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A Division of Eli Lilly and Company

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November 24, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncologic Drug Products, HFD-150
Attn: Mr. Alvis Dunson
1451 Rockville Pike
Rockville, MD 20852-1448

IND Safety Report

Subject: IND 40,061, MTA (LY231514) – Serial no. 194
Letter to Investigators Regarding Patients with High Baseline Homocysteine Levels

An updated multivariate analysis has been recently conducted for patients in the clinical trials with LY231514 (MTA) in an attempt to better understand patterns of toxicity and to identify factors that may predict patients at increased risk for serious toxicity. A preliminary report of this analysis was included as part of the LY231514 annual report (submission serial no. 191 submitted on November 8, 1999; Summary pages 1-5). As mentioned in the covering letter that accompanied the annual report, Lilly at that time decided to continue to collect baseline homocysteine levels and strongly recommended that investigators on LY231514 trials increase their vigilance following patients with high homocysteine levels.

Further analysis of baseline homocysteine levels for patients enrolled in trials with LY231514 has led to the following conclusions:

- Elevated baseline homocysteine levels significantly correlate with increased risk of both hematologic and non-hematologic toxicity

As a result of these observations and after communicating with several external consultants, Lilly has taken the following action to provide for improved safety for patients in LY231514 trials:

A global mailing to all investigators (excluding investigators in the two trials mentioned below) was sent out today (see attachment 1) informing investigators of the following:

- At this time patients with baseline homocysteine levels greater to (or equal to) 12 µM must be excluded from participation in LY231514 clinical trials (unless folic acid supplementation is being administered in a trial)

There are two clinical trials H3E-MC-JMAF (A Phase 2 Trial of LY231514 Administered Intravenously Every 21 Days in Patients with Gastric Cancer) and H3E-MC-JMAS (Phase 1 Trial of LY231514 with Folic Acid Supplementation in Patients with Locally Advanced or Metastatic Cancer) where folic acid is being administered. The first study is being conducted to determine if folate supplementation can improve toxicity. The second trial is testing whether the dose of LY231514 can be increased safely when folic acid is added. Patients with high baseline homocysteine levels will not be excluded from participation in these two trials.

As per a previous telephone conversation with Alvis Dunson, further communications to the FDA will be forthcoming shortly with more details of the updated safety analysis and proposals for future actions to lessen the serious toxic effects in patients with high homocysteine levels.

Please call Mr. John Worzalla at (317) 276-5052 or myself at (317) 277-3799 if there are any questions.

Sincerely,

ELI LILLY AND COMPANY

Gregory T. Brophy, PhD.
Director
U.S. Regulatory Affairs

Enclosure: Attachment

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Dear Investigator,

As part of ongoing endeavors to improve the safety of patients receiving LY231514 (MTA), we have been conducting an evaluation of toxicity resulting from the administration of MTA. You are aware that in each of our clinical trials, the protocol calls for the measurement of the vitamin metabolites homocysteine, cystathionine, methylmalonic acid, and methylcitrates. Our analysis of the correlation between nutritional status (as measured by these metabolites) and toxicity has shown that the homocysteine level of a patient directly correlates to the risk of both hematologic and non-hematologic toxicity. For example, it has been shown that homocysteine levels ≥12 μM are associated with a 59% probability of developing CTC Grade 4 hematologic toxicity or CTC Grade 3 or 4 non-hematologic toxicity while levels below 12 μM are associated with a 27% probability of developing this toxicity.

We have data which shows that multivitamin (including folic acid, B6 and B12) supplementation can be used to lower homocysteine levels and potentially decrease the degree of toxicity associated with MTA, and we will be discussing with the FDA appropriate actions to take based on this information. These actions may take the form of supplementing patients with multivitamins to lower homocysteine levels ≥12 μM before treatment, or excluding those patients with homocysteine levels ≥12 μM from MTA trials. You will receive additional information concerning final decisions on this issue.

In the interim, please take the following actions immediately:

- **Do not administer therapy with MTA until the patient's homocysteine value is reported to you.**
- **Until you receive additional information, do not treat any patient with a homocysteine level ≥12 μM.**
- **If a patient with a homocysteine level ≥12 μM has already been receiving treatment with MTA, the patient must sign a new informed consent form, based on the information contained in the first paragraph above, if they choose to remain on study after consultation with you. In light of the information presented here, we would recommend a full discussion between you and each patient.**

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As is the case with all cytotoxics, please continue to carefully monitor patients currently undergoing treatment with MTA for the following events:

- Febrile neutropenia
- CTC Grade 4 neutropenia > 5 days
- CTC Grade 3 or 4 neutropenia
- CTC Grade 4 thrombocytopenia
- Diarrhea or vomiting
- Mucositis

More detailed information on appropriate interventions is contained in the existing protocol.

Please forward this letter to your respective Ethics Committee(s). As soon as all the protocols are amended, they will be forwarded for implementation. The Informed Consent Documents will also require modification, and patients may need to be reconsented.

We realize this step is inconvenient for you and your patients, but it is of the greatest importance to protect the safety of every individual who participates in our trials. Thank you for your cooperation in this matter.

Yours Sincerely

ELI LILLY AND COMPANY

Paolo Paoletti, MD
Product Team Leader
Oncology New Product Development Team

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