodine-131 Anti-B1 Antibody (Murine) Radioimmunotherapy for Chemotherapy-Refractory Low-Grade B-Cell Lymphomas and Low-Grade Lymphomas that have Transformed to Higher Grade Histologies." In addition one of the sites (University of Nebraska) was also inspected for Protocol RIT-II-001, entitled "Multicenter, Phase II Dosimetry/Validation Study of 131Iodine-AntiB1(murine) Radioimmunotherapy for Chemotherapy-Refractory Low-Grade B-Cell Lymphomas and Low-Grade Lymphomas that have Transformed to Higher Grades" after the sponsor told the FDA that data from this site was missing. The inspections were conducted in accordance with CPGM 7348.811, the Inspection Program for Clinical Investigators.

Data audits were performed at the following five sites:

Clinical Site	Investigator	Date	Form 483	Classification
Kaiser/Vallejo	Dr. Fehrenbacher	8/99	No	VAI
Stanford University	Dr. Knox	8/99	Yes	VAI
Univ. of Michigan	Dr. Kaminski	9/99	Yes	VAI
Univ. of Washington	Dr. Press	9/99	Yes	VAI
Univ. of Nebraska	Dr. Vose	11/99	Yes	VAI

A Form FDA 483 was issued to Dr. Knox, Dr. Kaminski, Dr. Press, and Dr. Vose.

During the inspection of Dr. Fehrenbacher, it was discovered that none of the three subjects listed in the BLA for Kaiser/Vallejo were treated there. Instead, they were enrolled by Kaiser physicians and then sent to Dr. Knox to receive both the diagnostic and the therapeutic doses of the investigational product. Afterwards, they returned to the Kaiser system for follow-up care.

The clinical site inspectional findings are summarized below:

1. Failure to ensure that the investigation was conducted according to protocol and failure to protect the rights, safety, and welfare of a subject under the investigator's care.

One ineligible subject was enrolled by a subinvestigator of Dr. Fehrenbacher, and then sent to Dr. Knox for therapy. At the time of enrollment, Kaiser pathologists were uncertain of the correct diagnosis. They requested another opinion on the pathology from Stanford. However, Dr. Knox treated the subject was prior to the correct diagnosis of mantle cell lymphoma, which made him ineligible for therapy.

2. Failure to ensure that the investigation was conducted according to protocol

   a. Failure to obtain gamma camera background counts according to protocol. Dr. Kaminski and Dr. Vose.

   b. Failure to calculate and administer the correct therapeutic doses of the investigational product. Dr. Knox (2 subjects) and Dr. Press (3 subjects).

   c. Failure to administer pre-treatment doses of potassium iodide according to the protocol. Dr. Kaminski (6 subjects).

   d. Failure to assay the residual activity in the infusion set following the therapeutic dose, as required by the sponsor. Dr. Kaminski.

3. Failure to prepare and retain signed and dated consent forms. Dr. Knox (1 subject).

Untitled letter were issued to all five clinical investigators. As a result of these inspectional findings an inspection of the sponsor, Coulter Corporation, was performed in 11/00 and was classified NAI.

Mary Andrich

cc:

HFM-99	IND 3323
HFM-650	Elaine Cole
HFM-664	Pat Holobaugh
HFM-664	Access/CHRON
HFM-664	BIMO Summary File
HFM-573	Patricia Keegan
HFM-573	George Mills
HFM-594	Terrye Zaremba
HFM-573	Mary Andrich
HFM-570	Kaushikkumar Shastri
HFM-588	Karen Jones

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **June 17, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Labeling

Participants: **FDA/CBER/OTRR**: Karen D. Jones
Corixa: Jill Henrich

DISCUSSION:

I called Jill Henrich of Corixa regarding BLA STN 125011/0 in response to the questions that she emailed (see attached) on June 16, 2003 regarding vial, carton and dose pot labeling. The following agreements were reached:

- [redacted] b(4)
- [redacted]
- Corixa's plan to imprint the lot and expiration date on the end of the carton is acceptable. Mock-up must show where this information will be located.
- FDA is not asking for a statement on the lead pot indicating that it is [redacted]coded. However, FDA wants to ensure that the lead pots are [redacted]coded to avoid possible medication errors between dosimetric and therapeutic doses. Ms. Henrich confirmed that the pots are [redacted]coded and this information will be included in the User Instruction sheet. b(4

The call concluded.

Jones, Karen

From: Henrich, Jill [Jill_Henrich@corixa.com]
Sent: Monday, June 16, 2003 3:23 PM
To: Karen Jones (E-mail)
Cc: Henrich, Jill
Subject: Labeling questions

Questions regarding FDA labeli.

Karen,

Thank you for taking the time to discuss the outstanding items with me today. I am attaching additional questions we would like to receive feedback or clarification so that we can provide revised labels to you.

Best regards,
Jill Henrich
<<Questions regarding FDA labeling comments_061603.doc>>

Questions regarding FDA labeling comments:

1. 225 mg vial – Requested to add statement " [redacted] b(4)

   Is this accurate or is this a cut & paste error from 35 mg vial label? Shouldn't [redacted] ?
2. Dosimetric/Therapeutic Carton label (top and side panel) -
   Must " [redacted] ' appear twice on the carton? And if not, then may it appear only on the side panel?
3. Dosimetric/Therapeutic Carton label (top and side panel) – Requested that lot # and expiry date appear on both of these labels. Corixa plans to imprint this on the end of the carton. Is this acceptable? b(4)
4. [redacted]

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **June 16, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Labeling/ISS

Participants: **FDA/CBER/OTRR**: Karen D. Jones
Corixa: Jill Henrich

DISCUSSION:

Jill Henrich of Corixa called regarding the Tositumomab BLA, STN 125011/0. She informed me that Corixa plans to submit an updated ISS the first week of July 2003. She inquired whether the FDA would require that the package insert be updated at that time. Ms. Henrich also stated that the draft training manual and promotional materials will be sent in and questions Corixa has on labeling (in response to FDA comments on labels) would be sent in an email.

I responded that I would notify the reviewers of the plans for the ISS and request a response to Corixa's question. Once the email with labeling questions has been received, FDA will review them and will respond to Corixa.

The call concluded.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **June 4, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Dosimetry Software Discussion

Memo to the File:

Corixa requested a teleconference on May 16, 2003, to discuss why FDA indicated that Corixa's proposed dosimetry software will require a 510(k) submission. The call took place on May 22, 2003. As agreed during that call, Corixa provided the minutes documenting the discussion and agreements. Corixa submitted the minutes in an email sent to Ms. Karen Jones on June 4, 2003 (see attachment).

4 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓
_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 16

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **May 27, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: IR Letter Issues and package Insert

Participants: FDA/CBER/OTRR: Patricia Keegan, George Mills, Kaushikkumar Shastri, Satish Misra, Susan Jerian, Terrye Zaremba, Karen D. Jones,

Corixa Corporation: J. Henrich, M. Krieger, C. Jacobs, P. Stewart, S. Kroll, and other representatives
GSK: Meg Martin

DISCUSSION:

The discussion centered on the agenda provided to FDA via email by Corixa on May 23, 2003 (see attachment).

1. Will a revised training manual be sufficient to address comment 1 of the 5/21/03 IR letter? Are there any other documents that you would like submitted at this time?
   - FDA would like to see the training manual and the service center manual to assure consistency and the timeline for implementation. Corixa agreed to provide this information as red strikeout so that the changes can be easily viewed.

2. Re-treatment trial: FDA's concern with Corixa's proposal to enroll patients previously treated on studies CCBX001-048, 049 or 053 is missing information that is important to assess changes. One suggested eligibility criterion would be that patients should be those for whom Corixa has reviewed and confirmed registration procedures and that they have an acceptable quantity of information and sufficient analysis to permit an assessment of change. This would necessitate a reassessment of studies 048, 049 and 053: response time, actual images, HAMA status. Another possibility would be a paired analysis looking for systematic change in pre- vs. post dosing in a certain number of patients, showing changes that may be less dramatic than altered

biodistribution but which could serve. For an example, look at imaging follow-up protocol for Study 004 that would include scans to be done following discharge. Corixa noted that patients are now discharged immediately.

FDA asked that Corixa include a detailed concept sheet in their June 13, 2003, response to the IR letter that includes a summary of the eligibility criteria for study 048, 049 and 053. The date of initiation of the clinical study is not required now but the date of initiation of an animal study is requested. Corixa agrees to include the detailed concept sheet in the June 13, 2003 submission.

3. Evaluation of HAMA: Corixa will modify the two protocols for studies 049 and 053 to include collection of information about HAMA and prevention of patients from receiving in vivo diagnostic tests. The case report forms will be modified and will be submitted with the next SPA. For study 048, the study protocol is being evaluated by the IRB and the case report forms have been submitted for printing.
   - This is acceptable to FDA

With respect to item 4b(2) of the IR letter, FDA did not have enough information to assess the retrospective plan. If the plan is adequate, a prospective analysis may not be needed. Corixa will provide documentation of the test. HAMA testing will be repeated on all archived sera to be certain that the values are as originally reported. If problems are identified, the study will have to be done prospectively. Corixa will propose both a retrospective plan and a prospective plan.

4. Data collection and monitoring for myelodysplastic syndrome and secondary leukemias. Corixa plans to submit a plan for analysis of these events based on previous discussion with FDA and ODAC for the appropriate time interval. Data will be collected from the studies that support the BLA for patients alive until 10 years post-treatment. Corixa proposes to follow patients enrolled in studies 048, 049, 053 for 5 years as well as the patients in the expanded access program and will continue expedited reporting as long as FDA requires it.

FDA asked why 5 years is proposed. Corixa responded that this timepoint was discussed at ODAC as the appropriate time point. Dr. Keegan noted that ODAC did not have all the information and stated that plateaus for leukemia have not yet been seen on patients followed out to 8 years. More careful data collection is necessary. Corixa noted that IRBs closed down some of the long-term follow-up for older studies. Corixa has rewritten the protocols so that patients at one site can go onto a follow-up protocol.

FDA notes that, for new studies, patients should understand that at they are being recruited for both the initial study and the follow-up study. Corixa responded that the

consent forms clearly state that the patients will be followed out to 10 years. If IRBs pressure for administrative relief, the follow-up protocols will have to be written as separate protocols. FDA recommends that Corixa clearly specify in the contracts with the clinical sites that the studies require follow-up out to 10 years. Corixa agrees to detail what studies will be covered, 051 and 052 in the SPAs. Corixa expressed concern about how to handle the expanded access protocol. FDA committed to consider this issue further.

5. Corixa requested to discuss some additional issues in order to complete revisions to the package insert and training manual:

- Anterior and posterior images: Corixa should include both anterior and posterior imaging in the package insert as these were part of the clinical trials. Renal clearance obstructions would only show posteriorly. If only one can be done, FDA recommends posterior. Corixa noted that their analysis showed no difference in total body residence time. FDA responded that the restrospective analysis of the data did not cover all studies in terms of collection of good dosminetry data. FDA agreed to look at Corixa's retrospective study for purposes of developing a prospective study and then discuss with Corixa.
- FDA will accept either a — or —collimator but the collimator must be specified to handle 364 keV which is specific for Iodine 131. b(4)
- Biodistribution: FDA believes that altered biodistribution may or may not be associated with TBRT (total body residence time), and thus TBRT cannot be relied upon as a surrogate for altered biodistribution. FDA has not seen data to support safety. Corixa should propose a prospective plan, perhaps in the re-treatment protocol. Corixa will have to demonstrate that TBRT accurately predicts altered biodistribution.
- Stability and storage: Corixa has submitted data to the BLA that demonstrate adequate stability and storage of the drug product in a freezer with automatic defrost cycles. FDA noted that the CMC reviewer who reviewed the Nordion data is not present to discuss this issue.

Agreements: posterior and anterior are necessary to go forward. Corixa must ensure that dosing parameters in future studies are consistent with respect to the collimator 364 keV, speed of images, anterior vs posterior etc. Good quality data is the requirement. FDA can look at a proposal and can work out a design with Corixa.

6. CMC: 145 vials of BALL-1 cells will be analyzed by 6/13/04 as requested by T. Zaremba in a previous telecon. Corixa may be permitted to validate post-licensure. Preliminary information is expected to be available by June 13, 2003. The — assay should address concerns. The information can be sent to the CMC reviewer via email to expedite review. b(4)

The teleconference concluded.

Jones, Karen

From: Henrich, Jill [Jill_Henrich@corixa.com]
Sent: Friday, May 23, 2003 5:06 PM
To: Karen Jones (E-mail)
Cc: Henrich, Jill
Subject: Agenda for Tuesday 5/27 TC @ 11:30 EDT

AGENDA5-27-teleconference.doc

Hi Karen,

I left a voicemail message - I wanted to see if you were able to confirm the teleconference scheduled for Tuesday 5/27 @ 11:30AM EST. Assuming that we are a go for that TC, I am attaching our proposed agenda/list of items we would like to discuss and receive feedback on on this telecon.

The Dial-In Information is:
(877)-895-6183
Part. code: 754-5729

<<AGENDA5-27-telecon.doc>>
Regards,

Jill Henrich

AGENDA for FDA teleconference on Tuesday, May 27, 2003 (11:30 AM Eastern)

Discussion of May 21st IR Letter

1. Re: Comment 1: We believe that a revised training manual consistent with the recommendations in items a –f will answer this question. Will this be sufficient to answer this question? We will revise all procedures to be consistent. Are there any other documents that you would like submitted at this time?

2. Re: Comment 4(a): We will design a new study that addresses the request to characterize the profile of more than one administration of the BEXXAR therapeutic regimen. We would plan to enroll patients who have relapsed after their first BEXXAR treatment on Studies CCBX001-048, 049 or 053 to receive retreatment with BEXXAR on this new study. We also assume that these patients would still be required to be HAMA negative. How would you want rate of altered biodistribution to be assessed? Is this patient population acceptable to address this post marketing commitment?

   Please clarify the comment in bullet two regarding a date for initiation of an animal study. We assumed this may have been a typographical error and referred to the date for initiation of a clinical study. Is this correct?

3. Re: Comment 4(b): We plan to revise the CCBX001-049 and 053 studies in the next SPA review to clarify collection of information regarding HAMA and the prevention of patients from receiving any *in vivo* diagnostic tests. As previously proposed, we will also conduct retrospective analyses of the stored samples that are available. In addition, we will amend protocols 049 and 053 to include provisions for analyses of HAMA positive samples for interference of *in vitro* diagnostic tests. We would like to discuss our proposed plan to assure that it is adequate.

4. Re: Comment 4(c): We would like to discuss our proposed plan to respond to your concerns regarding collection of data on myelodysplasia/secondary leukemia.

5. Re: Comment 5: We will provide a revised package insert by end of day on Tuesday, May 27th. We have accepted the vast majority of the changes. The majority of our changes are consistent with what we believe you intended, but were modified to accurately reflect the methods that have been used. There are some items that we would like to discuss during our teleconference in order to allow us to complete our revisions to the package insert and training manual for submission. These are noted below.

4 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 17

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **May 22, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: IR Letter

Participants: FDA/CBER/OTRR: Karen D. Jones

Corixa Corporation: Jill Henrich.

DISCUSSION:

Jill Henrich called to discuss the timing of the SPA submissions and the IR letter. She stated that Corixa will respond to the letter by June 13, 2003 as per the requested timeline. With respect to the CMC issues, they hope to complete testing by June 13 (a contractor is involved) but the [redacted] method final report will probably not be ready by June 13 since the testing is done in [redacted] and takes at least 2 weeks to do. They will try to meet the goal. The request for resubmission of the SPA protocols can be met in July. I thanked her for the information and stated that I would inform the review team. The call concluded. b(4)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125011/0

MAY 21 2003

Monica Krieger, Ph.D.
Corixa Corporation
1124 Columbia Street, Suite 200
Seattle, WA 98104

Dear Dr. Krieger:

This letter is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act.

The Center for Biologics Evaluation and Research has completed the review of the clinical and chemistry, manufacturing, and controls (CMC) sections of your biologics license application for Tositumomab and Iodine I 131 Tositumomab (Bexxar®), including the amendments dated March 26, 2003, April 3, 17, 28 and 30, 2003 and May 12, 2003 submitted in response to our March 3, 2003 clinical and CMC discipline review (DR) letters. We also refer to telephone conversations between representatives of Corixa and this office on March 11, 2003 and April 21, 2003.

We have determined that the following information is necessary to take a complete action on your application. Each item refers to the indicated comment in our March 3, 2003 clinical or CMC DR letter:

1. We have reviewed the submission of April 3, 2003 responding to comment 8, and the submission of April 28, 2003, responding to the April 21, 2003 telephone conversation between you and Dr. Cindy Jacobs of Corixa, and Dr. George Mills and Ms. Karen Jones of this office and we have the following requests for information and modification to your proposed training program.

[redacted] b(4)

8 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 18

CONCURRENCE PAGE

cc: K. Webber, HFM-555
E. Bonvini, HFM-555
P. Swann, HFM-555
P. Keegan, HFM-570
DARP BLA file, HFM-585
T. Zaremba, HFM-594
K. Shastri, HFM-573
H. Luksenburg, HFM-573
M. Andrich, HFM-573
S. Jerian, HFM-573
G. Mills, HFM-573
S. Risso,HFM-500
K. Weiss, HFM-500

CBER:DARP:K.Jones:05-19-03:05-20-03:K.Townsend:5.20.2003:5.21.2003
(S:\Jonesk\125011-0 Tositumomab\IR Letter KJ 5-20-03.doc)

COMMUNICATION TYPE:

LETTER: Information Request Letter (IR): Clinical and CMC

SS Data Check:
- **Communication**

Division	Name/Signature	Date
OTRR/DARP	Karen D. Jones	5/21/03
OTRR/DMA		5-21-03
DARP		5-21-03
DCTDA		5-21-03
DARP	Kelly Townsend	5-21-03

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **May 20, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Package Insert Labeling

Participants: FDA/CBER/OTRR: Karen D. Jones

Corixa Corporation: Monica Krieger, Ph.D.

DISCUSSION:

Follow-up to 5-19-03 Tcon with Jill Henrich:

May 20, 2003
Dr. Krieger called to confirm the label wording in the box on line 715. She also indicated that she is available to discuss the 510(k) dosimetry software submission on May 22, 2003. She indicated that the goal for Corixa is to make changes to the label and return the label by May 23, 2003. The call concluded.

Jones, Karen

From: Krieger, Monica [krieger@corixa.com]
Sent: Tuesday, May 20, 2003 4:54 PM
To: 'Jones, Karen'
Subject: RE: Electronic WORD version of 5-16-03 Package insert

Thank you

-----Original Message-----
From: Jones, Karen [mailto:JonesK@cber.FDA.gov]
Sent: Tuesday, May 20, 2003 1:54 PM
To: 'krieger@corixa.com'
Subject: Electronic WORD version of 5-16-03 Package insert
Importance: High

Hello Monica,

Here is the WORD version of the revised PI sent to Jill Henrich on 5-16-03 via fax. It should be exactly the same as the version faxed. Please let me know if it is not the same.

<<125011 draft PI 5-16-03.doc>>

Thank you.

Karen Jones

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: May 20, 2003

From: Karen D. Jones, CBER/OTRR/DARP, HFM-588

To: Corixa Corporation
Tositumomab (Bexxar)
BLA, STN 125011/0 File

Subject: MS WORD version of Labeling

PARTICIPANTS: CBER/OTRR: Karen D. Jones

Corixa Corporation: Monica Krieger, Ph.D.

As requested by Corixa, on May 20, 2003, I sent the MS WORD version of the revised package insert to Monica Krieger at Corixa in follow-up to the paper version faxed to Jill Henrich of Corixa on May 16, 2003. Dr. Krieger emailed confirmation of receipt later this same date (4:54 pm).

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **May 19, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Package Insert Labeling

Participants: FDA/CBER/OTRR: Karen D. Jones

Corixa Corporation: Jill Henrich

DISCUSSION:

Jill Henrich of Corixa phoned to request that I email the FDA 5-16-03 revised version of the package insert in order to facilitate their consideration of the labeling. I agreed to do so. Ms. Henrich called to confirm the receipt of the labeling and noted that one of the diagrams appears to run off the page. She asked that the complete diagram be emailed to Dr. Krieger. The call concluded.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **May 16, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Dosimetry Software

Participants: FDA/CBER/OTRR: Karen D. Jones

Corixa Corporation: Monica Krieger, Ph.D.

DISCUSSION:

Monica Krieger of Corixa phoned to request a 15 min telecon to hear from CBER & CDRH what the rationale is as to why their proposed dosimetry software will require a 510(k) submission. Specifically, the legal counsel would like an explanation. She suggested dates and times for the telecon. I agreed to try to set up a telecon. The call concluded.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **May 15, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Miscellaneous

Participants: FDA/CBER/OTRR: Karen D. Jones

Corixa Corporation: Jill Henrich

DISCUSSION:

Jill Henrich of Corixa phoned to discuss the following:

- Corixa has submitted CMC information requested by Dr. Zaremba.
- ALPB has informed Corixa that a decision is required by OTRR as to whether BEXXAR will be approved under accelerated approval regulations. IF so, all of the promotional labeling must be submitted to ALPB for review prior to approval of the BLA. I stated that this issue is the subject of an internal FDA meeting to be held on May 16, 2003.
- Corixa will file software information to the IND for use in the clinic.
- The April 28, 2003 submission (serial number 057) should be sent to Michael Fauntleroy to confirm that the ESM non-repudiation document has been filed. I responded that I will see that Mr. Fauntleroy gets this information.
- Corixa is hoping to return the revised package insert to FDA next week.

The call concluded.

Package Insert Labeling Comments
Corixa Corporation, Bexxar (Tositumomab and Iodine I 131 Tositumomab BLA)
STN 125011/0
5-16-03

Today FDA is providing a revised draft Bexxar package insert. This revised package insert is DRAFT, and is subject to change. Please review each line carefully, as extensive revisions have been made. You will note numerous comments and questions that you will need to address. Please pay special attention to the Dosage and Administration section. Extensive revisions may still be required to this section. We are available for a telecon if you would like to discuss the revisions.

Thank you.

Karen Jones, RPM
FDA/CBER/OTRR/DARP

47 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 19

Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

Date: May 13, 2003

To: File STN 125011/0

From: Deborah Trout, BLA Committee Member, HFM-675

Through: Cynthia Kelley, Branch Chief, Branch 1, HFM-675

Subject: Review of Discipline Review Letter responses submitted April 3, 2003.

Comment 4: The firm's response appears adequate. In order to address agency concerns regarding verification of the sensitivity of the microbial challenge test used to validate the integrity of the container/closure system, Corixa and GSK performed a set of experimental studies where capillaries of known diameter were bored into glass vials. This approach would specifically introduce defects of known diameter into the glass. The punctured vials were evaluated directly via a microbial ingress test. The validation data demonstrated that the current test procedure is capable of detecting leaks of 5 microns or greater. The validated test method was then used to test media filled vials manufactured under normal filling conditions at Nordion. Media fill vials from Nordion batch number 2001008 MF was subjected to a microbial immersion leak test. The test organism was not recovered from any of the twenty vials tested. These vials passed this test for container/closure integrity

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **May 8, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Dosimetry Software Meeting Request

Participants: FDA/CBER/OTRR: Karen D. Jones

Corixa Corporation: Jill Henrich

DISCUSSION:

I phoned Jill Henrich and left a message indicating that CDRH had reviewed the information provided by Corixa with respect to the dosimetry software and had determined that a 510(k) submission would be required. This addresses the single question posed in the meeting request and obviates the need for the meeting. Therefore, I requested that Corixa submit a letter withdrawing the meeting request. The call concluded.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **May 7, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Miscellaneous

Participants: FDA/CBER/OTRR: Karen D. Jones

Corixa Corporation: Jill Henrich

DISCUSSION:

Jill Henrich of Corixa called to inform me that secure email has been established. I responded that I had not received any notification to this effect. Ms, Henrich then asked if there are any additional review issues that Corixa should be aware of. I stated that I did not have any concerns to communicate at this time. Ms. Henrich then stated that she has not been able to speak with the ALPB reviewer, Nancy Chamberlin yet. I responded that I would inform Ms. Chamberlin that Corixa would like to discuss promotional labeling. The call concluded.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **May 7, 2003 teleconference**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: BALL-1 cell reagent

Participants: FDA/CBER/OTRR: Terrye Zaremba, Ph.D.

Corixa Corporation: J. Henrich

DISCUSSION:

Dr. Terrye Zaremba of FDA contacted Jill Henrich of Corixa Corporation to request additional information on the BALL-1 cell reagent in order to assist her in the review of Corixa's April 4, 2003 response to the CMC DR letter.

Attachment: Email communication from Jill Henrich, Corixa Corporation responding to May 7, 2003 request.

Jones, Karen

From: Henrich, Jill [Jill_Henrich@corixa.com]
Sent: Thursday, May 08, 2003 4:37 PM
To: Terrye Zaremba (E-mail)
Cc: Karen Jones (E-mail); Henrich, Jill
Subject: Response to request for info

Hi Terrye,

Just wanted to follow-up and respond to you regarding your phone call yesterday. I think it will be easier if I respond by email so you have the directions in front of you to help you navigate.

Regarding the information requested on the BALL-1 cell reagent: The quick answer is that the cells are [redacted]. If you would like to review the specific data you can find it at the following location in BLA STN 125011. [redacted]

b(4)

[redacted]

Hopefully this answers your question(s) - as always, we will make ourselves available to discuss further.

I'm copying Karen so that she's aware of our conversation in case any additional follow-up will be needed or information submitted.

Best regards,

Jill

Jones, Karen

From: Henrich, Jill [Jill_Henrich@corixa.com]
Sent: Tuesday, May 06, 2003 7:39 PM
To: Karen Jones (E-mail)
Subject: Government Agency Contact Report
Pharmaceutical

Coulter

FDA telecon
04-14-03.doc (35 K..

<<FDA telecon 04-14-03.doc>>

Hi Karen,

This is a record of contact from 4/14/03. I know we had discussed sending you our contact reports for comment. Just wanted to make sure you had this one in case you would like to comment.

Regards,
Jill

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **May 2, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Labeling

Participants: FDA/CBER/OTRR: Karen D. Jones

Corixa Corporation: Jill Henrich and Mike Buckley

DISCUSSION:

I called Corixa to request additional information so that the labeling review can be completed:

- Regarding the pharmacy insert, where will it be found? Answer: [redacted]
- Which components in the [redacted] transport package will be labeled? Answer: [redacted]
- Is the [redacted] Package instruction sheet standard instructions; we do not see any reference to the [redacted] insert? Answer: yes
- For label 400047-A, dosimetric top label: only the top panel is provided. Is there information on the other panels? Answer: the labeling submission contained a top and side panel label.
- What is the expiration dating period for the 35 mg and 225 mg Tositumomab vials? The package label will have to have a separate lot number and expiration date based on the shortest dating period of wither the 25 or 225 mg vials. Ms Henrich responded that the 25 and 225 mg vials have the same expiration dating period.
- Please submit a mock-up of the entire transport package with labeling so that we can see how all go together. Include something to represent the dose pot. Only one of these should be submitted; it will not be part of the official file. Corixa agrees to submit the package.
- Please explain why the specific [redacted] and [redacted] concentration cannot be included on the labeling. Corixa: the product is very "hot" and is handled as little as possible.

b(4)

I thanked Corixa for this information. The call concluded.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND IIUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **May 2, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Miscellaneous

Participants: FDA/CBER/OTRR: Karen D. Jones

Corixa Corporation: Monica Krieger, Ph.D.

DISCUSSION:

I called Monica Krieger to inform her of the following:

- FDA will issue a letter today acknowledging that a major amendment to the BLA was received on April 7, 2003. This results in an extension of the review clock by an additional 3 months. I noted that the revised labeling is not going to be included with the letter.
- The April 25, 2003 submission will not be considered a type A meeting request because it is not intended to discuss issues that must be discussed to address a stalled review process (and the review process is not stalled). I noted that this request to discuss the dosimetry software is not an issue that must be addressed for approval of the BLA. I asked for a description of what information will be provided in the briefing package so to help me determine who should be invited to the meeting. Minimally a description of the software program and its use and validation would be required. I indicated that CDRH will have to be consulted on what other information will be required. Dr. Krieger stated that the meeting is not necessarily needed at this time since it is not required for BLA approval.
- I requested that all future contacts be made directly through me in order to permit the reviewers to complete their reviews. The exception to this request is DMPQ which should be directly contacted. Dr. Krieger agreed to this request.

The call concluded.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Our STN: BL 125011/0

MAY 02 2003

Monica Krieger, Ph.D.
Corixa Corporation
1124 Columbia Street, Suite 200
Seattle, WA 98104

Dear Dr. Krieger:

Reference is made to the amendment to your biologics license application received by the Center for Biologics Evaluation and Research on April 7, 2003.

This is to notify you that we consider your submission a major amendment under the Prescription Drug User Fee Act of 1992.

Since this major amendment was received within three months of the action due date on this application an additional three months will be added to the time by which CBER should complete its review.

Should you have any questions regarding this matter please contact the Regulatory Project Manager, Karen D. Jones, at (301) 827-5101.

Sincerely yours,

Earl Dye

for Glen D. Jones, Ph.D.
Director
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

CONCURRENCE PAGE

cc: DARP BLA file, HFM-585
T. Zaremba, HFM-594

CBER:DARP:K.Jones.:K.Townsend:5.2.2003
(S:\Jonesk\125011-0 Tositumomab\MAA Letter)

COMMUNICATION TYPE:

LETTER: Major Amendment Acknowledgment (MAA)

SS Data & RIS Data Check:
- **Communication**
- **Milestone: Major Amendment Close Date & Receipt Date In Ltr Should Match**

RIS Data Check:
- **Milestone: Confirm New Action Due Date (3 Month Extension)**

Division	Name/Signature	Date
OTRR/DARP	Karen D. Jones	5/2/03
DARP	Dye for Jones	5-2-03
DARP	Kelly Townsend	5-2-03

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **May 1, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Labeling Issue: Product Patented

Participants: FDA/CBER/OTRR: Karen D. Jones

Corixa Corporation: Jill Henrich

DISCUSSION:

This call initiated by Jill Henrich of Corixa was a follow-up to the April 30, 2003 telecon. She left a message stating that a fax was being provided of information on the trademark for BEXXAR. ms. Henrich also stated that Corixa's legal counsel, Kate McKerrigan is willing to discuss the issue further if CBER requires further clarification. The call concluded.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **April 29, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: New Submissions

Participants: FDA/CBER/OTRR: Karen D. Jones

Corixa: Jill Henrich

DISCUSSION:

Jill Henrich called on April 28, 2003 and left a message with a tracking number for the training manual submission. On April 29, 2003 I returned her call. Ms. Henrich informed me that a number of submissions are being submitted to the Corixa BLA file:

- A new Type A meeting request has been submitted to discuss validation of dosimetry software. The submission was referred to in the December 10, 2002 submission (# 049), section 5.0, regarding administration of an accurate dose. It contained the software reference and five attachments which included the software requirements and specifications. She indicated that the program validation will be completed by the end of this calendar week and Corixa will request a consultation from FDA. I confirmed that the submission has been received in CBER.
- The training manual was submitted last week in draft. The finalized version with hyperlinks and bookmarking will be shipped today for receipt tomorrow.
- Monica Krieger has contacted Joe Montgomery of CBER regarding secure email. The non-repudiation for electronic signatures form will be submitted today.
- In a previous teleconference with the agency, Dr. Mills had requested information on a reviewer's aid for the re-treatment protocol CP98-021. The protocol and the IND amendment information was submitted April 28, 2003.
- The response to the FDA Form 483 was submitted by MDS Nordion to OCBQ last week and the response to the FDA Form 483 for the Corixa site will be submitted today.

In response to a question, I informed Ms. Henrich that Nancy Chamberlin in ALPB will be her contact for promotional labeling. The call concluded.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **April 28, 2003 email communication**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Additional Information re: Corixa's Resonses 1 & 2 to CMC DR Letter

Participants: FDA/CBER/OTRR: Terrye Zaremba, Ph.D.

Corixa Corporation: J. Henrich

DISCUSSION:

Please see attached email communication dated April 28, 2003, between Jill Henrich of Corixa Corporation and Dr. Terrye Zaremba of FDA containing information requested in a teleconference on April 22, 2003, by Dr. Zaremba regarding Corixa's responses 1 and 2 to the CMC DR letter.

Zaremba, Terrye

From: Henrich, Jill [Jill_Henrich@corixa.com]
Sent: Monday, April 28, 2003 8:22 PM
To: Terrye Zaremba (E-mail)
Cc: Henrich, Jill
Subject: Response to IRF Questions

Response to IRF Questions 0428...

Hi Terrye,

Attached please find the responses to your questions regarding the IRF assay - as outlined in our submission BLA STN 125011/000/054, specifically Comments 1 and 2. I've taken your notes from our telecon and divided them up into individual 'Comments' and have provided our responses. Hopefully this will resolve a number of your outstanding questions/issues. I will call you tomorrow (Tuesday) to set up a time when we can discuss these in order to resolve any outstanding issues, and to discuss what will be formally submitted to the BLA. If you would like to respond and provide a good time to discuss this, let me know by email.

Best regards,

Jill Henrich

<<Response to IRF Questions 042803.doc>>

RECORD OF TELEPHONE CONVERSATION, BLA 125011, Corixa, BEXXAR

DATE: 4/22/03

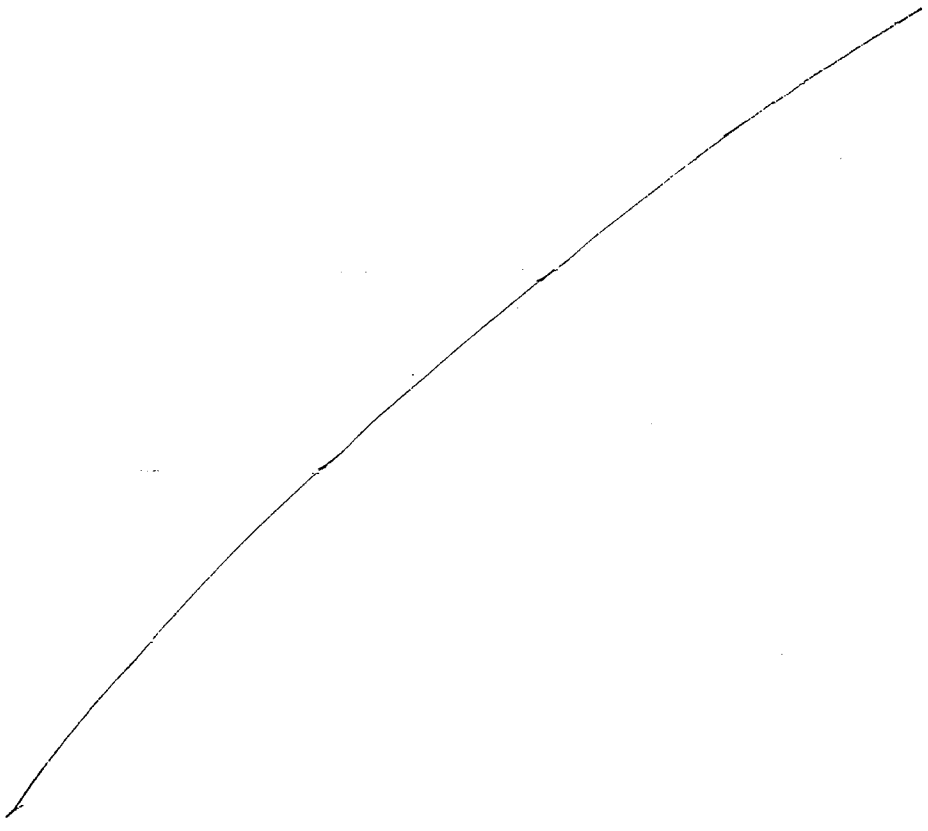
PARTICIPANTS:

CBER: Terrye Zaremba & Patrick Swann

Corixa: Jill Henrich, Mike Buckley, David Colcher, Vito Cieplak, Jeb VanDenburg, Darryl Maas

GSK: Marcia Frederici, Doug Nesta

PURPOSE: To discuss certain aspects of the IRF and saturation binding assays used to assess the BALL-1 reagent and potency of the Tositumomab products, submitted on 4/4/03 in response to CBER's CMC DR letter dated March 3, 2003.



b(4)

2 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 20

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **April 21, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Reference Issue: Training Manual

Participants: FDA/CBER/OTRR: George Mills, M.D., Karen D. Jones

Corixa and GSK: Monica Krieger, Cindy Jacobs,

DISCUSSION:

This teleconference was held at FDA's request to discuss Corixa's proposed response to item 8 of the clinical discipline review (DR) letter (the training program information) To facilitate their response Corixa sent an email on Friday, April 18, 2003 to Dr. George Mills that contained a table of contents and the overview for the training manual. Corixa is proposing to formally submit the revised training manual on 4/25/03 as a BLA amendment and will also make an informal email submission to Dr. Mills on 4/23/03.

Dr. Mills has the following comments:

- The table of contents and the overview appear to be acceptable.
- A major focus of question 8 of our 3/3/03 DR letter is the timing of implementation of the site training program.
- Clinical sites conducting trials under IND could institute the training program.

It was agreed that the training site program should include the following:

- Corixa may not ship product to any sites not trained.
- Clinical trial sites will be pilots.
- Changes in the PI will be implemented into the training manual.
- After pilot sites, Corixa will roll out the program to commercial sites.

Corixa expressed concern about receiving FDA comments on the package insert as soon as possible.

Dr. Mills informed Corixa that the proposed dosimetry software will be handled as an issue separate from the BLA itself. Dr. Krieger indicated that Corixa will submit a formal meeting request to discuss the dosimetry software.

The teleconference concluded.

Jones, Karen

From: Krieger, Monica [krieger@corixa.com]
ent: Friday, April 18, 2003 7:54 PM
'o: George Mills (E-mail)
Cc: Henrich, Jill; 'jonesk@cber.fda.gov'
Subject: Site Training Manual for BEXXAR Therapy <save>

Training
inual-TofC-Objective

<<Training Manual-TofC-Objectives Therapy.doc>>

Dr. Mills
Attached please find the Table of Contents and the Overview for the Site Training Manual. We expect to have a "draft final" ready on Wednesday next week. The official electronic version would be ready to submit on Friday. We would appreciate any comments on the Table of Contents and the Objectives so they could be incorporated early next week.

Since much of this document is based on our draft package insert we cannot finalize this document until we receive your comments on the PI. Perhaps you could let us know when you think you might have comments on the PI; then we can provide a date by which we can finalize this manual.

Also please let me know when you would like us to come out to demo the software.
Thank you
Best Regards,
Monica

8 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 21

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **April 14, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Corixa Response to Question 8 of the DR letter-Received 4/7/03
Reference Issue: Training Manual

Participants: FDA/CBER/OTRR: George Mills, M.D., Mary Andrich, M.D., Karen D. Jones

Corixa and GSK: Monica Krieger, Jill Henrich, Cindy Jacobs, Stanford Stewart, Patricia Stewart, Chris Hurff, Donna Edgerton, Jan Baughman, Rich Francovitch, Meg Martin

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DISCUSSION:

This teleconference was held at FDA's request to discuss Corixa's response to item 8 of the clinical discipline review (DR) letter (the training program information).

To facilitate discussion, a four page draft document was faxed to Corixa which described information submitted by Corixa and the corresponding deficiencies that FDA identified. The document is attached.

Dr. Mills discussed the faxed information in detail with Corixa representatives. He noted that Corixa had not responded to FDA's request to implement the requested clinical site-training program nor have they submitted the clinical site-training program for review. Further, they have not provided a date for submission of the clinical site-training program nor for implementation of the program. The information submitted in response to Question 8 is draft materials for a training program for individuals who will be training the clinical sites. The information does not appear to be finalized or completed.

- Corixa responded that the training program will be based on the information submitted which is intended for training of the trainers. They have not yet determined the date when they can submit the finalized training program.

- Dr. Mills stated that FDA expectations are that the training program is expected to be in place prior to the release of the commercial product and that the same training program should be in place for all commercial and clinical sites, including sites where previous clinical trials and ongoing trials are conducted. The training program manual should clearly define each person's responsibilities. When Corixa responds and submits the clinical site-training program, the submission should also include a timeline for implementation of the clinical site-training program. Corixa committed to retraining of all sites, clinical and commercial and will submit this information to FDA/CBER/OCBQ/ALPB as well as to the BLA file.

Dr. Mills also noted that some of the extensive information now found in the dosage and administration section of the proposed package insert could be considered for incorporation in the training program which may lead to consideration of a reduction in the size of the package insert. Those elements for consideration would include the tables for maximum effect mass graph, total body residence time and dosimetry activity hours. In addition to inclusion in the training program, these tables would then be provided as a separate and more readable document from the package insert with each shipment. Corixa agrees to address this issue with proposals for consideration.

The computer program discussed in Corixa's submission to aid in dose calculations was discussed. Corixa stated that the program will be "validated" at the end of April and will be submitted to FDA. Dr. Mills noted that the program is most probably a device and it will have to be reviewed by CDRH. Corixa offered to demo the program and will look into the question of whether this would be considered a Class 1 device.

Agreement:

When Corixa has finalized the training program it will be submitted to the BLA file along with expected dates of implementation. FDA encourages Corixa to request a teleconference prior to submission of the program to be sure all items have been addressed.

Corixa Question:

When will FDA return labeling comments? Dr. Mills and Ms. Jones indicated that FDA is actively working on the labeling and expects to provide comments to Corixa soon.

The call concluded.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **April 7, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: PMC Study and Labeling

Participants: FDA/CBER/OTRR: Karen D. Jones

Corixa: Jill Henrich

DISCUSSION:

I initiated the telephone contact to discuss administrative issues with Corixa's March 31, 2003 IND 3323 special protocol assessment submission containing Phase 4 post-marketing study protocols. Following this, we then talked about how FDA will respond to Corixa's proposed revisions to the package insert submitted March 26, 2003 and by email on April 7, 2003. I conveyed the position of the clinical review team members which is that FDA will respond to the official March 26, 2003 submission, not to the April 7, 2003 email. We then discussed how the agency will proceed if the April 3, 2003 submission is determined to be a major amendment. The call concluded.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **March 28, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Teleconference with Corixa representative, Jill Henrich 650-553-1958
Proposed April 4, 2003 submission in response to DR letters

DISCUSSION:

Tarrye Zaremba and Karen Jones of FDA called Jill Henrich of Corixa on 3/28/03 to discuss several issues as follows:

- **When is the response to the CMC discipline review (DR) letter going to be submitted?**
  - Ms. Henrich: The response to CMC DR issues will be submitted on April 4, 2003 for receipt on Monday, April 7, 2003. It will include the potency assay information. However, later in the conversation, Ms. Henrich clarified that the potency assay information from BI Pharma would be submitted on April 4, 2003, but it will not include the signed final validation report and test method from MDS Nordion. Corixa has a target submission date of April 14, 2003 for these items. Corixa can email the submission on the same date as the official submission is shipped in order to facilitate review.

- **When is Corixa planning to switch from tellurium-based iodine to fission based iodine.**
  - Ms. Henrich: Corixa is planning to initiate the switch in the next few weeks. The information will be submitted to the IND and will include a PK study (biodistribution) and a study on duration of response with 6 months of follow-up.

- **CBER has not received the official submission of the revised labeling and the training manual information that Corixa emailed and faxed. Has this been officially submitted as an amendment to the BLA?**
    - Ms. Henrich: The information has been submitted as amendment 052. Corixa can supply the tracking number.

- **CBER reviewers would appreciate receiving the training program SOP information in WORD format to facilitate review and comment. Can information for CLP 002, 004, 021 and 029 be provided in Microsoft WORD?**
    - Ms. Henrich: Yes, this can be done. She will submit the information via email as soon as possible.

Dr. Zaremba and Ms. Jones thanked Ms. Henrich for her time.
The call concluded.

Jones, Karen

From: Keegan, Patricia
Sent: Wednesday, March 26, 2003 9:57 AM
To: Misra, Satish; Jerian, Susan; Luksenburg, Harvey; Andrich, Mary; Jones, Karen; Mills, George
Subject: FW: Telecon minutes from 3/21/03 (Corixa)

Importance: High

FDA telecon
03-21-03.doc

I made some changes to the minutes. I think we could amend their minutes and send back FDA's amendments as our comments on the minutes.

-----Original Message-----
From: Jones, Karen
Sent: Tuesday, March 25, 2003 6:02 PM
To: Misra, Satish; Keegan, Patricia; Mills, George; Jerian, Susan; Luksenburg, Harvey; Andrich, Mary
Subject: FW: Telecon minutes from 3/21/03 (Corixa)
Importance: High

FYI:

K

-----Original Message-----
From: Henrich, Jill [mailto:Jill_Henrich@corixa.com]
Sent: Tuesday, March 25, 2003 5:11 PM
To: Karen Jones (E-mail)
Subject: Telecon minutes from 3/21/03

Karen,

Attached please find our minutes of the 3/21/03 teleconference.

Regards,
Jill Henrich
<<FDA telecon 03-21-03.doc>>

FDA Contact Report

Corixa Corporation

Product(s) or Establishment Involved: Bexxar, iodine I 131 tositumomab	Contacted by Company _____
BLA STN 125011 _____X_	
BB-IND 3323 _____	Contacted by Agency __X___
Date of Contact: 21 MAR 2003	

Attendees

FDA:Karen Jones, Patricia Keegan, George Mills, Satish Misra, Harvey Luksenberg, Susan Jerrian, Mary Andrich
Corixa: Stanford Stewart, Patricia Stewart, Stewart Kroll, Jill Henrich
Other: Meg Martin, Mike Hamilton

Signature:
Department: Regulatory Affairs

4 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 22

Government Agency Contact Report
Revised by FDA

Corixa Corporation

Product(s) or Establishment Involved: tositumomab, iodine I 131 tositumomab	Contacted by Company __X___
BLA STN 125011 ___X_____	
BB-IND 3323 _____	Contacted by Agency _____
Date of Contact: 11 March 2003	

Attendees:
FDA: Pat Keegan, George Mills, Susan Jerian, Satish Misra, Karen Jones, Harvey Luksenberg, Kaushikkum Shastri,
Corixa: Cindy Jacobs, Monica Krieger, Jill Henrich, Stanford Stewart, Stewart Kroll, Patricia Stewart
GSK: Mike Hamilton, Ashwin Kashyap

Purpose and Summary of Contact: Discuss the response to the 03 March 03 Clinical Discipline Review letter (timelines, updated ISS, training program, post marketing commitments, draft labeling)

See Attached

Signature:	Monica Krieger
Department:	Regulatory Affairs

Timeline for Response

- PK began the meeting asking about our ability to respond to the letter of March 2 in a piecemeal fashion. She asked that we discuss each part of the letter and a potential timeline.
- We agreed at the end of the meeting that any parts submitted prior to April 4 would be included in the April 4th submission. Thus, all the pieces would be together.

ISS

- -SK described the proposed analyses.
- -PK asked what was meant by the October 1 cutoff date for data. She indicated that we needed a cutoff data that was closer to the current date.
- -There was discussion regarding what data we were sending. SK indicated that patients on EAP were on follow up for two years; patients in other studies are in long-term follow-up. -PK stated that the EAP data was not useful in terms of the hematology data; it was useful for HAMA, TSH and SAEs (including MDS). -SK indicated that the amount of data missing in EAP was similar to the amount missing in the other studies. The conclusion was that Corixa agreed to bring the data cutoff date to February 1, 2003 for all the data and the SAEs.
- -PK asked whether we could provide dosing information in the datasets (what activity was actually administered). SK said that we would provide the same datasets as provided in October 2002. There would be an additional indicator field marked to indicate whether the investigator confirmed that the administered activity was the actual activity administered. SK asked for a clarification on question 10c and whether the confirmed dose meant confirmed activity. FDA agreed that they wanted the activity of I 131 in the syringe. In terms of the analysis they want two groups: known dose (confirmed) vs estimated dose (unconfirmed). They also want the m^2 and the weight (kg) for the patients. They will evaluate whether there are any patterns related to these measures. SK agreed this information would be provided. SK stated that there will be a dataset on MDS/AML for all patients, including length of follow-up, vital stats, study day onset/diagnosis, etc and it will be part of the integrated database, included in PTOUT.
- -PK requested that Corixa provide a quarterly update of the ISS in the future. There was discussion about whether this was requested in the telecon of September 13, 2002. Notes from the company and the Agency do not agree. To avoid any future confusion, Corixa and the Agency agreed to share meeting minutes. MK agreed for Corixa that we would provide quarterly updates in the future. [Note from FDA: A review of the BLA post-teleconference revealed that Corixa did submit written correspondence dated October 4, 2002 that included a commitment to provide an updated ISS in December 2002.]
- -Corixa indicated that we would send the ISS with the datasets on April 4.
- At a later point in the telecon, the agency asked if Corixa could send the database prior to the report. Corixa agreed to looking at whether this would be possible.
- At the end of the meeting SS said that we would like to treat non-melanoma skin cancers as a secondary malignancy. GM said they would like to look at this issue further prior to agreeing. Corixa agreed to include them in the present ISS as SAEs. We will discuss this again with the Agency at some point in the future.
- HL noted that with regard to the patients with MDS the Agency did not want a presumptive diagnosis. The FDA would like as much evidence of the diagnosis as possible. Those cancers not clinically aggressive (i.e., those cancers that "behave"

similar to those in non-immunosuppressed subjects) do not need to be classified as SAEs in the updated ISS. SS said that Corixa has been trying to obtain material from every patient. We have tried to obtain histologic specimens for all patients and have them reviewed by a hematopathologist. There may be some patients who will be classified without this histopathology review if the specimens are not available.

Commitments Regarding Training of Sites

- -PK asked whether we could provide a description of the training program. PK stated that the commercial training program should be more rigorous than that at the clinical sites.-MK noted that this had been provided in the submission of December 10. Corixa agreed to provide a current and updated version to the Agency.
- -PK asked whether we had agreed to only ship to certified sites. MK noted that this had also been included in the submission of December 10. Corixa noted that this was the procedure used by the Bexxar Service Center. The Agency asked for a copy of the Service Center Manual.
- -Corixa agreed to send the description of the training program and the service center manual by March 21.

Draft Labeling

- -The agency asked whether we could submit the draft labeling earlier than April 4. These could be submitted by fax or via secure e-mail. The package insert should be submitted in Microsoft WORD. MK asked whether draft package labels could be typed version of the labels rather than a mock up. F.DA agreed that typed would be acceptable. This would allow us to come to some general agreement.
- Corixa agreed to send drafts of the labeling at by March 21, 2003.

Post-marketing Commitments

- PK asked whether we intended to use the data from the SWOG trial. CJ said that we will not use this trial as a registration trial. She noted that the trial was being run under a SWOG IND.
- Corixa indicated that we were committed to the Bexxar vs Zevalin study. This protocol would be submitted to the IND under SPA. We will plan to provide by April 4. A charter for the DSM and stat plan will be included. KJ asked that Corixa provide a cross reference letter to the BLA. The response that we submit to the BLA should identify the study and the milestones in the BLA. We should also indicate the proposed claim for the package insert based on the study.
- CJ stated that we did not plan on conducting the Bexxar vs Rituxan study in the US since we were not being approved under Accelerated Approval. She said we would be doing the study in Canada and Europe to collect the safety information. PK said that we need to discuss this further at another time ensure we are capturing the LT safety issues requested from the ODAC.
- CJ indicated that we will have a proposal by April 4 to deal with the issues including: a Retreatment protocol, response to vaccination, and HAMA.
- CJ said that we would be collecting the data on all the cases of MDS.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: March 21, 2003 Time: 1:00 to 2:00 pm EST

From: Karen D. Jones, CBER/OTRR/DARP, HFM-588

To: Corixa Corporation
Tositumomab (Bexxar)
BLA, STN 125011/0 File

Subject: Post Marketing Commitments

PARTICIPANTS: CBER/OTRR: George Mills, Patricia Keegan, Susan Jerian, Harvey Luksenburg, Karen D. Jones, Mary Andrich

CBER/OBE/DB: Satish Misra

Corixa Corporation: Jill Henrich, Stewart Kroll, Stanford Stewart, Patricia Stewart

GSK: Mike Hamilton, Meg Martin

This teleconference was requested by FDA to discuss proposed Phase 4 studies that will be post marketing commitments.

DISCUSSION:

Please see attached minutes from Corixa that have been edited to incorporate FDA corrections.
As previously agreed to with Corixa, the edited minutes will be returned to Corixa informally via fax to facilitate understanding of the issues discussed and agreements reached.

The call concluded.

FDA Contact Report **Corixa Corporation**

Revised by FDA

Product(s) or Establishment Involved: Bexxar, iodine I 131 tositumomab	Contacted by Company _____
BLA STN 125011 _____X_	
BB-IND 3323 _____	Contacted by Agency __X___
Date of Contact: 21 MAR 2003	

Attendees

FDA:Karen Jones, Patricia Keegan, George Mills, Satish Misra, Harvey Luksenberg, Susan Jerian, Mary Andrich
Corixa: Stanford Stewart, Patricia Stewart, Stewart Kroll, Jill Henrich
Other: Meg Martin, Mike Hamilton

Signature:
Department: Regulatory Affairs

The purpose of the teleconference was primarily to discuss Corixa's post-marketing commitments.

Bexxar vs Zevalin

- PK asked whether this comparative safety trial was designed as a trial to demonstrate that Bexxar was non-inferior or that it was safer. SS replied that the primary endpoint is hematologic toxicity and it is designed to demonstrate superiority. PK asked whether the duration of toxicity would also be evaluated. SS responded that we intended to show a lower rate of hematologic toxicity. Duration of toxicity would be a secondary endpoint. He said that we would evaluate all adverse events including hospitalizations, infections, etc. SS confirmed that Corixa will be doing LT follow-up on patients for HAMA, TSH and MDS. The sample size is a total of 280 patients with 140 in each arm.
- PK commented that we might not be able to say something about (the incidence of) MDS, but could certainly on HAMA and hypothyroidism.
- PK asked if we are evaluating efficacy. SS responded that we would be using a MIRROR panel to evaluate efficacy as we have done in previous trials.

SWOG Trial

- PK said they had received an amendment on the SWOG trial. However, given Corixa's prior comments (an e-mail was sent prior to the meeting indicating that we would not be submitting this study for a modification of the label at this time), FDA will not consider this trial as a licensing trial and will not provide comments to SWOG on the adequacy of the revised trial for this purpose.

Bexxar vs. Rituxan

- SS confirmed that the trial will be the study that was submitted for Special Protocol Assessment. We will amend the protocol to change the type I error for labeling purposes to 0.01 (from 0.05) as requested.
- SS confirmed that we would be seeking a label change based on the study.

Retreatment Protocol

- SS indicated that Coulter had a Retreatment protocol that has been closed to accrual. He stated that we have not yet analyzed this data. We will be providing a timetable for data analysis and writing a report. We could at that point discuss whether the data was sufficient. The Agency had a number of questions.
- PK asked what was the protocol number. It was CP-98-021. She asked when it was submitted and whether in the interest of time, Corixa could resubmit the protocol, protocol amendments and the CRFs. She also asked whether the BI antibody had been used for the entire trial. Corixa responded that it probably was largely BI antibody for retreatment; however, a few patients may have received antibody produced by Lonza. The antibody source for original exposure was unrestricted and may have included Coulter, Lonza and BI-sourced material. PK indicated that it would be useful to know what

material that each patient had received on initial exposure and on retreatment..

- The Agency asked how many sites were involved; Corixa answered 6. The question was asked whether it was largely patient enrolled at Michigan.
- The Agency asked about the data on the population. JH responded that there was data in the Annual report. The Agency was looking to determine whether the population was heterogeneous. They will want to get a sense of the data:
    - Do we have data on HAMA
    - Was there altered biodistribution
    - What trials were the patients enrolled in initially
    - How much data is available on their prior experience with Bexxar

- SS reiterated that it was take us some time to do the report; but we think we can do it reasonably quickly.
- FDA noted that without a copy of the protocol and the information discussed above, FDA will be unable to determine whether this protocol can satisfy, in part, the PMC.
- FDA stated that the number of patients enrolled and the heterogeneity that likely occurred makes this study unlikely to be adequate as a single study to address this PMC and that Corixa should develop alternate, supplementary proposals as well and submit them as soon as possible.

HAMA testing

- PK commented on the information we submitted. She noted that simply testing HAMA+ sera and determining the serologic results using various clinical assays was not adequate. These data should be correlated with biodistribution and safety data to determine the significance of the HAMA value in individual assays.
- SS noted that we would be following these patients in the life after BEXXAR part of the two large studies. In those studies we would be evaluating whether there was any change to the treatment regimen due to their exposure to murine antibodies. In other words, this would be part of a prospective study to determine if treatment procedures were altered.
- The Agency requested a protocol on the ——— study indicating the number of samples, the age of samples, data on storage of samples. (The concern seemed to be whether these samples would still be representative of HAMA+ samples). Corixa indicated that we would retest the samples in the same central assay which yielded the initial positive result. The agency wanted to know what the initial results were on a HAMA test. SS said we did not know if their initial results were available since the patient had to be HAMA negative (i.e. that may be all the data we have). FDA stated that the initial and re-tested result data would be important in assessing whether storage conditions affected the assay results and thus whether the testing of stored samples would provide useful data. FDA also asked whether we know if there were sera from subjects who were not permitted to undergo

b(4)

therapeutic dosing due to positive HAMA results. Corixa indicated that we would go back and look to see if the raw data was available.

Vaccination Trial

- PK indicated they would probably have their colleagues in the vaccine group (OVRR) evaluate this protocol in conjunction with OTRR.

Material to be Submitted Next Week

- PK asked if we could submit the insert both as a pdf and as a WORD file. JH responded that we would do both. The Agency asked if the file was line numbered; JH responded yes.
- The Agency was looking for a training manual. They said they had reviewed the December 10 submission and this was not adequate. They are expecting an expanded version. They are looking to see:
  - Initiation package-
  - Users manual
  - Evaluation
  - Goals and accomplishments
  - Checklist to know if they are qualified
  - How they demonstrate what is accomplished
  - How trained

- GM asked about the package containers and vial labeling. JH said they would be ready Monday. GM asked about the names. JH said they would be named tositumomab and iodine I 131 tositumomab (either dosimetric or therapeutic dose). He asked if the cold dose was coming with the radiolabeled dose. [redacted] b(4) She noted that they are scheduled to arrive at the same location and at the same time.

Revisit Notes of Last Meeting:

- Re: characterizing patients with non-melanomatous lesions as secondary malignancies not SAEs. PK was unclear about the discussion since she was not on the phone. After discussion, she agreed with the plan that we would continue to report these as SAEs. She also asked how we are reporting cervical carcinoma *in situ*. SS noted these are reported as SAEs.
- Re: submitting an ISS by year-end. PK called our attention to our letter of October 4 indicating we would be submitting an ISS by year-end.
- Re: submitting items as a whole. PK noted that if we submit items to the BLA we do not need to resubmit the responses as a whole.

ADDITIONAL:

- PK said that in looking at our responses in totality (new analyses (safety/dose delivered), new data, etc) that we should be aware that this could be

considered a major amendment and that it would affect the action date. MK noted that this was a concern for the company since this presented a delay in product approval. Since FDA is not clear about how much will be new data, they'll give us the timeframes once they've received the data. KJ wanted us to clarify whether the submission would be an amendment to the BLA.(yes)

ACTIONS

- Regarding CP-98-021: resubmit the protocol, protocol amendments and the sample CRFs. For each subject, provide a line listing of the antibody source used in the original treatment as well as the protocol under which original treatment occurred and the antibody source for the retreatment.
- Check HAMA positive samples to see if we have information on number of samples, age of samples, storage of samples, and initial results on HAMA test (including what test)

Jones, Karen

From: Krieger, Monica [krieger@corixa.com]
Sent: Friday, March 14, 2003 2:47 PM
To: 'keegan@cber.fda.gov'
Cc: 'jonesk@cber.fda.gov'
Subject: Corixa Clinical Trials

Dear Dr. Keegan:

We thought it might be useful to summarize again the post-marketing trials we are planning prior to our telephone conversation, especially since we have had additional internal discussions and revised our plans for the Rituxan vs Bexxar study.

* Rituxan vs BEXXAR trial (-049 study): We will conduct this study under a US IND. Patients will be enrolled in the US, as well as in Europe and Canada. The study will include changes recommended by the Agency during the last Special Protocol Assessment.

* BEXXAR vs Zevalin trial (-053 study): We will send in the Protocol under SPA with the draft CRFs, SAP, DSM charter and monitoring plans. We view this trial as a safety trial comparing the two RIT products (Bexxar and Zevalin).
*
* SWOG trial: As we indicated, we do not intend to use this for a label claim. This is a SWOG IND, as such, altering the trial would be unlikely, if not impossible.

The following items will also be evaluated; these may be evaluated in one or more of the trials above.

* Retreatment Trial: We will conduct a Retreatment protocol and plan to submit an outline of the trial, plans and timelines.

* HAMA - Corixa will propose in vitro testing of samples that are HAMA positive and HAMA negative on a number of in vitro diagnostic tests that might be used routinely in a patient population of this age. Samples that are positive for HAMA will also be tested after removal of the HAMA. An outline and plan will be submitted. In addition, the Bexxar vs Zevalin trial will include obtaining information from patients on any treatments or in vivo diagnostic procedures that they were precluded from receiving as a result of being HAMA positive.

* MDS - We plan to continue follow-up in all trials or patients treated with BEXXAR. Long term safety endpoints will be included in both the B vs Z trial and the R vs B trial to allow for adequate assessment of the incidence of MDS.

* Vaccination trial - We will submit an outline of the trial, plans and timelines for a protocol after further discussion between Corixa and GSK.

Regards,
Monica Krieger

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: **March 13, 2003**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Teleconference with Corixa representative, Jill Henrich 650-553-1958
Telecon Request/Facility Issues

DISCUSSION:

I telephoned Jill Henrich of Corixa to advise her that upon review of the March 11, 2003 BLA amendment containing a request for a meeting to discuss facility-related issues, FDA is denying the request because there is insufficient reason to hold the formal teleconference at this time. Instead, FDA will hold an informal teleconference the week of March 24, 2003. Ms. Henrich was satisfied with this decision.

I then asked Ms. Henrich if Corixa would be available next week to have a discussion of the planned Phase 4 study of BEXXAR versus Rituxan. She statd that Corixa would be available to discuss this study any day except Monday, March 17, 2003.
The call concluded.

Addendum: I phoned Ms. Henrich on 3/14/03 and left a message to inform her that the telecon has beens et up for March 21, 2003 from 1:00 to 2:00 pm, EST.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date: March 11, 2003 Time: 2:30 to 3:30 pm EST

From: Karen D. Jones, CBER/OTRR/DARP, HFM-588

To: Corixa Corporation
Tositumomab (Bexxar)
BLA, STN 125011/0 File

Subject: Follow-up to FDA Clinical DR Letter Dated 3/3/03

PARTICIPANTS: CBER/OTRR: George Mills, Kaushikkumar Shastri, Satish Misra, Patricia Keegan, Susan Jerian, Harvey Luksenburg, Karen D. Jones

CBER/OBE/DB: Satish Misra

Corixa Corporation: Jill Henrich, Monica Krieger, Stewart Kroll, Cindy Jacobs, Stanford Stewart, Patricia Stewart

GSK: Mike Hamilton, Ashwin Kashyap

This teleconference was requested by Corixa in response to the March 3, 2002 DR letter (clinical) to clarify the information that FDA is asking Corixa to submit.

DISCUSSION:
The discussion was initiated by Dr. Keegan who urged Corixa to submit their response to the March 3, 2003 letter as soon as possible, preferably piecemeal. Dr. Keegan then stated that FDA would like a timeline for submission of the response to each portion of the letter.

Updated ISS

1. Corixa asked for clarification regarding the request for an updated ISS. They noted that the data cut-off date was 10/1/03 since all clinical studies have been completed. Additional data from the extended access protocol is still coming in and looks similar to safety data from other studies. Upon discussion the following agreements were reached:

- **The data cut-off for the safety update (ISS) will be February 1, 2003 and will include all the data and the SAEs.**
- **Thereafter, the database will be updated quarterly as reflected in CBER notes from the September 13, 2003 telecon. [Corixa stated that their notes of the 9/13/03 telecon are not in accord with CBER's notes; their notes reflect that it was agreed to submit this information at the end of the first quarter 2003. It is therefore agreed that meeting minutes will be exchanged in the future. Post-telecon note: a review of the BLA file shows that Corixa's 10/4/02 submission contains a commitment to submit the updated ISS by the end of the year 2002.]**
- **Dosing information will be provided in the ISS datasets that reflects the actual dose administered as opposed to the calculated dose. The confirmed dose can be segregated from the intended dose by an indicator field, for example, assigning a variable of 1 for the confirmed dose and a 0 for intended dose.**
- **In response to a question on letter item 10c, CBER confirmed that the term "dose" means the activity in the I-131 labeled therapeutic.**
- **The revised, updated ISS with the datasets will be submitted by 4/4/03. In response to CBER's request, Corixa will try to submit the database earlier, followed by the analyses.**
- **Non-melanoma skin malignancies will be classified as SAEs in the ISS if they are aggressive cancers similar to those seen in immunosuppressed subjects. FDA will review each case for severity and will then discuss with Corixa whether to classify them as secondary malignancies, not subject to reporting as SAEs.**
- **The dataset on myelodysplasia (MDS) and leukemia will be provided as a separate dataset that will include all patients and will include full clinical information such as the length of follow-up, vital statistics, etc. FDA noted that for MDS, Corixa should include conventional clinical criteria documentation of the diagnosis. Corixa noted that they have sought histologic material on each case presented in order to obtain an independent review, but this may not be possible for all patients.**

Training Program

2. **The following items regarding training were discussed:**
   - **Corixa should provide the revised training procedure to be used at clinical sites where the product is to be used commercially or in clinical trials, since the inspection revealed that the training program was inadequate. Corixa responded that information was submitted to the BLA in the December 10, 2002 submission. Corixa agrees to submit the current, revised training procedure.**

- **Regarding item 9, the service center manual, additional detail is required. Corixa noted that information was supplied in their December 10, 2002 submission. Corixa agrees to submit the service center manual.**
- **The revised training procedure and the service center manual will be submitted by March 21, 2003.**

Labeling

3. **Revised draft package insert labeling in Microsoft WORD format and draft package labeling will be submitted by fax or secure email by March 21, 2003. The draft package labeling does not have to be a printer's mock up version. The package insert will not include the updated safety information as of the February 1, 2003 cutoff. Those revisions can be made after the ISS is submitted to FDA.**

Post-Marketing Commitments

4. **Regarding proposed post-marketing studies:**

- **Regarding the SWOG clinical trial, CBER expressed concern that the first notification of the changes in the protocol came at the advisory committee meeting and recommended that Corixa improve the level of communication. Corixa responded that the SWOG trial data will not be used as a registration trial.**
- **The Bexxar vs. Zevalin clinical trial will be submitted as a Special Protocol Assessment to the IND, with a letter of cross-reference to the BLA, on April 4, 2003. The protocol submission will include the independent review charter, a statistical analysis plan and will indicate the proposed claim as well. The letter of cross-reference will outline the schedule for the study, as is customary for post-marketing commitments.**
- **The Bexxar vs. Rituximab protocol requires further discussion regarding the collection of more safety information and a longer follow-up period. It is agreed to hold a follow-up teleconference.**
- **The April 4, 2003 submission will include proposals for additional clinical studies that will address a re-treatment protocol, response to vaccination, and HAMA as it relates to receiving alternate therapies and myelodysplasia.**

Final Agreements:

- **Corixa will submit the response to the DR letter piecemeal to facilitate CBER review.**
- **Corixa agrees that a complete response to each item of the letter will be submitted by April 4, 2003 and that the last submission will also include all previous submissions.**

The call concluded.

Jones, Karen

From: Henrich, Jill [Jill_Henrich@corixa.com]
Sent: Monday, March 10, 2003 11:51 PM
To: Karen Jones (E-mail); George Mills (E-mail); Kaushikkum Shastri (E-mail); Satish Misra (E-mail)
Cc: Henrich, Jill
Subject: Info for 3/11 Telecon with Corixa

description of safety populati...

Attached is an outline of the safety population for tomorrow's discussion.

Dial In: (877) 895-6183
Part. code: 754-5729

<<description of safety population.doc>>

Clarification of Safety Update

The safety update will include the following studies.

Study	Enrollment	In Safety Datasets	ISS Population
RIT-I-000 (Phase I/II)	59	59	22
RIT-II-001 (Phase II)	47	47	47
RIT-II-002 Arm A	42	42	42
RIT-II-002 Arm B	36	36	0
RIT-II-002 Crossover	19	19	19
RIT-II-003 (First-line)	77	77	0
RIT-II-004 (Refractory)	61	61	60
CP-97-012 (Rituxan Failure)	43	43	40
CP-98-020 (EAP)	791	791	765
Total	1175	1175	995

The integrated safety population will include all patients who received iodine I 131 tositumomab in studies RIT-II-001, RIT-II-002, RIT-II-004, CP-97-012, and CP-98-020 and (per CBER's 03 March 2003 letter) the 22 patients from study RIT-I-000 who had relapsed/refractory low-grade NHL with or without transformation and were prescribed a total body dose of 65 or 75 cGy.

Analyses of adverse experiences will be performed separately for patients from CP-98-020 (EAP) and the other studies (non-EAP). Analyses of other safety endpoints (serious adverse experiences, hematological toxicity, chemistry, HAMA, TSH, MDS/AML, and secondary malignancies) will be presented for the 955 patient integrated safety population.

A data cutoff date of October 1, 2002 will be used for all of these studies. Additionally, a data cutoff date of March 1, 2003 will be used for serious adverse experience narratives in these studies.

A new dataset for MDS/AML will be created and include all patients. The dataset will include the usual patient identifiers, the length of follow-up, vital status at last follow-up, an indicator for whether the patient was diagnosed with MDS/AML, and the study day of onset.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

Date of Telecon: March 3, 2003

From: Karen D. Jones, CBER/OTRR/DARP, HFM-588

To: BLA 125011/0 file
Corixa Corporation
Tositumomab and Iodine I 131 Tositumomab

Subject: FDA Discipline Review Letters

PARTICIPANTS:
CBER/OTRR: Karen D. Jones, RPM, DARP

Corixa Corporation: Monica Krieger, Ph.D, and Jill Henrich, Regulatory Affairs

I placed a call to Monica Krieger to confirm the fax number and then faxed the clinical and the CMC discipline review letters to her. Jill Henrich called to confirm receipt of the letters and asked that the hard copies be sent to her office instead of Dr. Krieger's office. I responded that if the letters had not already been sent to the mailroom, I would send them to her office. The call concluded.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Our STN: BL 125011/0

MAR 0 3 2003

Monica Krieger, Ph.D.
Corixa Corporation
1124 Columbia Street, Suite 200
Seattle, WA 98104

Dear Dr. Krieger

This letter is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act.

The Center for Biologics Evaluation and Research has reviewed the chemistry, manufacturing, and controls section of your biologics license application for Tositumomab and Iodine-131-Tositumomab, including the amendment dated October 30, 2002. We also refer to the telephone conversation on November 19, 2002 between Jill Henrich, Mike Buckley and David Colcher of Corixa Corporation, Marcia Frederici and Doug Nesta of Glaxo Smith Kline, and Terrye Zaremba of this office. Preliminary comments and deficiencies identified during this review are summarized as follows:

1. As agreed during the November 19, 2002 telephone conversation, please submit:

   a.

   b.

   c.

   d.

   e.

2. Please submit a revised table of Stability Tests and Specifications (Table 1, page 188) that includes specifications for ____ binding and ____.

b(4)

3. In your October 30, 2002 response to item 15 you agreed to redevelop the SDS-PAGE silver staining method to improve consistency and performance prior to approval. Please submit representative results of the new Silver Staining method for SDS-PAGE gels along with the SOP for this assay.

4. Your response to item 18 is incomplete. Your response states that you plan to verify the sensitivity of the microbial challenge test by [redacted] b(4) . Please submit study results for the microbial challenge test method performed at GSK Laboratories using the methods and procedures outlined in protocol PRO-MGM-02-10.

These comments are being provided to you prior to the completion of our review of your entire application to give you preliminary, advance notice of manufacturing issues that have been identified. Please note that these comments are subject to change as the complete review of your application is finalized. Final comments, if any, will be communicated to you at a later date after the review of the application and establishment inspections are completed. You may, but are not required to, respond to these preliminary comments. If you respond, we may or may not consider your response prior to taking a complete action on your application. If your response is determined to constitute a major amendment, you will be notified of this decision in writing. Review of the remaining sections of your application is continuing.

Should you need additional information or have any questions concerning administrative or procedural matters, please contact the Regulatory Project Manager, Karen D. Jones, at (301) 827-5101.

Sincerely yours,

Terrye C. Zaremba

Terrye G. Zaremba, Ph.D.
Committee Chairperson
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

CONCURRENCE PAGE

cc: K. Webber, HFM-555
E. Bonvini, HFM-555
K.Weiss, HFM-570
DARP BLA file, HFM-585
T. Zaremba, HFM-594
D.Trout, HFM-675
J. Eltermann, HFM-670
C. Kelley, HFM-675
S.Risso, HFM-500

CBER:DARP:K.Jones:02-20-03:K.Townsend:2.25.2003:2.27.2003:3.3.2003
(S:\Jonesk\125011-0 Tositumomab\DR Letter (CMC))

COMMUNICATION TYPE:

LETTER: Discipline Review Letter: Identify Discipline - Pick One: CMC

SS Data Check:
- **Communication**

Division	Name/Signature	Date
OTRR/DARP	Karen D. Jones	3/3/03
OTER/DMA	Teresa C. Zaremba	3/3/03
DARP	K. Townsend	3/5/03

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Our STN: BL 125011/0

MAR 03 2003

Monica Krieger, Ph.D.
Corixa Corporation
1124 Columbia Street, Suite 200
Seattle, WA 98104

Dear Dr. Krieger:

This letter is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act.

The Center for Biologics Evaluation and Research has reviewed the clinical section of your biologics license application for Tositumomab (Anti B1) and Iodine-131-Tositumomab (Bexxar®), including the amendments dated March 4, 2002, July 3, 9, and 11, 2002, August 2, 2002, October 4 and 30, 2002, and November 14, 2002. Preliminary comments, deficiencies, and questions identified during this review are summarized as follows:

CLINICAL INFORMATION

Comments 1 through 7 reference our complete response (CR) letter dated March 12, 2002 and your responses dated October 4 and 30, 2002 and November 14, 2002.

1. Regarding your response to comment 1 in our March 12, 2002 CR letter, we have the following comments:

   a. The October 4, 2002 ISS dataset contains no new safety data over that contained in the March 4, 2002 submission, in which previous errors were corrected and safety data were augmented for a small number of patients. The "additional" patients in the ISS represent integration of previously submitted data provided in other datasets or new information on additional patients that consists only of demographic and baseline entry information. In addition, the data cut-off is more than one year ago (cut-off date of January 31, 2002 for RIT-I-000, RIT-II-001, RIT-II-002, RIT-II-003, RIT-II-004 and 4 patients enrolled in access studies, and cut-off date of February 8, 2002 for study CP97-012) and more than 18 months ago for all but 4 patients in the expanded access experience (cut-off date of August 31, 2001). Thus, the information in the ISS is out of date and is inadequate for the purpose of describing serious and delayed toxicities in product labeling. As you were informed during the September 13, 2002 telephone conversation, and as further discussed in comment 2 below, we will

be unable to provide an accurate assessment of the adverse event experience necessary for development and agreement on final labeling without the updated information on serious and delayed toxicities.

b. As stated during the meeting of April 24, 2002, we believe that there are sufficient data to characterize the incidence and severity of acute and common adverse events, specifically hematologic toxicity, through analyses in which missing data are imputed as "worst case". We note your concurrence with this approach during our meeting. We further note that rare toxicities cannot be easily assessed by this methodology and that additional studies to further characterize the incidence of rare and serious toxicities may be required. An updated safety database containing all new reports of serious adverse events, as well as narrative summaries of each event will be necessary to develop accurate labeling for your product. In addition, the post-marketing studies discussed in items 10 and 11 below should be adequately designed to supplement the safety information in this area, as should all ongoing studies being conducted under your IND.

2. With regard to your response to comment 2 in our March 12, 2002 CR letter, we have the following comments:

Your response is adequate except for the description of the incidence of myelodysplasia/secondary leukemias, which is misleading and in conflict with other parts of the submission. Specifically, you state that "Although the data from the Expanded Access Program result from shorter follow-up (median follow-up of 1.5 years) than that available on the remainder of the patients in the 620-patient integrated safety population, these data provide assurance that there is no marked increase in MDS/AML during the first 18 months post treatment with Iodine-131-Tositumomab." Only one patient in the group of 387 was noted to have developed MDS/AML. In an independent review of pathology material, this patient had evidence of pre-existing MDS at study entry. However, review of the previously unreported SAE narratives provided with this submission show that there are at least 8 previously unreported cases of MDS/AML among patients in the expanded access protocol and another study. These cases were not incorporated into the safety database and are not included in your analyses even though they represent a 50% increase in the number of such events.

You should submit an updated safety database that is adequate to permit us to derive the observed and cumulative incidence of MDS/AML in all patients for whom you have collected safety information. Please see additional comments on safety updates as described in item 6 below.

3. Your response to comment 3 of our March 12, 2002 CR letter is adequate.

4. Your response to comment 4 of our March 12, 2002 CR letter addresses our question, however, we disagree with your statements that inclusion of patients assessed by an insensitive measure (patients queried on whether they are currently taking thyroid replacement therapy) is an acceptable means of determining the incidence of hypothyroidism.

   For purposes of labeling and any other descriptive materials (e.g., promotional materials, investigator brochure), only determination of the cumulative incidence of hypothyroidism by a sensitive assay measure (i.e., TSH measurement) will be considered acceptable. Please acknowledge.

5. Regarding your responses to comments 5 and 6 of our March 12, 2002 CR letter, your studies of the Bexxar® therapeutic regimen showed evidence of activity (durable complete and partial responses) that are likely to predict clinical benefit in patients with chemotherapy refractory follicular lymphoma, with and without transformation. However, there are available therapies for this indication and the studies you conducted were not concurrently controlled. As discussed at the December 17, 2002 meeting of the Oncologic Drugs Advisory Committee (ODAC), the studies were inadequately designed to allow you to establish that your product provides an advance over these alternative treatments. Therefore, we conclude that you have failed to provide an adequate justification for accelerated approval for chemotherapy-refractory, Rituximab-naïve patients.

   With regard to study CP-97-012, and as advised by members of the ODAC, we agree that the Bexxar® therapeutic regimen shows substantial evidence of clinical benefit (durable complete and partial responses) in patients with follicular lymphoma refractory to both chemotherapy and Rituximab, with and without transformation. We request that you revise your proposed indication to patients who are refractory to both chemotherapy and Rituximab.

6. Your response to comment 7 of our March 12, 2002 CR letter is satisfactory. However, you state in the cover letter to your October 4, 2002 submission that "Corixa plans to provide an updated ISS, including all patients enrolled in the Expanded Access Protocol (EAP) by the end of the year". We have not received an updated ISS. We further note that you were informed in the September 13, 2002 teleconference that safety updates should be submitted quarterly during the period of BLA review. The ISS SAS dataset has not been updated with new safety information since March 4, 2002 and data for the majority of patients have not been updated for 12-18 months. Please submit the following:

a. A safety update within two weeks of receipt of this letter to permit continued review and drafting of an accurate label. Safety updates should include an updated database that incorporates all new adverse event and clinical data post-treatment for patients enrolled in clinical studies since September 2002 and all serious adverse events. It should also include narrative summaries for any new adverse events. We request a separate database for MDS/leukemia that should be submitted with the narrative report for each event within 15 days of receipt of a report of the event.

b. A statement certifying that the safety database provides data for the actual, measured dose that was administered (see item 10 below).

c. Written acknowledgment that you will submit safety updates on a quarterly basis prior to approval.

7. Your response to comment 8 of our March 12, 2002 CR letter is adequate.

We also have the following requests for additional information, including post-marketing studies:

8. The Agency's inspections of clinical sites conducted between November 12 and 15, 2002, identified serious deviations from the protocol. These deviations affected determination of the dose assessment, dose calculations, drug delivery system, quality control, and documentation. You should implement a training program to avoid such problems at sites where the product is used either commercially or for future clinical trials. You should develop policies and procedures so that product will only be shipped to sites that have successfully completed this training program. Please submit a detailed description of your proposed training program, including dates of proposed implementation and the criteria to be met as documentation of successful completion of training.

9. Provide a detailed description of the procedures to be employed in the shipping and distribution of the components of the Bexxar therapeutic regimen. The shipping procedures should ensure that:

a. Kits to be used for the first and second steps of preparation are distributed only to sites that have completed training in the methodology for dose assessment and dose calculation, drug delivery, quality control and documentation.

b. ALL components of the dosimetric step are shipped as a unit and that each component is clearly marked as part of a kit to administer the dosimetric dose.

c. ALL components of the therapeutic step are shipped as a unit and that each component is clearly marked as part of a kit to administer the therapeutic dose.

d. Clearly indicate the sites of preparation of the iodinated dosimetric and therapeutic doses.

10. Due to the practice at several major study sites to record the prescribed dose rather than the actual dose administered, we are unable to determine the toxicity profile according to the prescribed dose. In order to understand the scope and clinical impact of this deviation from the protocol, please provide the following:

a. In the next safety update (and all future ISS updates), provide the actual measured dose administered (if known). A flag or similar identifying character should be included in the database, identifying all patients for whom the actual dose was not measured (and thus is unknown).

b. Perform analyses of the incidence and duration of acute hematologic toxicities for all lineages (neutrophil, hemoglobin, and platelets) according to dose delivered, in which the analysis is limited to those patients for whom the actual dose delivered is known. Provide a separate analysis for safety for those patients for whom the actual dose delivered cannot be determined.

c. Perform analyses of the overall, complete and partial response rates for each of the five clinical studies, according to dose delivered, in which the analysis is limited to those patients for whom the actual dose delivered is known. Provide a separate analysis for efficacy for those patients for whom the actual dose delivered cannot be determined.

11. The following comments pertain to studies that you have identified and proposed to conduct as post-marketing studies. If you plan to conduct these studies, please submit a detailed protocol or, at a minimum, a detailed outline describing all design features of the study including sample size and justification, eligibility criteria with rationale, dosing regimens and duration, clinical assessments to be performed and their timing, and endpoints to be analyzed. In addition, please propose a schedule for conducting each study including all major milestones for the study, e.g. submission of finalized protocol to the FDA, completion of patient accrual, completion of the study, and submission of the final study report, SAS data sets and applicable revised labeling to the FDA.

a. You have identified the study being conducted by SWOG (Protocol S0016) as a post-marketing study to [redacted] b(4)
[redacted] The protocol was modified without consultation or notification to FDA (and was not submitted prior to revision of the protocol). You stated during the December 17, 2002, ODAC meeting that the protocol was modified to remove the control arm (CHOP alone). This modification substantially alters the protocol and, therefore, it may no longer be acceptable in support of a [redacted] If it is your intent to seek labeling claims based on this study, we request that you ensure that the study and all modifications are submitted to the FDA and request a specific meeting to discuss the adequacy of the study, as revised.

b. During the December 17, 2002 ODAC meeting, you stated your intent to conduct a study directly comparing Zevalin therapy with Bexxar® therapy. During the meeting, you also stated that the protocol would be submitted in January 2003. We have not received a protocol. Please clarify your intent with regard to conducting this study.

c. You have proposed a trial of Rituximab versus Bexxar® therapy in patients with lymphoma who have received at least one and no more than two prior chemotherapy regimens. The primary objective of this study is demonstration of a longer event free-survival (defined as progression, alternative therapy or death) in Bexxar®-treated patients as compared to those receiving Rituximab. Survival is a secondary objective. This trial should incorporate longer-term follow-up (at least 5 years as recommended by the ODAC, for delayed toxicities including hypothyroidism, myelodysplasia, and secondary malignancies) and for survival. The inclusion criteria should be limited to high-risk patients (e.g., not patients with minimal disease, easily encompassed in an RT field) such that the toxicities associated with this product are not likely to outweigh the benefits and for whom a less toxic therapy is unlikely to provide similar benefits.

Members of the ODAC identified several issues pertinent to clarifying the safety and ffectiveness of Bexxar® therapeutic regimen that may be obtained from postmarketing ıdies. We request that you propose studies to address the following issues:

To assess the safety and efficacy of more than one course of the Bexxar® therapeutic regimen. The proposal should focus on the rate of altered biodistribution and toxicity profile of more than one treatment course.

b. To collect information on the development of HAMA as it relates to the inability to receive alternative therapies (Bexxar® or other antibody-based treatment). Please discuss any plans on assessment of the impact of HAMA and interference with *in vitro* and *in vivo* diagnostic assays that utilize a murine or partially murine protein.

c. To collect data on myelodysplasia and secondary leukemias in patients enrolled in completed clinical studies, the expanded access experience, and all ongoing or planned clinical studies. Describe your proposal for analyses of these data to determine the relative risk of myelodysplasia and secondary leukemia in recipients of the Bexxar® therapeutic regimen.

d. To assess the impact of the Bexxar® therapeutic regimen on the response to vaccination. In particular, characterize the degree of impairment to vaccination as a function of the time interval following treatment at which response to vaccination recovers.

Please describe your plans to address the above issues in sufficient detail to permit our evaluation of the adequacy of the proposals. We request that your response include:

- A detailed protocol or, at a minimum, a detailed outline describing all design features of the study including sample size and justification, eligibility criteria with rationale, dosing regimens and duration, clinical assessments to be performed and their timing, and endpoints to be analyzed.

- Proposed schedule for conducting the study, including all major milestones for the study, e.g. submission of finalized protocol to the FDA, completion of patient accrual, completion of the study, and submission of the final study report, SAS data sets and applicable revised labeling to the FDA.

Please be advised that submission of complete protocols for review and comment should be made to your IND and may be cross-referenced in your response to this letter.

With regard to the proposed package insert submitted January 7, 2003, we have the following preliminary review comments:

a. The product under review is the Bexxar® therapeutic regimen, which consists of multiple agents administered in two discrete steps (dosimetric step and therapeutic step). Please revise the labeling to refer to these steps and, when required, the individual component within the kit for a specific step as "Bexxar®

[tositumomab]" or "radiolabeled Bexxar® [I-131-tositumomab]" without the appended "N", "D", and "T". Use of these qualifiers may lead to confusion as to whether individual components are appropriate for use separate from the kit.

b. The CLINICAL PHARMACOLOGY section should be revised to include information on the impact of the Bexxar® therapeutic regimen on CD20+ cell counts and on immunoglobulin levels.

c. The CLINICAL STUDIES section should be revised to include only the results of CP 97-012. Please incorporate a more detailed description of the patient population (e.g., total enrolled, total who were Rituxan-refractory), key inclusion criteria (including requirement for prior chemotherapy and Rituxan therapy, requirement for platelet count, limited marrow involvement with lymphoma, and restrictions on prior radiotherapy to red marrow), study design (single arm, historically controlled, multicenter), treatment plan (including dose reduction for mild thrombocytopenia), and outcomes. b(4)

d. The INDICATIONS AND USAGE section should be revised to limit the indication to patients who have relapsed or are refractory to chemotherapy and are also refractory to Rituxan. b(4)

e. The WARNINGS section of the proposed PI must be revised to include:

1) A section describing the extent of testicular irradiation and potential impact on fertility (based on radiation tolerance of this organ);

2) A section describing the risks of hypothyroidism and appropriate monitoring;

3) A section on the incidence of development of human anti-murine antibodies, with a description of the relationship between extent of prior treatment and risks.

4) A section on significance of altered biodistribution, potential risk factors for such an alteration (e.g., prior exposure to murine or partially murine proteins), and need to assess for altered biodistribution.

f. The BOXED WARNINGS section should be revised to include information on dosing as it relates to maximal doses and dose reductions for mild thrombocytopenia.

g. The PRECAUTIONS section should be revised to delete the information on thyroid function testing and HAMA testing and move this information under appropriate sections under WARNINGS.

h. The ADVERSE REACTIONS section should be revised to include the following:

1) A statement concerning the significance of adverse reaction data obtained from clinical trials (as described in the "Draft Guidance for Industry: Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics (June 21, 2000)" which can be found at http://www.fda.gov/cber/gdlns/cfadvers.htm.

2) Statements describing sources of the data, such that the number of patients enrolled in clinical trials with adequate oversight and those enrolled in unmonitored trials providing access to the study drug are clearly stated and distinguished rather than pooled.

3) A description of the characteristics of the patient population enrolled in the clinical studies and, where appropriate (see below), a description of the characteristics of the patient population enrolled in the expanded access experience.

4) The adverse event rates (with the exceptions described below) should be limited to the data from the clinical efficacy studies and the tabular display of adverse events should be revised to reflect the patients who received the proposed dose (including 22 patients in RIT-II-000 and 19 patients in RIT-II-Arm B that crossed over after disease progression). The event rate for organ systems (e.g., infectious, gastrointestinal, hematologic, etc.) should be provided as well as for the most common specific terms within each category. Provide a listing of the terms used to provide organ system per-patient event rates.

5) The description of delayed adverse events, specifically development of hypothyroidism and of myelodysplasia/leukemia, should be reported by cumulative incidence and include data from the entire safety database. Rates of these events should be reported at several time intervals, with 95% confidence intervals for each rate cited.

6) The description of serious adverse events should consider all information from clinical studies and from the expanded access experience. Any events of a serious nature, not included in the table of adverse events, should be provided in the listing according to frequency and severity.

i. The DOSAGE and ADMINISTRATION section is poorly written and provides inadequate directions for use. In particular, the description of preparation of the radiolabeled doses, in which antibody is combined in the same syringe prior to administration in the dosimetric and therapeutic steps is unclear and inadequately described. Please revise this section for clarity and completeness.

We reserve further comments on the labeling until the application is otherwise acceptable.

These comments are being provided to you prior to the completion of our review of your entire application to give you preliminary, advance notice of clinical issues that have been identified. Please note that these comments are subject to change as the complete review of your application is finalized. Final comments, if any, will be communicated to you at a later date after the review of the application and the establishment inspections are completed. You may, but are not required to, respond to these preliminary comments. If you respond, we may or may not consider your response prior to taking a complete action on your application. If your response is determined to constitute a major amendment, you will be notified of this decision in writing. Review of the remaining sections of your application is continuing.

Should you need additional information or have any questions concerning administrative or procedural matters, please contact the Regulatory Project Manager, Karen D. Jones, at (301) 827-5101.

Sincerely yours,

Terrye G. Zaremba, Ph.D.
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(S:\Jonesk\125011-0 Tositumomab\DR Letter)

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SS Data Check:
- Communication

Division	Name/Signature	Date
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