DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Michele Sharp, PharmD
Manager
U.S. Regulatory Affairs
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

RE: NDA: 21-677
Alimta® pemetrexed for injection
MACMIS # 14503

Dear Dr. Sharp:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a patient brochure (PM-38460) for Alimta® pemetrexed for injection submitted by Eli Lilly and Company (Lilly) under cover of Form FDA 2253. The patient brochure is misleading because it omits material facts and risk information essential to the safe and effective use of Alimta. The patient brochure thus misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 352(a) and 321(n). *Cf.* 21 C.F.R. §§ 202.1(e)(3)(ii).

Background

According to its FDA-approved product labeling (PI), Alimta is approved for two indications:

> Mesothelioma: ALIMTA in combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.
>
> Non-Small Cell Lung Cancer: ALIMTA as a single-agent is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.
>
> The effectiveness of ALIMTA in second-line NSCLC was based on the surrogate endpoint, response rate. There are no controlled trials demonstrating a clinical benefit, such as a favorable survival effect or improvement of disease-related symptoms.

As stated in the PI, the use of Alimta is also associated with a number of risks including the following Warning:

> **Pregnancy Category D –** ALIMTA may cause fetal harm when administered to a pregnant woman. Pemetrexed was fetotoxic and teratogenic in mice at i.p. doses of 0.2 mg/kg (0.6 mg/m^2) or 5 mg/kg (15 mg/m^2) when given on gestation days 6 through 15. Pemetrexed caused fetal malformations (incomplete ossification of talus and skull bone) at 0.2 mg/kg (about 1/833 the recommended i.v. human dose on a mg/m^2 basis), and cleft palate at 5 mg/kg (about 1/33 the recommended i.v. human dose on a mg/m^2 basis). Embryotoxicity was characterized by

> increased embryo-fetal deaths and reduced litter sizes. There are no studies of ALIMTA in pregnant women. Patients should be advised to avoid becoming pregnant. If ALIMTA is used during pregnancy, or if the patient becomes pregnant while taking ALIMTA, the patient should be apprised of the potential hazard to the fetus.

Additionally, the attached Information for Patients and Caregivers states:

> "**What should I tell my doctor before taking ALIMTA?**
> Tell your doctor about all of your medical conditions including if you:
>
> - **are pregnant or planning to become pregnant.** ALIMTA may harm your unborn baby." (emphasis in original)
>
> "**What should I avoid while taking ALIMTA?**
>
> - **Women who can become pregnant should not become pregnant during treatment with ALIMTA.** ALIMTA may harm the unborn baby." (emphasis in original)

Omission of Material Facts/Failure to State Indication

Promotional pieces are misleading if they fail to reveal facts that are material in light of the representations made in the pieces or with respect to the consequences that may result from the use of the drug as recommended or suggested in the pieces. The patient brochure omits material facts because it fails to present either approved indication for Alimta. Alimta is approved for two indications, which are noted above, neither of which is presented in whole or in part in this piece. Also omitted is the material fact that approval of the NSCLC indication was based on the surrogate endpoint, response rate, and that there are no controlled trials demonstrating a clinical benefit, such as a favorable survival effect or improvement of disease-related symptoms. Instead, the brochure simply states on page 5, "ALIMTA is a **chemotherapy** drug used to treat certain types of cancer." (emphasis in original).

The failure to specifically state either approved indication is exacerbated not only by vague reference to unspecified cancers, but also by the fact that the brochure provides information and references for a number of other types of cancers for which Alimta is not indicated, potentially creating the misleading impression that Alimta is approved to treat a wide range of cancers. This is particularly concerning because, for some of these cancers, there exist therapies that have proven to confer clinical benefit. Because the statement on page 24, "This list of resources is intended to provide you with additional education and support resources and is not necessarily intended to suggest that ALIMTA is approved for those cancers listed," fails to indicate what Alimta <u>is</u> approved for, it does not correct this misleading impression.

The failure to include Alimta's indication(s), including the important limitation to the NSCLC indication, is also exacerbated by other statements in the brochure that create the misleading impression that treatment with Alimta has been proven to confer clinical benefits in the treatment of unspecified cancers. For example, the brochure says – "After your last treatment is completed, you might expect that you will resume your daily routine and that you will go back to your life as you knew it. However, you may discover, as many cancer survivors do, that you want or need to establish a 'new

normal.' This new normal will include new interests, new priorities, and new thoughts." – implying that Alimta has been proven to confer clinical benefits, such as improvement of disease-related symptoms.

Omission of Risk Information

The patient brochure is also misleading because it fails to reveal an important warning regarding pregnancy. Specifically, the brochure fails to reveal that Alimta may cause fetal harm when administered to a pregnant woman and that pregnant women should be so advised, and that patients considering pregnancy should be advised to avoid becoming pregnant while taking Alimta.

Conclusion and Requested Action

For the reasons discussed above, the patient brochure is misleading because it omits material facts and omits important risk information in violation of 21 U.S.C. §§ 352(a) and 321(n). *Cf.* 21 C.F.R. §§ 202.1(e)(3)(ii).

DDMAC requests that Lilly immediately cease the dissemination of violative promotional materials for Alimta such as those described above. Please submit a written response to this letter on or before August 11, 2006, stating whether you intend to comply with this request, listing all violative promotional materials for Alimta such as those described above, and explaining your plan for discontinuing use of such materials.

Please direct your response to the undersigned 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, facsimile at 301-796-9878. In all future correspondence regarding this matter, please refer to MACMIS # 14503 in addition to the NDA 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 Alimta comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Carrie Newcomer, PharmD
Consumer Promotion Analyst
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Carrie Newcomer

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