



NDA 21-492/S-004
NDA 21-492/S-005

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

Attention: Mark Moyer
Senior Director, Drug Regulatory Affairs

Dear Mr. Moyer:

Please refer to your supplemental new drug applications dated December 19, 2003, and August 23, 2004, received December 19, 2003, and August 24, 2004, respectively, 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 February 3, March 26, April 30, May 13, 19 (2), and 27, June 3, 7, and 10, July 22 and 28, September 17 and 29, October 14, 21 (2), and 26, and November 4, 2004.

Supplemental new drug application 004 provides for the use of ELOXATIN™ in combination with infusional 5-FU/LV, for the adjuvant treatment of stage III colon cancer patients who have undergone complete resection of the primary tumor. The indication is based on an improvement in disease-free survival, with no demonstrated benefit in overall survival after a median follow up of 4 years.

“Changes Being Effected” supplemental new drug application 005 provides for the addition of “immuno-allergic hemolytic anemia” and “colitis (including *Clostridium difficile* diarrhea)” to the **ADVERSE REACTIONS** section, **Postmarketing Experience** subsection of the package insert.

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated “FPL for approved supplements NDA 21-492/S-004 and S-005.” Approval of this submission by FDA is not required before the labeling is used.

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. We are waiving the pediatric study requirement for this application.

We remind you of your postmarketing study commitment in your submission dated November 4, 2004. The commitment is listed below.

1. All patients in the MOSAIC trial should be followed for efficacy until death or for at least 6 years with submission of study reports annually and a final study report submitted by the 3rd quarter of 2007.

In addition to the formal postmarketing commitment listed above, we have the following postmarketing requests which you have agreed upon as outlined in your submission dated November 4, 2004.

Two toxicities of the oxaliplatin combination need to be studied further. They are:

2. Hepatotoxicity, the actual incidence, characteristics and progression of which is not known. It should be assessed in a prospective, randomized adjuvant study in which regular monitoring of liver function tests are performed until resolution of the toxicity; and
3. Increased prolongation of prothrombin time and INR on oral anticoagulants that is associated with hemorrhage. The incidence of this toxicity should be evaluated in a randomized trial.

We also remind you of your outstanding postmarketing study commitment in your submission dated June 24, 2002. The commitment is listed below.

Commitment #7

Design and conduct a study to examine the safety of administering repeated doses of oxaliplatin 85 mg/m squared 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.

Protocol Submission: Submitted

Study Start: Started

Final Report Submission: Delayed

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.”**

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Oncology Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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cc: Mark Gaydos
Director, Promotion Review and Labeling
Sanofi-Synthelabo, Inc.
90 Park Avenue
New York, NY 10016

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

/s/

Richard Pazdur
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