WASHINGTON LEGAL FOUNDATION
2009 MASSACHUSETTS AVENUE, NW
WASHINGTON, D.C. 20036
(202) 588-0302

August 3, 2006

By Facsimile [301-796-9877]
and First-Class Mail

Thomas Abrams, RPh, MBA
Director
Division of Drug Marketing, Advertising, and Communications
10903 New Hampshire Ave.
Bldg 22 Rm 1400
Silver Spring, MD 20903-0002

Re: NDA # 21-677
Alimta® (pemetrexed for injection)
MACMIS # 14503

Dear Mr. Abrams:

On July 27, 2006, the Division of Drug Marketing, Advertising, and Communications (DDMAC) sent an untitled letter to Eli Lilly and Company (Lilly) alleging that a patient brochure for Alimta® (pemetrexed for injection) misbranded the drug "in violation of" 21 U.S.C. §§ 352(a) and 321(n), because it "omits material facts and risk information essential to the safe and effective use" of the drug. The untitled letter asserts, in essence, that certain information must appear twice in promotional materials. It also posits interpretations that appear to be based solely on the individual judgments of DDMAC employees, and not on empirical data demonstrating how patients actually responded to the brochure. In both respects, the untitled letter represents a continuation of policies respecting drug manufacturer speech that raise important legal issues. For the reasons discussed below, the letter should be withdrawn. Additionally, DDMAC should undertake a systematic review of its policies and procedures to assure that they are consistent with and do not go beyond relevant constitutional and statutory authorities.

Double Disclosure Requirement

According to DDMAC, the patient brochure is misleading because it "fails to reveal" the pregnancy-related risk information appearing in the FDA-approved labeling for Alimta. In fact, all of this information appears in full FDA-approved prescribing information that accompanies the brochure. Thus, patients who receive the brochure have immediate access to all of the information that DDMAC alleges is missing. Moreover, the information—because it appears in

the prescribing information—is presented in precisely the manner dictated by FDA. DDMAC's allegation that the brochure is misleading because it omits this information is therefore factually untenable.

Nor does DDMAC have a credible legal or policy argument in support of its allegation. We have repeatedly explained some of the reasons that DDMAC's position is problematic. For example, it is unsupported by FDA regulations and inconsistent with FDA's established policy against overwarning.

WLF has repeatedly raised this issue with DDMAC in previous correspondence. From the warning and untitled letters issued by DDMAC since WLF began its monitoring program, it is apparent that DDMAC has an established practice and policy of prohibiting manufacturers from disseminating promotional materials unless risk information appears twice—once in the "main body" or "creative" part, and again in the accompanying prescribing information or brief summary. Until DDMAC has provided a sufficient basis for this approach, no warning or untitled letters should be issued on the ground that a manufacturer has omitted risk information by failing to present that information in two places.

Omission of "Precise Approved Indication"

DDMAC contends that the patient brochure "misbrands" Alimta because it omits the drug's "precise approved indication." WLF emphasizes—again—that the very information that DDMAC claims is absent is actually present in the accompanying prescribing information. All of the arguments that WLF has advanced in the risk disclosure context apply equally to DDMAC's demand that a manufacturer disclose the "precise approved indication" twice in each promotional piece.

It is not clear to WLF how including the approved indication for Alimta in the brochure is "essential" to the safe and effective use of the drug, as DDMAC contends. The patient brochure is simply that—a brochure for <u>patients</u>. Because Alimta is available by prescription only, and is an infused drug that can be administered only in a health care facility, it is simply impossible for a patient to use the drug without extensive health care practitioner involvement. Whatever may be the case for promotional materials aimed at health care practitioners, it simply defies common sense that the risks and benefits of the drug would be influenced by having the "precise approved indication" included in the patient brochure. (Indeed, WLF believes that a statement of the type the untitled letter purports to require, to the effect that Alimta has not been shown to improve survival or disease-related symptoms, might inappropriately discourage patients from using Alimta. In any event, given the severity of the diseases for which Alimta is indicated, DDMAC should—at a minimum—evaluate patient interpretation of such a statement.)

DDMAC asserts that the brochure's "failure" to disclose the approved indication is "exacerbated" by "vague reference to unspecified cancers" and by the general information provided in the brochure regarding cancer treatment generally. It is hard to see how providing the type of educational and resource information included in the patient brochure presents a public health risk. FDA has itself recognized the public health need for patient education

information, by issuing a draft guidance document encouraging manufacturers to disseminate disease awareness materials. *See* Guidance for Industry: "Help-Seeking" and Other Disease Awareness Communications by or on Behalf of Drug and Device Firms (Jan. 2004) (draft), *available at* http://www.fda.gov/cber/gdlns/helpcomm.pdf. In the absence of data demonstrating that patients are misled by the brochure into believing that Alimta has been approved by FDA for indications beyond those appearing in the approved labeling, or that Alimta is safe and effective in types of cancers for which safety and effectiveness data do not exist, DDMAC simply cannot credibly—or lawfully—purport to forbid Lilly from providing general cancer education information to patients.

Finally, DDMAC claims that the brochure's "failure" to disclose the approved indication is "also exacerbated" because "other statements" imply misleadingly that Alimta "has been proven to confer clinical benefits in the treatment of unspecified cancers." As an example, DDMAC points to a reference in the brochure to establishing a "new normal" after treatment is completed. According to DDMAC, this statement means that "Alimta has been proven to confer clinical benefits, such as improvement of disease-related symptoms." Again, WLF reminds DDMAC that this interpretation, which is not necessarily intuitive, must be corroborated by survey data demonstrating that patients ascribe to the brochure the same meaning.

Conclusion and Requested Action

For the reasons discussed above, we request that DDMAC immediately withdraw the untitled letter to Lilly and cease the issuance of warning and untitled letters and advisory correspondence that contains allegations the same as or similar to those described above. We request that you review, in a systematic fashion, all of your policies and procedures to ensure that they provide sufficient room for sponsors to disseminate, and health care practitioners and patients to receive, truthful and non-misleading information about prescription drugs. We request, further, that you respond to the numerous legal and policy issues we have raised in our correspondence with you since last year.

The deficiencies described in this letter do not necessarily constitute an exhaustive list. It is DDMAC's responsibility to ensure that its actions comply with the First Amendment, and do not exceed FDA's statutory authority.

Sincerely,

Richard A. Samp
Chief Counsel

cc: Sheldon Bradshaw (GCF-1)