

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-492**

**Approval Letter**



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<sup>2</sup> 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 3<sup>rd</sup> 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

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/  
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Robert Temple  
8/9/02 06:22:23 PM

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER  
NDA 21-492**

**Approvable Letter**



DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 21-063

JUN - 1 2000

Food and Drug Administration  
Rockville MD 20857

Sanofi-Synthelabo, Inc.  
9 Great Valley Parkway  
Malvern, PA 19355

Attention: Mark W. Moyer  
Director, Regulatory Affairs

Dear Mr. Moyer:

We acknowledge receipt of your May 18, 2000 correspondence notifying us that you are withdrawing your July 22, 1999 new drug application (NDA) for Eloxatin (oxaliplatin) for Injection in combination with 5-fluorouracil and leucovorin for first-line treatment of advanced colorectal cancer.

Therefore, in accordance with 21 CFR 314.65, this application is withdrawn as of the date of our receipt of your notification, May 19, 2000. This withdrawal does not prejudice any future filing of the application. You may request that the information contained in this withdrawn application be considered in conjunction with any future submission.

As of the date of your request to withdraw this application, all reviews of the pending NDA had been completed. Outlined below are the deficiencies noted with your application; these should be addressed in any resubmission.

Clinical:

Results of two randomized clinical trials in previously untreated patients with advanced metastatic colorectal cancer were submitted. In Study 2962 a biweekly 5-FU + Leucovorin regimen with or without Eloxatin was studied. In Study 2961 a daily for five days chronomodulated 5-FU + Leucovorin regimen with or without Eloxatin was studied. Although an effect of Eloxatin was seen on response rate and time to progression in both studies, neither study showed improved survival in the Eloxatin arms. An effect on survival or other demonstrated clinical benefit is considered essential to a conclusion that initial therapy of colorectal cancer is effective.

In Study 2962 no effect on overall survival was found using the protocol specified Log Rank unadjusted analysis. Only certain exploratory analyses suggested an effect on survival. These used a variety of adjustments for baseline factors such as prior radiotherapy, LDH, prior surgery for primary site, prior surgery for metastases and CEA, as well as adjustments for other non pre-specified variables including post-study chemotherapy, post-study oxaliplatin, post-study CPT-11 and post-study CPT-11 and/or oxaliplatin, post-study chemotherapy and/or surgery and post-study surgery. The factors used in the Cox regression model were selected after study completion and introduce a potential bias. These results are highly analysis dependent and the nominal p-

values cannot be considered reliable. In Study 2961 there was not even a trend toward a favorable effect on survival.

In Study 2962 there was no favorable effect on performance status, weight change, pain scores or disease-related symptoms. There was also no favorable effect on quality of life using the EORTC QLQ-C30 instrument. In Study 2961 there was no planned assessment of these parameters.

Several phase 2 non-comparative clinical trials of Eloxatin in advanced metastatic colorectal cancer were also submitted. In second-line chemotherapy there were two trials of Eloxatin in combination with 5-FU and Leucovorin and two trials of single agent Eloxatin. In first-line chemotherapy there were two trials of single agent Eloxatin. All of these trials, like Studies 2961 and 2962, indicate activity of Eloxatin as manifested by tumor shrinkage. But these clinical trials did not assess patients to determine whether there was symptomatic improvement and cannot assess survival effects.

In summary, the data submitted do not support a claim that Eloxatin has been shown to be effective in the treatment of colorectal cancer.

#### Clinical Pharmacology and Biopharmaceutics:

- 1. Dose Reductions in Renal Impairment.** You demonstrated that the AUC of platinum was increased after a dose of 130 mg/m<sup>2</sup> Eloxatin and its clearance decreased, in patients with moderate renal impairment. You proposed 20% dose reductions of Eloxatin at both dosing regimens in patients with renal impairment. However, the pharmacokinetics of Eloxatin are not proportionate to dose, and a 20% dose reduction cannot be assumed to produce a proportional decrease in AUC. For the same reason, these findings cannot be extrapolated to the 85 mg/m<sup>2</sup> Eloxatin regimen. You should therefore examine the effect of defined dose reductions on Eloxatin/platinum AUC in patients with moderate renal impairment in order to provide appropriate dose reductions for labeling. These studies should be done for both dosing regimens.
- 2. Assay.** The analytical methodology was limited to the assessment of total platinum. These measurements include both active and inactive species/metabolites of Eloxatin. As a result, the pharmacokinetic information is limited and potentially misleading because some of the inactive species may be very long-lived. You demonstrated the ability to separate oxaliplatin and some of the active species with nonvalidated assays. Future pharmacokinetic studies should employ validated assays that specifically quantify oxaliplatin and active metabolites (mono-aqua monochloro DACH platinum, dichloro DACH platinum, diaqua DACH platinum, etc.).

Chemistry:

1. A specification for platinum content in the drug substance needs to be established.
2. You will need to establish a bulk compounded solution holding time and revise the Master Batch Record accordingly. Note that the holding time should be supported with appropriate microbiological data.
3. We would like you to confirm that no reprocessing operations for the drug product are proposed.
4. The pH range in the drug product specifications should be tightened to more closely reflect manufactured batch data.
5. Information regarding procedures used to sample the drug product for release testing should be provided.
6. Based upon batch release data as well as stability data the proposed impurity specifications appear to be too broad. Tighten the impurity specifications for both release and stability. Revised stability protocols should be submitted reflecting changes that will be made to the impurity specifications.

Microbiology:

1. The specifications for bulk solution bioburden (NMT \_\_\_\_\_) are too high for a parenteral drug product.
2. The 'in-use' microbiological test method for the reconstituted/diluted drug product does not address the central concern of the proposed 24 hour, room temperature, storage period. That is, will the drug product, diluted in 5% dextrose, support the growth of microorganisms that may be inadvertently introduced during reconstitution and/or dilution. This is particularly important because the Material Safety Data Sheet for Eloxatin for Injection (volume 1.5, page 76) states that the minimum inhibitory concentration for some common microorganisms (0.4 to > 1 mg/mL) is greater than the minimum concentration of the diluted drug (0.1 mg/mL). In order to answer this question it is necessary to introduce microorganisms into the diluted drug product and determine if their numbers increase over the course of the test period.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should provide the following information covering all indications, dosage forms, and dose levels:

1. Details of any significant changes or findings.
2. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will facilitate review.
3. Retabulation of study drop-outs with new drop-outs identified. Discuss if appropriate.
4. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.
5. Any information that suggests a substantial difference in the rate of occurrence of common, but less serious, adverse events.
6. Summary of worldwide experience on the safety of this drug.
7. English translations of any approved foreign labeling not previously submitted.

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

Sincerely,

RS

6/1/00

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

NDA 21-063

Page 5

cc:

Archival NDA 21-063

HFD-150/Div. Files

HFD-150/CWilson

HFD-150/Hirschfeld/Johnson/Liang/Sarker/Duffy/Andrews/Booth/Rahman/Rothmann/G.Chen

HFD-101/ADRA

DISTRICT OFFICE

Drafted by: clw/May 22, 2000

Initialed by: Pease/5-25-00; Booth/Rahman/5-26-00; GChen/Hirschfeld/5-30-00; Johnson/5-31-00

final: CWilson/5-31-00

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WITHDRAWN (WD)

*Pease  
6-1-00*

NDA 21-063

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

FEB 11 1999

Attention: Mark W. Moyer  
Director, Drug Regulatory Affairs

Dear Mr. Moyer:

Please refer to your December 14, 1998 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Eloxatin® (oxaliplatin) for Injection.

The application seeks approval of Eloxatin® for the "treatment of advanced colorectal cancer in combination with 5-FU-based chemotherapy." The application, however, is actually seeking approval of Eloxatin® for two separate indications: for the treatment of advanced colorectal cancer in combination with 5-FU-based chemotherapy in previously untreated patients, and for the treatment of advanced colorectal cancer in combination with 5-FU-based chemotherapy in previously treated patients that are refractory to 5-FU-based chemotherapy.

The initial submission contained eight "Primary Studies": two randomized, controlled trials in previously untreated patients with advanced colorectal cancer (EFC2961 and EFC2962); two single-arm studies in patients with measurable, advanced colorectal cancer who had progressed while receiving or within 2 months of receiving a 5-FU/leucovorin regimen (EFC2917 and EFC2964); and four single-arm studies of oxaliplatin monotherapy in previously untreated (EFC2960 and EFC2963) and previously treated patients (EFC3105 and EFC3106) with advanced colorectal cancer. Electronic data on a ninth study, the JCO study comparing the de Gramont 5-FU/leucovorin regimen with the Mayo/NCCTG regimen, was initially submitted only as an electronic file.

We have given your application a preliminary review, and we find it is not sufficiently complete to merit review. Thus, it will not be filed as a new drug application within the meaning of section 505(b) of the Act.

We are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

1. Please refer to the minutes of FDA-Sanofi meetings held on November 22, 1996, October 8, 1997, and October 8, 1998, and to FDA comments provided by facsimile

transmission on April 17, 1998 in response to your general correspondence (serial number 062) submitted to IND — on February 27, 1998. The minutes and comments express the Agency's concern that for both the previously untreated and treated patients, the 5-FU regimens utilized in the Eloxatin® studies have not been demonstrated to be at least equivalent in safety and efficacy to the Mayo/NCCTG regimen. Two studies comparing the Mayo/NCCTG combination of leucovorin/5-FU to other 5-FU regimens demonstrated an improvement in survival with the Mayo/NCCTG regimen, and provided the basis for FDA's approval of this regimen for the treatment of patients with advanced colorectal cancer. At the FDA-Sanofi meetings, it was agreed that in order to establish that the de Gramont regimen is at least as good as the Mayo/NCCTG regimen, the database for the JCO study comparing the two regimens would need to be submitted. Hard copy data tabulations for the JCO study were not included in the original submission and the electronic file was not readable. The hard copy database that was provided on January 28, 1999 in response to our January 27, 1999 telephone request is insufficient. A copy of the JCO protocol and all amendments and complete individual patient data from this study must be submitted. Among the missing data items are:

- a. All tumor measurements on all lesions at all time points;
  - b. Dates of onset and resolution of adverse events;
  - c. Outcomes of adverse events and actions taken in treatment and/or evaluation of such events;
  - d. Results of physical examinations, including relevant physical findings such as jaundice, hepatomegaly, ascites, etc.;
  - e. Results of relevant laboratory determinations, such as liver function tests, blood counts, CEA, etc.
2. All of the data entries, field names, column and row headings, case report forms, etc. in the application that are in French must be translated into English.
  3. The minutes of the FDA-Sanofi meetings also include the Agency recommendation that a comparative study, e.g., oxaliplatin vs. Camptosar™, should be performed in the previously treated (refractory) population. At the October 8, 1998 meeting, it was stated that accelerated approval of oxaliplatin was unlikely because of the availability of Camptosar™ and that demonstration of clinical benefit would be required for full approval. The subsequent demonstration of a survival benefit for Camptosar™ treatment in patients with metastatic colorectal cancer whose disease has recurred or progressed following 5-FU-based therapy, and its approval for this indication, have set a new standard. Drugs seeking approval for the treatment of patients with colorectal cancer that is refractory to 5-FU regimens must now be compared to Camptosar™ in randomized, controlled trials. Since studies EFC2917 and EFC2964 do not include a comparison to Camptosar™, their study designs are inappropriate for the proposed claim.

4. The minutes of the FDA-Sanofi meetings also state that for the refractory indication, where patients are being used as their own controls, you must document the prior chemotherapy regimen, demonstrate that it was a satisfactory regimen, and provide convincing evidence that patients have refractory disease. The FDA comments of April 17, 1998, make it clear that "a critical element in evaluating the refractory indication is the convincing demonstration that patients were truly refractory to prior treatment" and that "this will rest heavily upon adequate documentation of prior therapy, of the responses to such therapy, and of progression in relation to prior therapy." The following data should have been submitted:
  - a. Component drugs, schedules, and treatment dates of the chemotherapy regimen(s) received prior to entry;
  - b. Date and nature of best response and duration of same following each chemotherapy regimen;
  - c. Date of progression on each chemotherapy regimen;

Although not a basis for the refusal to file, the organization and format of the efficacy data for tumor response and progression make the review quite tedious and prone to errors. Instead of providing data on tumor measurements for a single patient on one page, multiple patients are included on a single page and the columns for these patients extend for several pages. In addition, patient visits are not always listed in sequence. These deficiencies are best addressed by submitting these data as an electronic database that meets FDA requirements. The submitted database should 1.) contain a definition of field names and field contents where abbreviations or codes are used, 2.) should be in English, and 3.) should be accompanied by an annotated key that interprets the various entries and defines each variable (particularly those containing calculated quantities). An annotated case report form with the field and variable names would be quite helpful. If desired, FDA is willing to discuss other formats for submitting the data.

Within 30 days of the date of this letter, you may request in writing an informal conference about our refusal to file this application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusions, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3). If you do so, this application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference.

FDA will refund 75% of the user fee submitted with the application. If you decide to file this application over protest, the filing of this application over protest will be regarded by the Agency as a new original application for user fee purposes, and will be assessed a user fee applicable to a new submission.

If you have any questions, contact Debra Catterson, Project Manager, at (301) 827-1544.

Sincerely,

*S*

*M.D. 2/11/99*

Robert Justice, M.D.  
Acting Director  
Division of Oncology Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

cc:

Archival NDA 21-063  
HFD-150/Div. Files  
HFD-150/KKobayashi  
HFD-150/JJohnson  
HFD-150/RJustice  
HFD-150/CLiang  
HFD-150/LZhou  
HFD-150/HZheng  
HFD-150/PAndrews  
HFD-150/BBooth  
HFD-150/ARahman  
HFD-150/KKoti  
HFD-150/GChen  
HFD-150/LVaccari  
HFD-150/DPease  
HFD-150/DCatterson  
HFD-344/GTurner  
HFD-95/DDMS  
HFD-810/DNDC Division Director  
DISTRICT OFFICE

Drafted by: dmc/February 4, 1999

Initialed by:

DPease/2.5.99  
JJohnson/2.5.99  
CLiang/2.5.99  
LZhou/2.5.99  
HZheng/2.5.99  
PAndrews/2.5.99  
BBooth/2.5.99  
ARahman/2.5.99  
KKoti/2.5.99  
GChen/2.5.99  
RJustice/2.11.99

final: dmc/2.11.99

filename: c:/mydocuments/oxaliplatin/rtf letter.doc

**REFUSAL TO FILE (RF)**