DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

December 15, 2005

Nadine D. Cohen, Ph.D.
Senior Vice President, Regulatory Affairs
Biogen Idec Inc.
14 Cambridge Center
Cambridge, MA 02142

Re: BLA# 125019
Zevalin® (ibritumomab tiuxetan)
MACMIS #13690

Dear Dr. Cohen:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a RESULTS 2004 Coding Update brochure (brochure) for Zevalin® (ibritumomab tiuxetan) which was disseminated at the American Society of Health-Systems Pharmacists Summer Meeting in June 2005. DDMAC has concluded that the brochure is false or misleading because it makes claims about who may benefit from Zevalin but omits risk information and material facts regarding the indication for Zevalin. The brochure thus misbrands the biologic in violation of the Federal Food, Drug, and Cosmetic Act (Act) 21 U.S.C. §§ 352(a) and 321(n). In addition, it appears that the brochure was neither submitted to FDA on Form FDA 2253 at the time of initial dissemination or initial publication, as required by 21 CFR 601.12 (f)(4), nor submitted to FDA 30 days prior to the intended time of initial dissemination or initial publication as required by 21 CFR 601.45. This brochure raises significant public health and safety concerns because it suggests that Zevalin is safer and more effective than has been demonstrated by substantial evidence or substantial clinical experience. Cf. 21 CFR 202.1(e)(6)(i).

Background

Zevalin was licensed as an accelerated approval biological product in accordance with 21 CFR 601.41.

According to the Indications and Usage section of the approved product labeling (PI), "Zevalin, as part of the Zevalin therapeutic regimen, is indicated for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma, including patients with Rituximab refractory follicular non-Hodgkin's lymphoma. Determination of the effectiveness of the Zevalin therapeutic regimen in a relapsed or refractory patient population is based on overall response rates. The effects of the Zevalin therapeutic regimen on survival are not known."

The PI for Zevalin includes important Boxed Warnings, Warnings, Precautions and Adverse Reactions. A summary of the pertinent safety issues is included below:

Boxed Warnings, Warnings and Adverse Reactions

The Boxed Warnings and Warnings sections of the PI describe fatal and severe infusion reactions, prolonged and severe cytopenias, severe mucocutaneous reactions and secondary malignancies. The Warnings section also notes that Zevalin is pregnancy category D.

Adverse Reactions

In addition to the adverse effects listed in Warnings, the Adverse Reactions section of the PI describes the most serious adverse reactions as infections (predominantly bacterial in origin), hemorrhage while thrombocytopenic (resulting in deaths), allergic reactions (bronchospasm and angioedema), and myeloid malignancies and dysplasias.

The Adverse Reactions section describes the most common toxicities as neutropenia, thrombocytopenia, anemia, gastrointestinal symptoms (nausea, vomiting, abdominal pain, and diarrhea), increased cough, dyspnea, dizziness, arthralgia, anorexia, anxiety, and ecchymosis.

The Adverse Reactions section describes the following severe or life-threatening adverse events occurring in 1-5% of patients as pancytopenia (2%), allergic reaction (1%), gastrointestinal hemorrhage (1%), melena (1%), tumor pain (1%), and apnea (1%).

Omission of Important Risk Information

The brochure presents statements regarding the indication for Zevalin on the top of page 4. This presentation provides information on the type of patient who may benefit from the Zevalin therapeutic regimen but provides insufficient information regarding the risks of treatment. The brochure only presents the following risk information from the Boxed Warning and the Warnings sections of the PI at the bottom of page 2, "DO NOT TREAT PATIENTS WITH <100,000 PLATELETS/mm^3" and "THE MAXIMUM ALLOWABLE DOSE OF Yttrium-90 ZEVALIN IS 32.0 mCi (1,184 MBq)." These two statements are not sufficient to communicate the risks of Zevalin. The brochure omits most of the risk information from the Boxed Warning, Warnings, Precautions and Adverse Reactions sections of the PI for the Zevalin therapeutic regimen. This misbrands the drug. See 21 U.S.C. §§ 352(a) and 321(n). Merely disseminating the PI with this promotional material, with reference to the enclosed full prescribing information, is not sufficient to overcome these violations.

Omission of Material Fact

The brochure states, "Biogen Idec offers the Zevalin Patient Assistance Program to facilitate access to Zevalin therapy for patients with relapsed or refractory low-grade, follicular or transformed B-cell non-Hodgkin's lymphoma, including patients with Rituximab-refractory follicular B-cell non-Hodgkin's lymphoma." However, this presentation of the indication omits the following material fact from the Indications and Usage section of the PI, **"Determination of the effectiveness of the Zevalin therapeutic regimen in a relapsed or refractory patient population is based on overall response rates. The effects of the Zevalin therapeutic regimen on survival are not known**."

[emphasis added] The presentation is misleading because it omits material facts from the PI regarding the indication for the Zevalin therapeutic regimen (i.e., it was approved using a surrogate endpoint and that its clinical benefit has not been established.) See 21 U.S.C. § 352 (a).

Failure to Submit

These materials were not submitted to FDA on Form FDA 2253 at the time of initial dissemination or initial publication, as required by 21 CFR 601.12 (f) (4). Furthermore, these materials were not submitted to FDA 30 days prior to the intended time of initial dissemination or initial publication as required by 21 CFR 601.45.

Conclusion and Requested Action

The brochure is false or misleading because it fails to present most of the risk information for Zevalin and contains a misleading presentation of the indication in violation of the Act and FDA's implementing regulations. See 21 U.S.C. 352(a) and 321(n). In addition, these materials were not submitted to FDA as required by 21 CFR 601.12 and 21 CFR 601.45.

DDMAC requests that Biogen Idec immediately cease the dissemination of violative promotional materials for Zevalin such as those described above. Please submit a written response to this letter on or before December 29, 2005, stating whether you intend to comply with this request, listing all violative promotional materials for Zevalin such as those described above, and explaining your plan for discontinuing use of such materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266., facsimile at 301-796-9877. In all future correspondence regarding this matter, please refer to MACMIS# 13690 in addition to the BLA 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 Zevalin comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

Carole Broadnax, R.Ph., Pharm.D.
Regulatory Review Officer
Division of Drug, Marketing, Advertising, and Communications