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December 3, 1999

IND Safety Report Follow-Up and Request for FDA Input

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

Subject: IND 40,061, MTA (LY231514) -- Serial no. 195
Supplementation with Folic Acid and Vitamin B_{12} To Reduce Toxicity In Patients Receiving LY231514

Recently, Lilly sent a letter to investigators informing them to exclude patients with high baseline homocysteine levels from participation in LY231514 clinical trials (see submission serial number 194 to IND # 40,061 dated November 24, 1999). This letter was sent to all LY231514 investigators except for investigators in two studies (H3E-MC-JMAF and H3E-MC-JMAS) where patients are currently receiving folic acid supplementation. In the interest of patient safety, this action was taken preceeding formal protocol amendments.

In the cover letter to the FDA accompanying the November 24 letter Lilly stated that the exclusion of patients with high baseline homocysteine levels was a preliminary action, Lilly also indicated that a further communication would be sent to the FDA with details of the updated safety analysis together with a plan for an intervention to lessen serious toxic effects in patients with high baseline homocysteine levels. The updated safety analysis (see attachment) again reinforces the relationship between high baseline homocysteine levels and the potential for serious toxicity after treatment with LY231514 as shown by the following:

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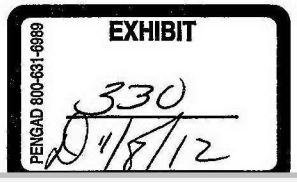

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- Elevated homocysteine level at baseline is highly correlated with severe toxicity (e.g. neutropenia, neutropenia accompanied by infection, diarrhea).

- Drug-related death is highly correlated with severe toxicity.

- Preliminary data from an ongoing study in gastric cancer (H3E-MC-JMAF) in a small number of patients has shown that at standard doses (500 mg/m^2), LY231514 has demonstrated activity in the presence of folic acid supplementation.

- LY231514 may be escalated as high as 925 mg/m^2 when accompanied by folic acid supplementation at a schedule of 5 mg orally daily for two days before, the day of, and two days after LY231514 administration (Study H3E-MC-JMAS). Data from this study shows that in patients with elevated homocysteine levels, this amount of supplementation causes homocysteine levels to drop below 10 μM and causes no change in patients that do not exhibit an elevated baseline homocysteine level.

- It is well known that elevated homocysteine levels are an indicator of poor nutritional status, and recently, elevated homocysteine levels have also been shown to be a predictor of mortality in cardiovascular disease. A study of homocysteine levels in 1788 middle-aged and elderly volunteers has shown that an elevated homocysteine level of 14 μM or greater puts a patient at increased risk for death caused by cardiovascular disease [Annals Internal Medicine 131:321-330, 1999].

- Folic acid supplementation of 400 μg daily in elderly patients with elevated homocysteine levels has been shown to substantially reduce plasma homocysteine levels within two weeks. The level continues to drop slightly for another two weeks, and then plateaus [International Journal for Vitamin and Nutrition Research 69:187-93, 1999]. Brouwer and coworkers showed that low dose folic acid (250 μg – 500 μg) intervention significantly decreases homocysteine levels. An eight week washout period was not sufficient for blood folate and plasma homocysteine levels to return to baseline. [American Journal of Clinical Nutrition 69:99-104, 1999] Niyikiza et al have shown that in patients who are not supplemented, homocysteine levels do not change over the course of treatment with LY231514 [Annals of Oncology, Supplement 4, 9: Abstract 609, 1998].

Based on this analysis, we have concluded that the following interventions are appropriate for ongoing trials.

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For the ongoing phase I trials of LY231514 in combination with another cytotoxic agent where the top dose level has been reached:

- Any patient with a baseline homocysteine level ≥12 μM will be excluded from enrollment. For these trials, this is a continuation of the policy mentioned in the November 24, 1999 letter to investigators (IND submission 194).

In all other trials, the following actions are being implemented. The initial action to exclude patients with high baseline homocysteine levels was taken to prevent serious toxicity to a sub-set of potential patients. Further analyses and discussions with a number of external consultants led to the conclusion that an overall safety benefit to patients might be better served through the addition of dietary supplementation to patients receiving LY231514 rather than exclusion of certain high-risk patients. Thus the following actions are being implemented.

Because there is a strong link between severe toxicity and elevated homocysteine levels as well as severe toxicity and drug-related death, the strategy of reducing homocysteine levels prior to treatment with LY231514 in these trials is being implemented. The following actions are being taken via another "letter to investigator" to promote the immediate interest of patient safety. Formal protocol amendments will be submitted as soon as possible. The implementation schema is as follows:

1) Each patient will have a blood sample drawn for the measurement of a baseline homocysteine level.

2) Each patient will begin a daily supplement of 350 – 1000 μg folic acid with 500 μg being the recommended dose. In countries where folic acid is not available, a multivitamin containing 350 – 1000 μg folic acid will be an acceptable substitute. This supplementation will continue daily as long as the patient is on study.

3) At this time, each patient will receive 1000 μg vitamin B12 as an intramuscular injection. (As mentioned in the introduction of the attached safety analysis, elevated homocysteine may also be caused by vitamin B12 deficiency in a small percentage of patients.) This will be repeated after every nine weeks cycle as long as the patient remains on study.

4) After at least seven days of folic acid supplementation, patients may begin to receive treatment with LY231514

5) It is recommended that any patient currently on study begin folic acid and B12 supplementation as well. Any patient falling into this category may receive his or her next regularly scheduled dose of LY231514 providing

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he or she has had at least two days of folic acid supplementation and one B12 injection.

For purposes of safety and study integrity, these steps will be implemented immediately in the ongoing randomized phase III study in malignant mesothelioma (H3E-MC-JMCH, A Single-blind Randomized Phase 3 Trial of MTA plus Cisplatin versus Cisplatin in Patients with Malignant Pleural Mesothelioma; see attachment for the letter being sent to the JMCH investigators). This will provide a unique opportunity to study the effects of folic acid and B12 supplementation on toxicity and efficacy in a homogenous patient population. The implementation steps for all other studies will be addressed immediately following completion of modifications in this randomized trial.

Re-evaluation of the prevalence of toxicity will be performed after 100 - 150 patients receiving the proposed supplementation of folic acid and B12 have been enrolled and have received at least two cycles of treatment.

Possible alternative methods to supplement folic acid and B12 will be evaluated and may be proposed for future trials.

Therefore Lilly asks DODP for a prompt review of these proposals to supplement LY231514 patients with folic acid and vitamin B_{12}. We believe that these actions will promote patient safety and not adversely effect the primary and secondary outcomes of the LY231514 registration trial for mesothelioma where approximately 40% of patients have high baseline homocysteine levels. In the JMCH study (the mesothelioma registration study), we are implementing the administration of folic acid and vitamin B_{12} to all patients in the LY231514 plus cisplatin arm as well as the cisplatin alone arm to preserve the integrity of this single-blind study. At the present time almost half of the planned number of patients (280) are enrolled in study JMCH. At the end of the study, we intend to compare the toxicity and other outcomes of those patients supplemented with folic acid and vitamin B_{12} versus those patients who did not receive this supplementation

Because of the implications for patient safety and also because of the potential effects on a registration trial, Lilly respectfully requests that we be notified by December 10 regarding DODP concurrence with these actions. We are available any time for a teleconference should DODP want to discuss these actions. Lilly is in the process of amending protocols for the LY231514 studies and await DODP comments before these protocol amendments are finalized.

Lilly is closely monitoring patient safety and attempting to find potential predictors that may identify patients at increased risk. The identification of

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elevated baseline homocysteine level as a predictor for toxicity and the steps taken to prevent this are a potential advance for chemotherapy with LY231514. We thank DODP with their continuing assistance regarding the development of LY231514.

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

Enclosures (2)
LY231514 (MTA) Safety Analysis
Copy of "Letter to Investigator" for JMCH

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