Lilly

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December 22, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
c/o Mr. Alvis Dunson
5600 Fishers Lane
Rockville, MD 20857

Expedited Review Requested

Subject: IND 40,061, MTA (LY231514) **Serial No. 201**
Response to FAX to Lilly from the FDA on December 21, 1999

In a FAX sent on December 21, 1999 from Mr. Alvis Dunson to Lilly, it states that the FDA Medical Officer reviewing LY231514 does not support the Lilly decision to add vitamins to its ongoing pivotal trial in mesothelioma. This FAX from the FDA further states that "the pivotal trial in malignant mesothelioma (H3E-MC-JMCH) should not be altered at this stage". Later in the December 21 FAX, it mentions that "the information provided in the Annual Report (serial #191) about the toxicities in the trial (pages 45-46) does not appear to support the addition of vitamins".

Lilly has further information regarding toxicity in the mesothelioma registration trial (H3E-MC-JMCH) since the annual report that was submitted (serial number no.191) on November 8 (the cut-off date for data in the annual report was September 10). It is the information contained in the additional data discussed below that prompted the action to supplement patients with folic acid and vitamin B12 in the ongoing pivotal mesothelioma trial.

In response to the Medical Officers comments in the December 21, 1999 FAX (the responses below are in the order of the reasons presented by the FDA)

1) Lilly plans to submit a statistical analysis plan describing how the data can be compared before and after vitamin supplementation. Protocol amendment H3E-MC-JMCH(c) being sent today under separate cover (serial number 200) describes analysis for toxicity in cycles where patients did and did not receive vitamin supplementation.
2) Lilly is committed to completing this 280 patient trial in malignant mesothelioma even if the results are positive at interim analysis. The addition of vitamins does not signify any change in our commitment to complete this registration trial.
3) There is additional information concerning toxicity in the mesothelioma registration trial since the annual report. As of December 21, 1999 there have been six patient deaths reported to Lilly for the mesothelioma registration trial in a total of 129

patients randomized between the two arms of this trial. The deaths were distributed as follows:

For the patients receiving cisplatin, but not LY231514, there has been one death, which has been attributed to progressive disease.

For the patients receiving LY231514 plus cisplatin, there have been five deaths, three of which have been classified as possibly or probably drug related (the other two deaths have been attributed to progressive disease).

The "LY231514 Safety Analysis" (submitted as an attachment to the FDA on December 3, 1999; serial no. 195) provided evidence for the strong relationship between high baseline homocysteine and severe toxicity for patients treated with LY231514. In the mesothelioma trial, more than 40% of patients have high baseline homocysteine levels. Because of the differences observed in mortality in the two arms of the trial and knowing that a high proportion of future LY231514 patients would be at risk for severe toxicity due to their high baseline homocysteine level, Lilly felt that action to ensure patient safety was warranted.

Lilly consulted a number of oncology experts regarding this patient safety concern, including Drs. Hilary Calvert, Mark Green, Richard Gralla, and Paul Bunn. In addition, Lilly consulted with Dr. Robert Allen, an expert in the area of folic acid metabolism. These consultants were in unanimous agreement that intervention was necessary to promote patient safety in the LY231514 trials. They all further suggested that supplementation with folic acid would offer the best chance of reducing serious toxicity to the broadest patient population. These experts felt that supplementation with low levels of folic acid would not adversely affect efficacy of LY231514. There were many discussions as to the optimum way that vitamin supplementation would protect the patients from toxicity. Eventually Lilly went with the recommendation to supplement with a low amount of folic acid (in the range of the FDA recommended daily dietary allowance) together with vitamin B12 (to possibly protect the small proportion of patients who might not benefit from folic acid alone). Because Lilly feels that the addition of folic acid together with vitamin B12 is necessary for patient safety, we are strongly committed to the use of these vitamins in the mesothelioma registration trial. We are aware that there are implications of this action for the LY231514 label. Lilly believes that the primary endpoint of survival as well as the secondary efficacy endpoints for the malignant mesothelioma registration trial will not be negatively affected by the supplementation with vitamins. As mentioned in Section 3 of the "LY231514 (MTA) Safety Analysis" (attachment to serial no. 195) folic acid has ameliorated toxicity in a phase 2 gastric cancer study and there have been several patients with confirmed partial responses in this study.

If the Medical Officer still does not support adding vitamins to this ongoing mesothelioma registration trial after reviewing the additional toxicity evidence provided in this letter, then Lilly would please request a face to face meeting at DODP's earliest convenience. Due to the impact of such an evaluation for an ongoing registration trial, Lilly requests that consideration be given to grant such a meeting as a Type A meeting under the February 1999 Guidance for Industry, "Formal Meetings with Sponsors and Applicants for PDUFA Products". The topic for discussion at this meeting would be as follows:

What are the implications of Lilly's decision to promote safety in patients treated with LY231514 by supplementing them with amounts of folic acid in the range of the

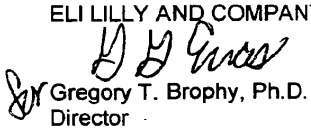
FDA recommended daily dietary allowance (together with vitamin B12) in the ongoing mesothelioma registration trial (H3E-MC-JMCH)?

If such a meeting is necessary, Lilly will make a submission with details and specific questions for this meeting as per the guidance listed above. Lilly will request a meeting to occur within 30 days of FDA's receipt of such a meeting request.

Please contact Mr. John F. Worzalla at (317) 276-5052 or me at (317) 277-3799 if you require any additional information or clarification.

Sincerely,

ELI LILLY AND COMPANY



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