CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125011

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125011/0

JUN 27 2003

Corixa Corporation
Attention: Monica Krieger, Ph.D.
Vice President, Regulatory Affairs
1124 Columbia Street, Suite 200
Seattle, WA 98104

Dear Dr. Krieger:

We are issuing Department of Health and Human Services U.S. License No.1614 to Corixa Corporation, Seattle, Washington, under the provisions of Section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. This license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license you are authorized to manufacture Tositumomab and Iodine I 131 Tositumomab. Tositumomab and Iodine I 131 Tositumomab, administered as a therapeutic regimen, 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.

b(4)

Under this license, you are approved to manufacture Tositumomab drug substance and final drug product at [redacted]. Unlabeled vials of Tositumomab drug product will be shipped to McKesson BioServices in [redacted] for labeling, packaging and distribution. Iodine I 131 Tositumomab final drug product will be manufactured, labeled, packaged, and distributed by MDS Nordion in Ottawa, Ontario, Canada. In accordance with approved labeling, your product will bear the proprietary name Bexxar® and will be marketed as two separate components. The dosimetric component will contain one 35 mg single-use vial and two 225 mg single-use vials of Tositumomab and 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 therapeutic component will contain one 35 mg single-use vial and two 225 mg single-use vials of Tositumomab and one or two single-use vials 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 dating period for Tositumomab shall be 36 months from the date of manufacture when stored at 2-8 °C. The dating period for dosimetric Iodine I 131 Tositumomab shall be 14 days when stored at -20°C and the dating period for therapeutic Iodine I 131 Tositumomab shall be 5 days when stored at -20°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The expiration date for the packaged product containing one 35 mg vial of Tositumomab and two 225 mg vials of Tositumomab shall be dependent on the shortest expiration date of either component. The dating period for the bulk drug substance shall be —months when stored at — C. The dating period for the packaged bulk drug substance shall be —months when stored at —°C. Results of ongoing stability studies should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots. The stability protocols in your license application are considered approved for the purpose of extending the expiration dating period of your Tositumomab drug substance and drug product as specified in 21 CFR 601.12. b(4)

You are not currently required to submit samples of future lots of Tositumomab and Iodine I 131 Tositumomab to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2. FDA will continue to monitor compliance with 21 CFR 610.1 requiring assay and release of only those lots that meet release specification.

Any changes in the manufacturing, testing, packaging, or labeling of Tositumomab and Iodine I 131 Tositumomab, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval consistent with 21 CFR 601.12.

We acknowledge your written commitments to conduct postmarketing studies as described in your letters of June 25, 2003, and June 27, 2003, as outlined below:

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70:

1. To conduct an open-label efficacy trial of Rituximab versus the 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 the Bexxar® therapeutic regimen as compared to those receiving Rituximab.

   The final protocol will be submitted for special protocol assessment review by August 15, 2003, patient accrual will be initiated by January 2, 2004, patient accrual will be completed by March 3, 2006, and the study will be completed by September 7, 2003, and the final study report will be submitted by May 9, 2008.

2. 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.

   The final protocol will be submitted for special protocol assessment review by September 15, 2003, patient accrual will be initiated by January 1, 2004, patient accrual will be completed by July 1, 2005, the study will be completed by July 1, 2006, and the final study report will be submitted by February 1, 2007.

3. To conduct a single-arm, open-label, multicenter, Phase 2 trial evaluating the pharmacokinetics, safety, and efficacy of retreatment with the Bexxar® therapeutic regimen in patients who have had duration of response of at least 6 months in the studies CCBX001-049 and CCBX001-053. The primary objective of the study (Study CCBX001-054) 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.

   The final protocol will be submitted by October 16, 2003, patient accrual will be initiated by March 29, 2004, patient accrual will be completed by October 2, 2006, the study will be completed by October 2, 2006, and the final study report will be submitted by September 29, 2008.

4. 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 the Bexxar® therapeutic regimen or Rituximab while participating in the trial described in Study CCBX001-049. This study will assess the impact of the anti-lymphoma therapies on development of protective antibody titers to recall and new antigens.

   The final companion protocol will be submitted by August 29, 2003, and the patient accrual will be initiated by January 2, 2004, patient accrual will be completed by March 3, 2006, the study will be completed by September 3, 2007, and the final study report will be submitted by May 9, 2008.

5. To collect information on patients who become seropositive for human anti-mouse antibody (HAMA) after treatment on studies CCBX-001-049 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 studies CCBX001-049 and CCBX001-053 and submitted as a separate stand-alone report, CCBX001-056. This final study report will be submitted by September 9, 2008.

6. To conduct a retrospective study, CCBX001-0057, and a prospective sub-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, CCBX001-0057, stored sera samples will be assayed from patients who became HAMA seropositive following initial therapy with the Bexxar® therapeutic regimen as initial therapy. The final protocol for the retrospective study will be submitted by September 30, 2003, assay development will be completed by December 31, 2003, assay of sera will be completed by February 28, 2004, data analysis will be completed by March 31, 2004, and the final study report will be submitted by June 3, 2004.

The prospective sub-study, CCBX001-058, will be conducted on sera from patients in the trials described in studies CCBX001-049 and CCBX001-053 who become HAMA seropositive following treatment. The final protocol for the prospective sub-study will be submitted by October 30, 2003, patient accrual will be completed by February 1, 2005, the study will be completed by August 1, 2005, and the final study report will be submitted by January 1, 2006.

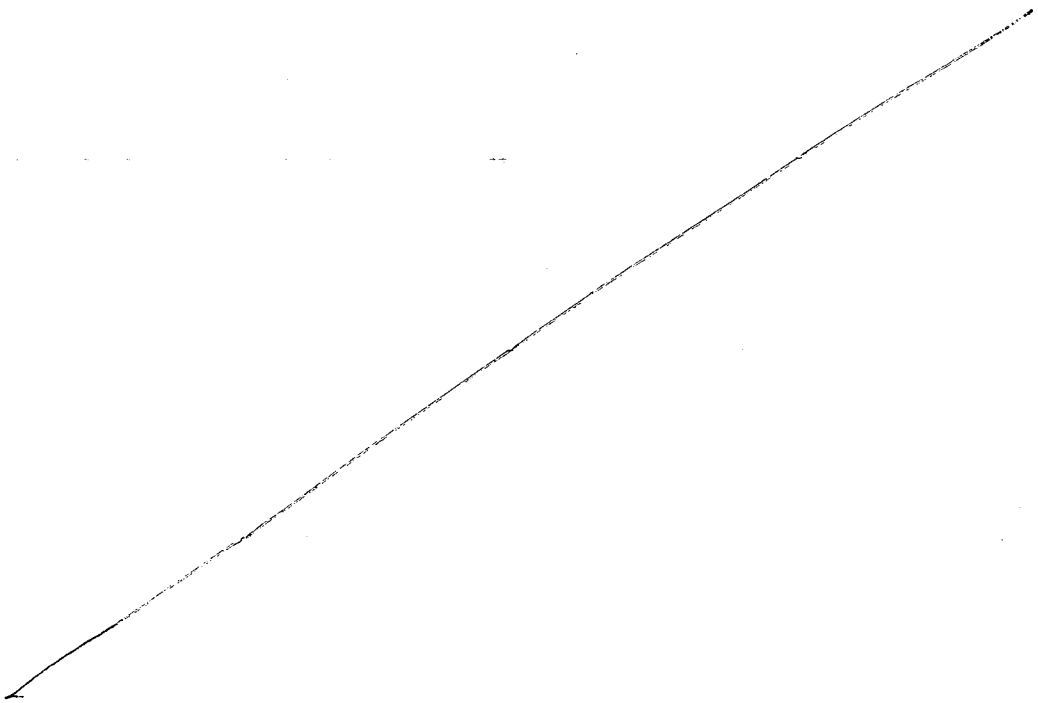
7. To collect information regarding the occurrence of myelodysplasia/acute leukemia in studies involving the Bexxar® therapeutic regimen, including studies in your BLA, BL 125011/0; other studies not contained in the BLA; and those studies that are being designed to address post-marketing commitments or other regulatory requirements as listed in your June 25, 2003 letter. You will submit this information as interim reports containing an integrated analysis designated as described in CCBX001-059.

The integrated analysis plan for CCBX001-059 will be submitted by September 30, 2003. On an annual basis, you will submit interim study reports. The final study report will be submitted by December 31, 2013.

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

A complete plan for the quality assurance program (CCQA001-01) will be submitted by September 30, 2003, and a report will be submitted by June 30, 2004.

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70:



b(4)

You should submit clinical protocols to your BB-IND 3323 with a cross-reference letter to STN BL 125011. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to STN BL 125011. In addition, under 21 CFR 601.70, you must submit an annual postmarketing status report to STN BL 125011. For each reportable commitment, you must provide a description, the original schedule, the status, and an explanation of the status including the number of patients or subjects enrolled to date and the total planned enrollment. We may publically disclose information regarding postmarketing studies subject to the reporting requirements of 21 CFR 601.70. You should label prominently all submissions, including supplements, relating to postmarketing study commitments, for example, as follows "**Postmarketing Study Protocol,**" "**Postmarketing Study Final Report,**" "**Postmarketing Study Correspondence,**" or "**Annual Report on Postmarketing Studies.**" You may refer to the April 2001 Draft Guidance for Industry: Reports on the Status of Postmarketing Studies – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 for further information.

As you know, the regulatory responsibility, review and continuing oversight for this product will transfer from the Center for Biologics Evaluation and Research to the Center for Drugs Evaluation and Research effective June 30, 2003. However, all correspondence, except as provided below, should continue to be addressed to the CBER Document Control Center, (HFM-99), 1401 Rockville Pike, Suite 200N, Rockville, Maryland 20852-1448, until further notice.

It is required that adverse experience reports be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted in accordance with 21 CFR 600.81. Postmarketing adverse experience reports and distribution reports should be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448. All adverse experience reports should be prominently identified according to 21 CFR 600.80.

You are required to submit reports of biological product deviations in accordance with 21 CFR 600.14. All manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution, should be promptly identified and investigated. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, a report must be submitted on Form FDA-3486 to the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Rockville, MD 20852-1448.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit three draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2253 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Branch, HFM-602, 1401 Rockville Pike, Rockville, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Sincerely yours,

Steven A. Masiello
Director
Office of Compliance and
Biologics Quality
Center for Biologics
Evaluation and Research

Sincerely yours,

Sharon T. Risso, M.A.
Acting Director
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

Enclosure:
Final draft labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125011/0

JUL 14 2003

Corixa Corporation
Attention: Monica Krieger, Ph.D.
Vice President, Regulatory Affairs
1124 Columbia Street, Suite 200
Seattle, WA 98104

Dear Dr. Krieger:

This letter is in regard to your biologics license application for Tositumomab and Iodine I 131 Tositumomab submitted under Section 351 of the Public Health Service Act and to the approval letter dated June 27, 2003.

As described in your June 27, 2003, letter and as discussed during the July 1, 2003, telephone conversation between Jill Henrich of your office and Karen D. Jones of this office, the reporting schedules for two postmarketing commitment studies were incorrectly listed in the approval letter. We have revised the reporting schedules for postmarketing commitments numbers 1 and 3 as follows:

1. Correction of the completion date for Study CCBX001-049 (page 2, item 1, paragraph 2 of the June 27, 2003 letter): The reporting schedule now reads, "The final protocol will be submitted for special protocol assessment review by August 15, 2003, patient accrual will be initiated by January 2, 2004, patient accrual will be completed by March 3, 2006, the study will be completed by September 3, 2007, and the final study report will be submitted by May 9, 2008."

2. Correction of the completion date for Study CCBX001-054 (page 3, item 3, paragraph 2 of the June 27, 2003 letter): The reporting schedule now reads, "The final protocol will be submitted by October 16, 2003, patient accrual will be initiated by March 29, 2004, patient accrual will be completed by October 2, 2006, the study will be completed by [redacted], and the final study report will be submitted by September 29, 2008."

The corrected dates above supersede the dates provided to you in the June 27, 2003, letter. We apologize for this error.

We also would like to clarify that sterile, packaged bulk drug substance may also be stored at 2-8 °C for 12 months.

If you have any questions, please contact me at (301) 827-5101.

Sincerely yours,

Karen D. Jones

Karen D. Jones
Acting Branch Chief
Division of Application Review and Policy
Office of Therapeutics Research and Review
Center for Drug Evaluation and Research