DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

March 16, 2004

Dr. Steven Gillis
Chairman and Chief Executive Officer
Corixa Corporation
1124 Columbia Street, Suite 200
Seattle, WA 98104

Re: STN: BL 125011
BEXXAR® (Tositumomab and Iodine I 131 Tositumomab)
Review #030818020

WARNING LETTER

Dear Dr. Gillis:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) reviewed a video that describes the mechanism of action (BEX039RO) ("video") for BEXXAR® (Tositumomab and Iodine I 131 Tositumomab) submitted by Corixa Corporation (Corixa) under cover of Form FDA 2253. The video is false or misleading because it omits material risk information and overstates the efficacy of BEXXAR in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 352(a) and 321(n), and FDA implementing regulations 21 CFR § 1.21.

Background

The Indications and Usage section of the approved physician labeling (PI) for BEXXAR states:

> "The BEXXAR therapeutic regimen (Tositumomab and Iodine I 131 Tositumomab) is 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. The BEXXAR therapeutic regimen is not indicated for the initial treatment of patients with CD20 positive non-Hodgkin's lymphoma. The BEXXAR therapeutic regimen is intended as a single course of treatment. The safety of multiple courses of the BEXXAR therapeutic regimen, or combination of this regimen with other forms of irradiation or chemotherapy, has not been evaluated."

Because of the serious risks associated with BEXXAR treatment, the PI includes a Boxed Warnings section that states:

> **Hypersensitivity Reactions, including Anaphylaxis**: Medications for the treatment of severe hypersensitivity reactions should be available for immediate use. Patients who develop severe hypersensitivity reactions should have infusions of the BEXXAR therapeutic regimen discontinued and receive medical attention (See WARNINGS).
>
> **Prolonged and Severe Cytopenias**: The majority of patients who received the BEXXAR therapeutic regimen experienced severe thrombocytopenia and neutropenia. The BEXXAR therapeutic regimen should not be administered to patients with >25% lymphoma marrow involvement and/or impaired bone marrow reserve (see WARNINGS and ADVERSE REACTIONS).
>
> **Pregnancy Category X**: The BEXXAR therapeutic regimen can cause fetal harm when administered to a pregnant woman.
>
> **Special requirements**: The BEXXAR therapeutic regimen (Tositumomab and Iodine I 131 Tositumomab) contains a radioactive component and should be administered only by physicians and other health care professionals qualified by training in the safe use and handling of therapeutic radionuclides. The BEXXAR therapeutic regimen should be administered only by physicians who are in the process of being or have been certified by Corixa Corporation in dose calculation and administration of the BEXXAR therapeutic regimen.

BEXXAR treatment is also associated with many other risks as described in the Warnings, Precautions, and Adverse Reactions sections of the PI. Some of these risks include:

> **Prolonged and Severe Cytopenias.** The most common adverse reactions associated with the BEXXAR therapeutic regimen were severe or life-threatening cytopenias (NCI CTC grade 3 or 4) with 71% of the 230 patients enrolled in clinical studies experiencing grade 3 or 4 cytopenias. These consisted primarily of grade 3 or 4 thrombocytopenia (53%) and grade 3 or 4 neutropenia (63%). The time to nadir was 4 to 7 weeks and the duration of cytopenias was approximately 30 days. Thrombocytopenia, neutropenia, and anemia persisted for more than 90 days following administration of the BEXXAR therapeutic regimen in 16 (7%), 15 (7%), and 12 (5%) patients respectively (this includes patients with transient recovery followed by recurrent cytopenia)....The sequelae of severe cytopenias were commonly observed in the clinical studies and included infections (45% of patients), hemorrhage (12%), a requirement for growth factors (12% G- or GM-CSF, 7% Epoetin alfa) and blood product support (15% platelet transfusions, 16% red blood cell transfusions).
>
> **Hypersensitivity Reactions Including Anaphylaxis.** Hypersensitivity reactions, including anaphylaxis, were reported during and following administration of the BEXXAR therapeutic regimen. Emergency supplies including medications for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines, and

corticosteroids, should be available for immediate use in the event of an allergic reaction during administration of the BEXXAR therapeutic regimen. Patients who have received murine proteins should be screened for human anti-mouse antibodies (HAMA). Patients who are positive for HAMA may be at increased risk of anaphylaxis and serious hypersensitivity reactions during administration of the BEXXAR therapeutic regimen.

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

Infusional Toxicity: A constellation of symptoms, including fever, rigors or chills, sweating, hypotension, dyspnea, bronchospasm, and nausea, have been reported during or within 48 hours of infusion. Sixty-seven patients (29%) reported fever, rigors/chills, or sweating within 14 days following the dosimetric dose. Although all patients in the clinical studies received pretreatment with acetaminophen and an antihistamine, the value of premedication in preventing infusion-related toxicity was not evaluated in any of the clinical studies. Infusional toxicities were managed by slowing and/or temporarily interrupting the infusion. Symptomatic management was required in more severe cases. Adjustment of the rate of infusion to control adverse reactions occurred in 16 patients (7%)….Adjustments included reduction in the rate of infusion by 50%, temporary interruption of the infusion, and in 2 patients, infusion was permanently discontinued.

Omission of Risk Information

Promotional materials are false or misleading if they fail to reveal facts material in light of representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. The video is misleading because it presents effectiveness claims for BEXXAR but fails to provide any risk information. As described above, the BEXXAR therapeutic regimen is associated with many serious and significant risks. Omission of any mention of those associated risks raises serious public health and safety concerns.

False or Misleading Safety Claims

The Animation presents the following claims with accompanying visuals of radiation affecting tumor cells:

"BEXXAR is designed to seek out CD20 positive B cells and deliver both immunotherapy and radiotherapy to tumors. Tositumomab, the monoclonal antibody component of BEXXAR seeks out and binds to CD20 on the cell surface. While the antibody induces immunogenic responses, the isotope emits beta radiation to kill tumor cells not accessible to the antibody."

> "The BEXXAR therapeutic regimen has demonstrated efficacy in patients with bulky tumors, yet the relatively short pathlength is thought to minimize radiation to surrounding healthy tissues."

These claims and accompanying visuals minimize the risks of BEXXAR treatment by suggesting minimal harmful effects on surrounding healthy tissue, when in fact, the drug is associated with cytopenia. The video fails to disclose that BEXXAR has profound adverse effects on normal cells. The antibody portion of BEXXAR is directed against the CD20 antigen, which is found on the surface of both normal and malignant B lymphocytes; therefore, BEXXAR is not "targeted" specifically to non-Hodgkin's lymphoma cells.

The video claims: "Because Iodine 131 is rapidly eliminated over a few days through renal excretion; residual exposure to radiation is minimized. With the Iodine 131 in BEXXAR, radioactive material that doesn't attach to targeted cells is rapidly eliminated by the body." The claim suggests that the elimination rate of Iodine 131 is the relevant rate with respect to toxicity. However, the Iodine 131 is not lone Iodine; it is attached to Tositumomab. Iodine I 131 Tositumomab is cleared from the body much more slowly than Iodine 131. Because cell death is associated with ionizing radiation from the radioisotope, the slower elimination rate allows more time for the ionizing radiation from the Iodine I 131 Tositumomab to cause cell death in both normal and tumor cells. Clinical studies with BEXXAR have documented numerous toxicities from the Iodine 131 radiation.

The video claims: "First an infusion of the unlabeled antibody called Tositumomab is administered….Next, the patient is given a short infusion of the tailored radioactive dose of the BEXXAR therapeutic regimen." The video omits material steps including a material risk-related fact that, to use Bexxar safely, it is necessary to look for altered distribution of the Iodine I 131 Tositumomab dosimetric dose. As stated in the PI, "Assess biodistribution. If biodistribution is altered, the therapeutic step should not be administered." Alteration of the biodistribution of Iodine I 131 Tositumomab would suggest the presence of: immune response, HAMA; organ dysfunction, e.g., urinary tract obstruction; or improper preparation of the Iodine 131 Tositumomab imaging agent. The subsequent administration of the therapeutic dose of Iodine I 131 Tositumomab could jeopardize patients who are positive for HAMA because they may be at increased risk of anaphylaxis and serious hypersensitivity reactions. BEXXAR is a relatively new treatment and health care providers may be unaware of the hazards associated with administering BEXXAR to patients with altered biodistribution.

Unsubstantiated Effectiveness Claims

Promotional materials are false or misleading if they represent or suggest that a prescription drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience. Specific examples of false or misleading efficacy claims for BEXXAR include:

The video claims: "Because unlabeled Tositumomab is already bound to circulating B cells, the radiolabeled antibodies preferentially target tumor cells [emphasis added]." The claim suggests that Tositumomab can target tumors when, in fact, it binds to the CD20 antigen on normal pre-B lymphocytes and mature B lymphocytes, as well as malignant B lymphocytes. The purpose of the initial administration of Tositumomab is to allow the Iodine I 131 Tositumomab to stay in the circulation longer. However, we are not aware of substantial evidence or substantial clinical experience demonstrating that Iodine I 131 Tositumomab preferentially targets tumor cells.

The following claims suggest that the components of BEXXAR may be administered alone and that each component separately has anti-tumor effects for non-Hodgkin's lymphoma, when, to FDA's knowledge, this has not been demonstrated:

> "The antibodies induce immunogenic responses, including apoptosis, complement-dependent cytotoxicity, and antibody-dependent cellular toxicity."

> "BEXXAR is designed to seek out CD20 positive B cells and deliver both immunotherapy and radiotherapy to tumors."

As stated in the PI, "Possible mechanisms of action of the BEXXAR therapeutic regimen include induction of apoptosis, complement-dependent cytotoxicity, and antibody-dependent cytotoxicity mediated by the antibody." (Emphasis added.) The clinical studies that support the approval of BEXXAR were not designed to demonstrate the mechanism of action or efficacy of the antibody, Tositumomab, alone. BEXXAR was licensed based on studies demonstrating effectiveness of the "single" action of BEXXAR, i.e., there is no separate evaluation or approval for Tositumomab, I 131 Tositumomab, or 131-Iodine alone to treat patients with CD20 positive, follicular, non-Hodgkin's lymphoma, with and without transformation, whose disease is refractory to Rituximab and has relapsed following chemotherapy. If you have data to support these claims, please submit it to FDA for review.

Conclusions and Requested Actions

You have disseminated a Mechanism of Action Video that omits material facts regarding important risk information for BEXXAR and makes misleading safety and efficacy claims in violation of the Act and implementing regulations. 21 U.S.C. §§ 352(a) and 321(n); 21 CFR § 1.21.

DDMAC requests that Corixa immediately cease the dissemination of all promotional materials for BEXXAR that contain the same or similar violations described above and provide a plan of action to disseminate accurate and complete information to the audience(s) that received the violative promotional materials. Please submit a written response to this letter on or before March 30, 2004, describing whether you intend to comply with this request, listing all promotional materials for BEXXAR that contain the claims described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857, facsimile at 301-594-6771. In all future correspondence regarding this matter, please refer to Review #030818020 in addition to the STN number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for BEXXAR comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in regulatory action, including seizure or injunction, without further notice.

Sincerely,

Thomas W. Abrams, R.Ph., M.B.A.
Director
Division of Drug Marketing,
Advertising, and Communications