DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-492

Sanofi-Synthelabo, Inc.
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Attention: Mark Moyer
Director, Drug Regulatory Affairs

Dear Mr. Moyer:

Please refer to your new drug application (NDA) dated June 24, 2002, received June 24, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Eloxatin™ (oxaliplatin) for Injection.

We acknowledge receipt of your submissions dated April 15, May 17, July 12, July 17, July 18 (two), July 19 (two), July 25, and July 31, 2002, August 9, 2002 (two).

This new drug application provides for the use of Eloxatin (oxaliplatin) for Injection in combination with infusional 5-FU/LV for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed during or within 6 months of completion of first line therapy with the combination of bolus 5-FU/LV and irinotecan.

We have completed the review of this application, as amended, according to the regulations for accelerated approval, and have concluded that adequate information has been presented to approve Eloxatin (oxaliplatin) for Injection for use as recommended in the enclosed labeling text. Accordingly, the application is approved under 21 CFR 314 subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced accelerated approval regulations.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-492." Approval of this submission by FDA is not required before the labeling is used.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further

adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your commitment to conduct post-marketing studies (Subpart H post-marketing commitments) specified in your submission dated August 9, 2002. These commitments, along with the completion dates agreed upon, are listed below:

1. Complete the study whose initial results were submitted for review in NDA 21-492: EFC4584 (Multi-center, Randomized, Three Arm Study of 5-Fluorouracil/Leucovorin or Oxaliplatin or a Combination of 5-Fluorouracil and Oxaliplatin as Second-Line Treatment of Metastatic Colorectal Carcinoma). Submit the mature survival data and analysis in a final study report for review by 2004, second quarter.

2. Complete study EFC4585 (Multi-center, Randomized, Two Arm Study of Irinotecan versus the Combination of Oxaliplatin with Irinotecan as Second Line Treatment of Metastatic Colorectal Cancer). Submit the mature survival data in a full study report for review by 2005, third quarter.

3. Complete study EFC7462 (Randomized, Phase 3 trial of Combinations of Oxaliplatin, 5-Fluorouracil and Irinotecan as Initial Treatment of Patients with Advanced Adenocarcinoma of the Colon and Rectum). Submit the full study report for review by 2003, third quarter.

4. Complete study L8125 (Randomized Trial Evaluating Oxaliplatin Combined with Two Different 5-Fluorouracil Regimens in Patients with Previously Untreated Advanced Colorectal Cancer). Submit the full study report for review by 2005, second quarter.

5. Complete the adjuvant treatment study EFC3313 (Multicenter International Study of Oxaliplatin/5FU/LV in the Adjuvant Treatment of Colon Cancer – MOSAIC TRIAL). Submit the full study report for review by 2004, third quarter.

6. Complete the adjuvant treatment study EFC7112 (Clinical Trial Comparing 5-FU plus Leucovorin and Oxaliplatin with 5-FU/LV for the Treatment of Patients with Stage 2 and 3 Carcinoma of the Colon). Submit the full study report for review by 2007, first quarter.

Final study reports should be submitted to this NDA as supplemental applications. For administrative purposes, all submissions relating to these post-marketing commitments must be clearly designated "Subpart H Post Marketing Commitments."

In addition, we note additional post-marketing commitments, specified in your submission dated August 9, 2002, that are not a condition of the accelerated approval. These commitments, along with any completion dates agreed upon are listed below:

7. Design and conduct a study to examine the safety of administering repeated doses of oxaliplatin 85 mg/m^2 in combination with infusional 5-FU/LV, at the doses and schedule recommended in the product label, in patients with varying degrees of renal impairment. This study should include patients with normal renal function, minimally impaired renal function, and moderately impaired renal function. The study should be designed to assess whether there are differences in safety between each of the different subgroups of renal impairment and a control group with normal renal function. Differences in proportions of patients with all grades and grade 3/4 gastrointestinal, neurological, renal and hematological toxicities, differences in time to onset and duration of grade 3/4 neurotoxicity, and differences in proportions of patients who require dose reductions should be evaluated. A subgroup of patients with severe renal toxicity should also be considered for study, possibly at a lower starting dose. Submit the full study report for review by 2004, third quarter.

8. Submit reports of all medication errors, both potential and actual, that occur within the United States with oxaliplatin for two years following the date of approval. Potential errors should be reported and summarized quarterly. All actual errors should be submitted within 15 days regardless of patient outcome. Yearly reports of potential and actual errors occurring with oxaliplatin should be submitted for two years following the date of approval.

9. To decrease potential medication errors of substitution of oxaliplatin for other platinum drugs, at the time of next printing, redesign the oxaliplatin product packaging so that the “oxali” prefix to the name appears in a different font color and/or size.

10. Complete the study EFC4759 (Single Arm Phase 2 study of Oxaliplatin as Third-Line Treatment of Metastatic Colorectal Carcinoma). Submit the full study report for review by 2004, third quarter.

11. Complete the study EFC 4760 (Randomized, Phase 2 Trial of Infusional 5-FU versus Infusional 5FU/Oxaliplatin in 3rd line Treatment of Metastatic Colorectal Carcinoma). Submit the full study report for review by 2004, first quarter.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or

initial publication of the advertisement.

Please submit one market package of the drug product when it is available.

We remind you of your commitment to provide the 36-month stability data update by annual report. Thereafter, at least one production batch of each dose, manufactured by the approved manufacturer and packaged in the approved package configuration will be placed on stability at 25°C/60% RH annually.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Christy Wilson, Consumer Safety Officer, at (301) 594-5761.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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

/s/

Robert Temple
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