CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
NDA 21-492

Administrative Documents

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-492	Efficacy Supplement Type SE-	Supplement Number
Drug: Eloxatin (oxaliplatin) for Injection	Applicant: Sanofi-Synthelabo, Inc.	
RPM: Christy Wilson	HFD-150	Phone # (301) 594-5761
Application Type: (X) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	( ) Standard (X) Priority
• Chem class (NDAs only)	1
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	December 24, 2002
❖ Special programs (indicate all that apply)	( ) None Subpart H (X) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) (X) Fast Track – **granted May 10, 2002** (X) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	Included in package
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	N/A
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	RTF – February 11, 1999 Withdrawn – June 1, 2000
• Status of advertising (approvals only)	( ) Materials requested in AP letter (X) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None (X) Press Release – sponsor and FDA ( ) Talk Paper ( ) Dear Health Care Professional Letter (X) **Other** – FDA issued Question and Answer webpage (X) **Other** – FDA issued ASCO, ONS, and NCI burst e-mail
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	Included in package
• Most recent applicant-proposed labeling	Included in package
• Original applicant-proposed labeling	Included in package
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DDMAC review of PI – 7/2/02 DSRCS review of PPI – 7/24/02 DMETS review of tradename – 7/16/02
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Included in package
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A – sponsor labels are acceptable
• Applicant proposed	Included in package
• Reviews	CMC review – 7/23/02
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	Included in package
• Documentation of discussions and/or agreements relating to post-marketing commitments	Included in package
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Included in package
❖ Memoranda and Telecons	Included in package
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	June 8, 2000 and August 25, 2000

	and December 12, 2000
• Pre-NDA meeting (indicate date)	December 11, 2001 and January 28, 2002 and March 22, 2002
• Pre-Approval Safety Conference (indicate date; approvals only)	July 29, 2002
• Other	May 10, 2001 and August 30, 2001
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Included in package
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	Included in package
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	Included in package
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Included in package
❖ Demographic Worksheet *(NME approvals only)*	Included in package
❖ Statistical review(s) *(indicate date for each review)*	Joint review with clinical
❖ Biopharmaceutical review(s) *(indicate date for each review)*	Included in package
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	Included in package
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	July 23, 2002
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	July 23, 2002
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	July 22, 2002
❖ Facilities inspection (provide EER report)	Date completed: June 28, 2002 and July 15, 2002 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	(X) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N21-492: July 22, 2002 N21-063: March 31, 2000 I [redacted] April 16, 1993
❖ Nonclinical inspection review summary	N/A

❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

7/2/02

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

/s/

Christy Wilson
8/16/02 09:18:12 AM

ITEM 13. PATENT INFORMATION

Pursuant to § 505 of the Federal Food, Drug and Cosmetics Act (FFDCA), as amended by the Drug Price Competition and Patent Term Restoration Act of 1984, applicants hereby submit information on each patent that claims the drug, drug product, or a method of using the drug and with respect to which a claim of infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use or sale of the drug product described in this application.

United States Patent Number	Expiration Date	Type of Patent	Patent Owner
5,420,319	April 7, 2013	Drug	Debiopharm S.A.
5,338,874	April 7, 2013	Drug	Debiopharm S.A.
5,290,961	January 12, 2013	Drug	Debiopharm S.A.

The following party is authorized to receive notice of patent certification under § 505(b)(3) and (j)(2)(B) of the FFDCA and §§ 314.52 and 314.95 of 21 C.F.R.

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

REQUEST FOR EXCLUSIVITY

Pursuant to §§ 505(j)(4)(D)(ii) and 505(c)(3)(D)(ii) of the Federal Food, Drug and Cosmetics Act, applicants are requesting a five-year period of marketing exclusivity from the date of approval of this NDA for oxaliplatin.

This request for exclusivity is based upon the following:

(a) No active ingredient of the drug product for which approval is being sought has ever been approved in another drug product in the United States either as a single entity or as a part of a combination product; and

(b) No active ingredient of the drug product has ever been previously marketed in a drug product in the United States.

ITEM 14. PATENT DECLARATION

No patent declaration is required, as U.S. Patent Nos. 5,420,319, 5,338,874 and 5,290,961 do not cover a formulation, composition and/or method of use of oxaliplatin.

Michael D. Alexander

MICHAEL D. ALEXANDER
Sr. Managing Attorney, Intellectual Property
Sanofi-Synthelabo Inc.

EXCLUSIVITY SUMMARY for NDA # 21-492 SUPPL #

Trade Name Eloxatin Generic Name oxaliplatin

Applicant Name Sanofi-Synthelabo, Inc. HFD- 150

Approval Date August 9, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X_/

      If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain:
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

/S/

_____

Signature of Preparer Date

Title: Consumer Safety Officer

Signature of Office or Division Director Date

cc:
Archival NDA 21-492
HFD-150/Division File
HFD-150/Wilson
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Richard Pazdur
8/16/02 02:18:32 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : NDA 21-492 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: 6-24-02 Action Date: August 9, 2002

HFD-150 Trade and generic names/dosage form: Eloxatin (oxaliplatin) for Injection

Applicant: Sanofi-Synthelabo, Inc. Therapeutic Class: 1P

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Eloxatin, used in combination with infusional 5-FU/LV is indicated 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. The approval of Eloxatin is based on response rate and an interim analysis showing improved time to radiographic progression. No results are available at this time that demonstrate a clinical benefit, such as improvement of disease-related symptoms or increased survival (see CLINICAL STUDIES).

Is there a full waiver for this indication (check one)?

☑ Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☑ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, pleas e see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	kg____	mo.____	yr.____	Tanner Stage____
Max____	kg____	mo.____	yr.____	Tanner Stage____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study

- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

cc: NDA 21-492
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD- 960
301-594-7337**

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, pleas e see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD- 960
301-594-7337

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/s/

Christy Wilson
8/16/02 02:13:57 PM
CSO

ITEM 16. DEBARMENT CERTIFICATION

Sanofi-Synthelabo, Inc., hereby certifies that it did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [section 306(a) or (b)] of the FD&C Act in connection with this application.

Mark W. Moyer

Mark Moyer
Director
Drug Regulatory Affairs

Division Director's Memorandum

Date: August 8, 2002
NDA: 21-492
Sponsor: Sanofi-Synthelabo
Proprietary Name: Eloxatin (oxaliplatin) Injection

Introduction:

Oxaliplatin in combination with infusional 5-FU/LV was not approved after a previous NDA was submitted r for the first-line treatment of advanced colorectal cancer. Two randomized controlled trials were submitted in that application, neither designed with the relevant primary endpoint of survival. Although in each study the oxaliplatin arm was statistically significantly superior in the pre-specified study primary endpoint, progression free survival in one study and response rate in the other, no improvement in overall survival was noted in either study. The applicant has now submitted a single randomized, controlled, three arm trial that evaluated oxaliplatin in combination with infusional 5-FU/LV, single agent oxaliplatin and an infusional 5-FU/LV arm for treatment of advanced colorectal cancer patients whose disease had relapsed or progressed during or within 6 months of first line therapy with bolus 5-FU/LV and irinotecan. The primary endpoint of the trial is survival, but there was a pre-specified plan to evaluate response rate after 450 patients were enrolled, to support potential accelerated approval. The radiographs were assessed by a central blinded independent radiology group. The results of the response rate analysis and an interim analysis of time to radiographic documentation of disease progression were submitted for review to support accelerated approval for the proposed indication:

ELOXATIN in combination with 5-FU/LV is indicated for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial 5-FU/LV + irinotecan therapy.

Chemistry/Manufacturing and Controls:
See the Chemistry review of Dr. Haripada Sarker, Ph.D.

The USAN chemical name of oxaliplatin is: SP-4-2-(1R,2R)-(cyclohexane-1,2-diamine-2 N,N'(oxalato(2-)-. 2 O 1 ,O 2]platinum(II). It is a white to off-white powder. Oxaliplatin is an organometalic coordination complex, with the platinum atom chelated with a 1,2-diaminocyclohexane group and an oxalate group. The pKa study on oxaliplatin indicated that the molecule is neutral with no dissociation in solution. Multiple batch records, including the microbiological limits, demonstrate the batch to batch consistency of the oxaliplatin drug substance. Primary and secondary stability studies support the stability of oxaliplatin drug substance in the solid state up to 36 months at normal condition using the commercial container/closure system.

The drug product, oxaliplatin for injection (Eloxatin) is formulated as a sterile lyophilized powder at two strengths 50 mg and 100 mg/vial, for reconstitution with water for injection or 5%. Oxaliplatin lyophilized powder is found to be stable up to 36 months using commercial container/closure systems, and at normal condition. However, the reconstituted drug products are

stable up to 24 hours at 2-8°C (36-46° F). After final dilution with 250-500 mL of 5% Dextrose Injection, USP, the shelf life is 24 hours at room temperature and at ambient light.

MANUFACTURING SITE COMMENT

Preclinical:
See the review of Pharmacology/Toxicology reviewer, Dr. Wendolynn Schmidt. Oxaliplatin demonstrates *in vitro* cytotoxic or antiproliferative activity against a variety of murine and human tumor cell lines. Oxaliplatin as a single agent demonstrated *in vivo* antitumor activity against a variety of murine tumor models and human xenograft model in athymic mice.

Oxaliplatin was negative in the Ames test, but was positive in all other genotoxicity tests, *i.e.*, mouse lymphoma assay for mammalian cells (TK locus), mouse micronucleus assay, and chromosome aberration assay for human lymphocytes in culture. Oxaliplatin was mutagenic and clastogenic both in the presence or absence of metabolic activation. Based on net values (≥ 4) obtained from the integrative assessment for assignment of concern, there are significant degrees of concern for developmental and reproductive toxicity for the endpoints of fertility, developmental mortality, and alterations to growth in humans from the exposure to oxaliplatin at the clinical dose proposed.

The carcinogenicity of oxaliplatin has not been studied in animals. However, based on the similar mechanism of action and genetic toxicity as cisplatin, which has sufficient evidence of carcinogenicity in animals and humans, oxaliplatin should be presumed to be a trans-species carcinogen.

Biopharmaceutics:
See Dr. Brian Booth's review of oxaliplatin for Division of Biopharmaceutics.

Using a validated assay, the applicant demonstrated that the pharmacokinetics of platinum from oxaliplatin at a dose of 85 mg/m^2 are described by a three-compartment open mammalian model with $t_{1/2}$'s of 0.43, 16.8 and terminal elimination half-life of 391 hours. The pharmacokinetics of oxaliplatin appear to be linear between 40 and 130 mg/m^2. Oxaliplatin is rapidly hydrolyzed *in vivo* to yield a number of active and inactive platinum species.

The pharmacokinetics of platinum from oxaliplatin are not affected by 5-FU, nor are the pharmacokinetics of 5-FU affected by oxaliplatin at a dosage of 85 mg/m^2. At the dose of 130 mg/m^2, oxaliplatin appears to increase the plasma concentration of 5-FU by approximately 20%. Oxaliplatin is extensively protein bound (approximately 90 to 95 % in vivo), but it did not mediate displacement interactions with erythromycin, salicylate, valproate, granisetron or paclitaxel.

Cytochrome P-450 isozymes do not metabolize oxaliplatin, and the platinum is excreted predominantly via the renal route (over 50% in 5 days). Oxaliplatin is eliminated primarily by renal excretion - 50 % of platinum is excreted in the urine after a single dose. A study was conducted to assess the effect of renal impairment on the pharmacokinetics of single agent oxaliplatin in patients with a variety of cancers using a dose-escalation scheme and renal impairment criteria that differed from the FDA recommendations. FDA re-analysis indicated that the $AUC_{0\text{-}48hr}$ of platinum in patients with mild, moderate and severe renal impairment increased by approximately 60, 140 and 190% respectively, compared to patients with normal renal function. The pharmacokinetic evaluation of oxaliplatin is based on analyses of total platinum ultrafiltrate, and it is unknown what pharmacokinetic changes actually occur in biologically

active platinum moieties. There are no PD data available for evaluation. Because the safety data available from this renal impairment study were limited (limited patient numbers) and only single agent oxaliplatin was administered (the combination of oxaliplatin with 5-FU increases the incidence of some of the toxicities associated with 5-FU), no recommendations regarding the relative safety of administering oxaliplatin to patients with varying degrees of renal impairment could be made on the basis of the phase 1 study. There are also no efficacy or safety data available for administration of reduced doses of oxaliplatin to patients with varying degrees of renal impairment. The product label was written to include cautionary statements regarding administration of oxaliplatin in patients with renal impairment.

Clinical/Statistical:

The study was designed with an interim analysis of response rate to support accelerated approval until mature survival data could establish the clinical benefit. The randomized, controlled design and the use of a blinded independent radiology consultant group bolsters the persuasiveness of the tumor response data. The final independent reviewer tumor response was relatively low, 13 patients (9%, CI 4.6-14.2), but statistically significantly higher than the infusional 5-FU/LV control arm (0%, CI 0-2.4%) ($p = 0.0002$). Two patients (1%, CI 0.2-4.6%)) on single-agent oxaliplatin had partial responses. The independently reviewed radiographic time to progression analysis (an interim analysis performed with 49% of events) showed a significant prolongation of time to progression, but 18% of patients were excluded from the analysis by censoring at time zero. Of these 82 patients, 25 were censored because the radiographs that had been performed by the investigator were either not reviewed, or were not considered evaluable by the independent reviewer. Statistically significant prolongation of time to progression was observed both in this evaluable patient analysis based on the independent radiologist review and in a separate time to progression analysis that defined events based on the investigator's assessment of radiographic progression, clinical evidence of disease progression and patient death. Given the unblinded nature of the trial and the degree of bias potentially introduced by the investigator in assessing disease progression, the FDA found the analysis based on blinded independent reviewer analysis more persuasive.

The FDA review team performed an exploratory analysis performed in an effort to reduce the number of patients excluded from the independent reviewer analysis, by including the investigator documented radiographic disease progression date, if it existed, despite lack of independent review. In addition, if there was a radiograph that the investigator evaluated as stable disease and subsequently called progression on a clinical basis, the patient was censored at the unconfirmed stable disease (SD) evaluation. In this exploratory analysis, which added 25 events to the analysis (21 PD and 4 SD), time to radiographic progression was again found to be statistically significantly prolonged on the oxaliplatin and 5-FU/LV combination regimen. The combination regimen had a median TTP of 4.5 months compared to 2.6 months for infusional 5-FU ($p< 0.0001$). Acknowledging the limitations of all time to progression analyses evaluated in this NDA, the FDA believed that the significant prolongation in time to progression combined with the statistically significant improvement in response rate provided support for the accelerated approval of oxaliplatin.

The safety profile of oxaliplatin combined with infusional 5-FU appears to be predictable and manageable. The regimen has many of the usual toxicities associated with cytotoxic chemotherapy regimens. The addition of oxaliplatin to 5-FU/LV enhances the diarrhea (Grade 3/4 diarrhea occurred in 11% of patients on the 5-FU/LV/oxaliplatin arm, 4% on the oxaliplatin alone arm and 3% on the 5-FU/LV alone arm) and neutropenia associated with infusional 5-FU/LV. The principal hematologic toxicity associated with the oxaliplatin combination regimen

is neutropenia. While Grade 4 neutropenia did not occur in patients receiving oxaliplatin alone in the submitted randomized study, 26 patients (17%) on the 5-FU/LV/oxaliplatin combination arm had Grade 4 neutropenia, and Grade 3/4 febrile neutropenia occurred in 9 (6%). Grade 3 thrombocytopenia occurred in 5%. The nausea and vomiting associated with oxaliplatin can be managed with 5-HT3 receptor antagonists and/or dexamethasone.

Neurotoxicity associated with oxaliplatin infusion is common and in general is reversible and does not interfere with activities of daily living, although adjustments and compensations may have to be made while the neurotoxicity is manifest. The study population was patients with metastatic colorectal cancer that relapsed or was refractory to a first line colorectal regimen and therefore represents a poor prognosis group.

For several years, investigators have categorized oxaliplatin neurotoxicity events in two groups based symptoms and duration. An acute symptom complex consisted of cold sensitive spasms and loss of sensation. A chronic symptom complex described progressive paresthesia and dysesthesia, loss of proprioception, and impairment of daily living that was claimed to be proportional to cumulative dose. The data submitted did not support this characterization because either symptom complex could occur as an acute or a persistent event, and there was not a demonstrated cumulative dose threshold for the "cumulative" event.

In the current analysis, neurotoxicity was categorized as either acute (lasting less than 2 weeks) or persistent (duration of 2 weeks of greater). The onset of persistent neurotoxicity can occur at any cumulative dose and is not necessarily preceded by any episodes of acute toxicity. The spectrum of symptoms included numbness, tingling, pain, dysesthesia, paraesthesia, or sensitivity in the distal extremeties, legs, hip, arm, eye, jaw, throat, mouth, gums, lips, or tongue. Symptoms may or may not be exacerbated or induced by contact with cold temperature including beverages, foods, or objects. About 2% of patients had pharyngo-laryngeal spasms that may be accompanied by a sense of loss of air, shortness of breath, or, as one patient stated, "bees in the throat" that can occur without warning. All patients in the study survived the laryngeal toxicity, which had a median duration of 7 days.

In any given cycle at least 30% of patients will have a neurotoxic event. Having an event in one cycle is not predictive of subsequent events, although there were patients who had events with every cycle. The population of patients having an event varied, so that over the course of the study about 75% of all patients had at least one neurotoxic event.

Data are inadequate to determine whether dose adjustment, dose delay, or increasing infusional time are useful to decrease or abrogate neurotoxicity. Patients should avoid exposure to cold temperature, objects, or liquids such as ice for easing the pain of mucositis.

<u>Labeling Issues:</u>

The major labeling issues identified in the review of this application included whether the time to radiographic disease progression analysis based on blinded independent review of the radiographic tumor assessments performed on study should be included in the label. The FDA review team performed an exploratory analysis to reduce the number of patients who had been excluded from the independent reviewer analysis (by censoring at time zero) by incorporating patients whose films were read only by the investigator in the analysis. The FDA agreed to include the time to radiographic progression data in the label, as long as the limitations of the

analysis were explained, including the fact that it was an interim analysis with only 49% of the events available, and the fact that if the best blinded evaluation of the progression data were to utilized in this analysis, either a substantial proportion of the patients had to be excluded, or some unblinded data (investigator assessment of radiographic progression) had to be allowed in a "hybrid" independent/investigator analysis of radiographic disease progression.

There were two major safety issues addressed in labeling. One was dosing in the setting of renal impairment and the other was how best to describe the neuropathy recognized with oxaliplatin treatment and tabulate the number of patients affected by the two types of neuropathy.

Because only the platinum ultrafiltrate levels had been measured in the renal impairment pharmacokinetic study, not the individual biologically active platinum moieties, and no data exist to show a pharmacodynamic relationship between the platinum ultrafiltrate AUC levels and either safety or efficacy, no recommendations for dose modification based on renal impairment could be made in the label. The following information was provided in the Precautions section of the label:

Patients with Renal Impairment The safety and effectiveness of the combination of ELOXATIN and infusional 5-FU/LV in patients with renal impairment has not been evaluated. The combination of ELOXATIN and infusional 5-FU/LV should be used with caution in patients with preexisting renal impairment since the primary route of platinum elimination is renal. Clearance of ultrafilterable platinum is decreased in patients with mild, moderate, and severe renal impairment. A pharmacodynamic relationship between platinum ultrafiltrate levels and clinical safety and effectiveness has not been established. (see CLINICAL PHARMACOLOGY)

Neurotoxicity

The sponsor revised the neuropathy categories based on the FDA suggested classification and analysis. The categories used were acute (duration less than 14 days) and persistent (duration 2 weeks or longer). The adverse event tables were revised to reflect the reclassification and figures were recalculated. The dose reduction and modification sections were revised to reflect the protocol recommendations but with the understanding that the protocol recommendations were not followed always in the study.

Data Integrity Issues:

As detailed in the Clinical Inspection Summary by Dr. U from DSI, four US sites were audited (Dr. R. Ramanathan, MD Pittsburg, PA; Dr. S. Bernard, MD Chapel Hill, NC, Dr. A. Benson, MD, Chicago, IL, and D. Haller, MD Philadelphia PA) Because Dr. Haller had been recently inspected earlier this year

. his site was not re-inspected. Dr. U stated in his clinical inspection summary for this NDA that all audited subjects existed, fulfilled eligibility criteria and were available for the duration of the study. He reported that all enrolled subjects received the assigned study medication, had the protocol specified parameters followed, completed the study, and had their primary efficacy endpoint data captured as specified in the protocol. There were some deviations from protocol and in record keeping at some sites and instances of inadequate adverse event reporting were discovered, but were not believed to be of such clinical significance that subjects should be excluded from the analyses.

Drug Name:

DMETS identified potential confusion related to both of two proposed names for oxaliplatin, "Eloxatin" and "Eloxatine". The potential errors related to "Eloxatin" were "cefoxitin" and . The potential errors related to "Eloxatine" were "loxitane" and . Oxaliplatin has been marketed in Europe for the last years using the trade name "Eloxatin". After substantial discussion with the division, the review team decided that they would not take the recommendation of DMETS and ask the applicant to change the name of the product for the United States market.

The ISS of the NDA included information on at least two medical errors in the world-wide marketing experience in which oxaliplatin was mistakenly substituted for carboplatin, resulting in oxaliplatin overdosage. These errors were reportedly made based on the generic names. There is previous experience with platinum compounds being substituted for each other – cisplatin and carboplatin. Based on this prior experience, DMETS recommended that the applicant highlight the "oxali" prefix in the generic name on the product packaging through change of color in the font or change in font size. This change in packaging to be done at the time of next printing was included as a phase 4 commitment.

Pediatric Considerations:

The applicant was granted a pediatric waiver because colorectal carcinoma is an extremely rare disease in children. No pediatric Written Request has been sent to the applicant, although they received a request for proposals of pediatric studies that could be included in a subsequent Written Request.

Conclusions:

The division recommends approval of the NDA under Subpart H regulations, accelerated approval. The applicant is evaluating oxaliplatin in the treatment of colorectal cancer several ongoing randomized, controlled trials. Any one of those trials have the potential for showing that there is clinical benefit associated with oxaliplatin in the treatment of this disease. The survival data from the study submitted for review in this NDA (Study EFC 4584), which enrolled a refractory disease population, are maturing and demonstration of a favorable survival advantage in this trial would clearly support the conversion from accelerated approval to standard approval. The additional trials are being conducted in the settings of first-line treatment of metastatic colorectal cancer and adjuvant treatment of colon cancer. Meeting the following Subpart H commitments would represent due diligence in the attempt to demonstrate the clinical benefit associated with oxliplatin treatment of colon cancer.

The following trials have the potential for verifying and describing clinical benefit associated with oxaliplatin:

1. Complete the study that was 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 the 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 the 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, first quarter.

4. Complete the 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.

The additional phase 4 commitments, that are not required to demonstrate clinical benefit for conversion of accelerated approval to standard approval are listed below. These include a trial to evaluate safety of administration of oxaliplatin in patients with renal insufficiency and provisions to address the concerns that there is a potential for medical errors based both on the trade name, Eloxatin, and the generic name (mistaken substitution of oxaliplatin for carboplatin). There are two additional trials evaluating oxaliplatin in third-line treatment of colorectal carcinoma that have also been requested in this group of phase 4 commitments.

7. Design and conduct a study to examine the safety of administering repeated doses of oxaliplatin 85 mg/m^2 in combination with 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 compared to 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 ¾ 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.

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 oxaliiplatin 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, you should 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.

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
8/22/02 02:28:25 PM
MEDICAL OFFICER

COMPETING PRODUCT DETERMINATION

DRUG: oxaliplatin

NDA: 21-492

APPLICANT: Sanofi Pharmaceuticals, Inc.

MEETING REQUESTED: NDA review (rolling)

INDICATION: For the treatment of patients with advanced colorectal cancer who have progressed after receiving 5-FU/LV and irinotecan (CPT-11), Saltz Regimen.

Competing Products:

Approved Products: none

ASCO, ONS, + NCI

burst emails

From the American Society of Clinical Oncology.
In collaboration with the Food and Drug Administration (FDA), and as a service to our members, ASCO will provide information about newly approved therapies for cancer patients. This will allow the agency to inform oncologists and professionals in oncology-related fields of recent approvals in a timely manner. Included in the email from the FDA will be a link to the product label, which will provide the relevant clinical information on the indication, contraindications, dosing, and safety. The following is a message from Dr. Richard Pazdur:

To : ASCO membership (domestic USA, embargo date August 9, 2002)

From : Richard Pazdur, M.D.
Director, Division of Oncology Drug Products
-Center for Drug Evaluation and Research, FDA

On August 9, 2002, the Food and Drug Administration (FDA) approved oxaliplatin (Eloxatin™, Sanofi-Synthelabo, Inc) for use in combination with infusional 5-fluorouracil (5-FU) and leucovorin (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. The approval of oxaliplatin is based on the response rate and improved time-to-tumor progression observed in an ongoing trial that will assess survival. There are no mature controlled trials that demonstrate a clinical benefit, such as improvement of disease-related symptoms or increased survival.

A multicenter, randomized, three-arm study was conducted in the U.S. and Canada. Patients were randomly allocated to either infusional 5-FU/LV, single-agent oxaliplatin, or the combination of infusional 5-FU/LV plus oxaliplatin (see package insert for doses and administration schedules). Thirteen of 152 patients (9%) in the combination oxaliplatin and 5-FU/LV arm experienced partial tumor responses, compared to 2 patients in the single-agent oxaliplatin arm, and none in the infusional 5-FU/LV arm ($p = 0.0002$). The median time-to-tumor progression was improved by approximately 2 months in the oxaliplatin plus infusional 5-FU/LV combination arm compared to the 5-FU/LV arm in an interim analysis (4.6 versus 2.7 months).

Common adverse events associated with the combination treatment include peripheral neuropathy, nausea, vomiting, diarrhea, abdominal pain, stomatitis, dyspnea and fatigue. The diarrhea and myelosuppression normally associated with 5-FU/LV are accentuated by oxaliplatin. Acute (lasting less than 14 days) or persistent (14 days or greater) neuropathies, often exacerbated by exposure to cold (temperature, objects, or liquids) were associated with oxaliplatin. An acute syndrome of pharyngolaryngeal dysesthesia characterized by dysphagia or dyspnea may also occur. The majority of neurotoxic events were reversible. Neutropenia is the major hematologic toxicity.

Full prescribing information, including clinical trial information, safety, dosing, drug-drug interaction and contraindications is available at
http://www.fda.gov/cder/foi/label/2002/21492lbl.pdf

This application received Fast Track designation, Priority Review status, and Accelerated Approval. The review time for this application was 7 weeks from final submission.

The approval announcement itself will also be available at
http://www.fda.gov/cder/cancer/whatsnew.htm

For further information related to oncology drug approvals, regulatory information, and other oncology resources, please refer to the FDA "Oncology Tools" web site at www.fda.gov/cder/cancer.

"ASCO periodically e-mails its membership messages of professional interest. If you would prefer not to receive these messages, reply to this e-mail with the word REMOVE in the subject field. You will receive one additional e-mail message to confirm your removal from this e-mail list."

In collaboration with the Food and Drug Administration (FDA), and as a service to our members, the Oncology Nursing Society will provide information about newly approved therapies for cancer patients. This will allow the FDA to inform ONS members of recent approvals in a timely manner. Included in the email from the FDA will be a link to the product label, which will provide the relevant clinical information on the indication, contraindications, dosing, and safety. The following is a message from Dr. Richard Pazdur:

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FDA Press Release

FOR IMMEDIATE RELEASE **Media Inquiries: 301-827-6242**
P02-25 **Consumer Inquiries: 888-INFO-FDA**
August 12, 2002

FDA APPROVES ELOXATIN FOR COLORECTAL CANCER

The Food and Drug Administration (FDA) today announced the approval of Eloxatin (oxaliplatin) injection for use in combination with infusional 5-fluorouracil (5-FU) and leucovorin for the treatment of patients with colorectal cancer whose disease has recurred or become worse following initial therapy with a combination of irinotecan with bolus 5-FU and leucovorin. The combination including Eloxatin was shown to shrink tumors in some patients and delay resumed tumor growth. There are as yet no data on the effects of the combination on survival.

FDA reviewed the marketing application for Eloxatin in seven weeks, the fastest review to date for a cancer drug. FDA was able to review and approve this drug so rapidly because the agency utilized the "rolling review" procedures that are available under new drug applications designated

-More-

as "Fast Track." Drugs in development that have the potential to be an advance in treatment for a serious illness may be identified as "Fast Track" drugs. Under this designation, rolling applications allow for the submission of some components of the application before the remaining sections are completed and submitted to the agency. For Eloxatin, the first piece of the rolling application was submitted on April 15, 2002, and the last portion on June 24, 2002.

"Patients diagnosed with colorectal cancer will now have access to another treatment option for this disease," said Health and Human Services Secretary Tommy G. Thompson. "I want to commend FDA for reviewing the drug's safety and effectiveness so quickly."

A multi-center, randomized, controlled study compared the effectiveness and safety of Eloxatin alone, infusional 5-FU/leucovorin alone (a standard type of treatment for colorectal cancer), and the combination of these two treatments in patients who had either relapsed, or progressed while on or shortly after standard treatment. Although the individual drugs had very little effect, the

combination resulted in a greater number of patients having tumor shrinkage and led to a delay in resumption of cancer growth.

"Even though long-term benefits such as increased survival have not yet been demonstrated," said Dr. Lester M. Crawford, FDA Deputy Commissioner, "early studies have shown that Eloxatin may have significant benefit for many patients."

Eloxatin is intended for use by physicians experienced in the use of cancer agents. A black box warning detailing this use and highlighting anaphylactic-like reactions associated with Eloxatin is included in the labeling. Eloxatin can have a toxic effect on nerve endings that may result in either an acute or cumulative pattern of side effects. This may result in the feeling of numbness or tingling, especially in the hands or feet or around the mouth or throat. For some patients these symptoms may be worsened by exposure to cold. This side effect usually occurs within hours or days of dosing. Another side effect is impairment in performing ordinary daily tasks such as difficulty buttoning clothes. This condition generally improves after the treatment is complete.

-More-

Other common side effects of Eloxatin are vomiting, diarrhea, anemia, increased risk of bleeding or infection, or allergic reaction. Women should be advised to avoid becoming pregnant while receiving this treatment, because it may cause harm to the fetus.

Cancers of the colon and rectum (colorectal) are the fourth most commonly diagnosed cancers and rank second among cancer deaths in the United States. About 150,000 new cases of these cancers occur each year, and they cause approximately 56,000 deaths.

Eloxatin is manufactured by Ben Venue Laboratories and distributed by the French pharmaceutical company Sanofi-Synthelabo.

####

27 pages redacted from this section of the approval package consisted of draft labeling

N/A

Sponsor agreed with approved labeling - Same as Division's proposed labeling

21 pages redacted from this section of the approval package consisted of draft labeling

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 24, 2002

TO: Richard Pazdur, M.D., Director
Division of Oncologic Drug Products
HFD-150

VIA: Christy Wilson, CSO
Division of Oncologic Drug Products
HFD-150

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Regulatory Health Project Manager
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Anne Trontell, M.D., M.P.H., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Patient Labeling for Eloxatin (oxaliplatin), NDA 21-492

The patient labeling which follows represents the revised risk communication materials for Eloxatin (oxaliplatin) and has been reviewed by our office. The revisions reflect changes in format, wording, and organization that are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. Comments are bolded, italicized, and underlined.

5 pages redacted from this section of the approval package consisted of draft labeling

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

/s/

Jeanine Best
7/24/02 04:49:37 PM
CSO

Anne Trontell
7/31/02 05:04:29 PM
MEDICAL OFFICER

DMETS Review

Tradename

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: 6/4/02	DUE DATE: 7/16/02	ODS CONSULT #: 00-0085-1

TO: Richard Pazdur, MD
Director, Division of Oncology Drug Products

THROUGH: Christy Wilson
Project Manager, Division of Oncology Drug Products

PRODUCT NAME:	**NDA SPONSOR: Sanofi-Synthelabo Inc.**
Eloxatin® (Primary name) **Eloxatine®** (Alternate name) (Oxaliplatin for Injection) 50 mg and 100 mg **NDA#: 21-492**	

SAFETY EVALUATOR: Charlie Hoppes, RPh, MPH

SUMMARY: In response to a consult from the Division of Oncology Drug Products (HFD-150), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary names "**Eloxatin®**" and " **Eloxatine®**" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:

DMETS does not recommend the use of the proprietary name, Eloxatin®. However, DMETS has no objections to the use of the proprietary name, Eloxatine®. In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product. This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

/S/ /S/

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Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: July 8, 2002

NDA# 21-492

NAME OF DRUG: **Eloxatin®** (Primary name) or **Eloxatine®** (Alternate name)
(Oxaliplatin for Injection) 50 mg and 100 mg

NDA HOLDER: Sanofi-Synthelabo Inc.

I. INTRODUCTION:

This consult is written in response to a request from the Division of Oncologic Drug Products (HFD-150) for an assessment of the proposed proprietary names Eloxatin and Eloxatine. The container labels, carton labeling and package insert labeling were reviewed for possible interventions in minimizing medication errors.

The original trade name proposed for this product under NDA 21-063 was Eloxatin. However, the firm later changed the name to Eloxatine due to a protest from Schering who believes that Eloxatin is similar to their product, Eulexin (flutamide). On 3/20/00, the Division requested a review of the proposed proprietary name, Eloxatine. Potential for confusion of Eloxatine with Fluoxetine, Paroxetine, Loxapine, Mexiletine, Vinblastin, and Vincristine was evaluated. However, on 6/2/00, DMETS concluded that Eloxatine was acceptable. Due to procedural problems, the application, NDA 21-063, was re-filed under NDA 21-492. The sponsor has now indicated that the preferred name for this drug product is Eloxatin with Eloxatine as an alternate name. Since Eloxatine had already been reviewed, prescription analysis studies were conducted only for Eloxatin.

PRODUCT INFORMATION

Eloxatin and Eloxatine are the proposed proprietary names for Oxaliplatin for Injection. Oxaliplatin is indicated for the treatment of colorectal cancer in combination with 5FU. It will be available in vials containing 50 mg and 100 mg of oxaliplatin. The recommended dosage for Eloxatin is 85 mg/m^2 every 2 weeks.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Eloxatin and Eloxatine to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies for each name, consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names Eloxatin and Eloxatine. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified four proprietary names that were thought to have the potential for confusion with Eloxatin and Eloxatine. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage. Although the name Loxapine had already been evaluated in DMETS consult 00-0085 for potential confusion with Eloxatine, the Expert Panel expressed renewed safety concerns and requested that the name be re-evaluated.

2. DDMAC did not have concerns about either name with regard to promotional claims.

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 00-02, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/tmdb/index.html.

[5] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Eloxatin or Eloxatine	**Oxaliplatin Injection, 50 mg and 100 mg**	**85 mg/m^2 IV every 2 weeks**	
Loxitane® (Loxapine)	Loxapine Capsules, 5 mg, 10 mg, 25 mg and 50 mg Loxapine Liquid Concentrate, 25 mg/mL Loxapine Injection 50 mg/mL in 10 mL vials	60 mg to 100 mg per day by mouth 50 mg every 4 to 6 hours IM only	SA/LA (proprietary name) SA (established name)
Cefoxitin (Mefoxin®)	Cefoxitin for Injection, 1g, 2 g, and 10 g	1 g to 2 g every 4 to 8 hours	SA/LA
Enoxacin (Penetrex®)	Enoxacin Tablets, 200 mg and 400 mg	200 to 400 mg every twelve hours	SA

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary names to determine the degree of confusion of Eloxatin with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 106 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescriptions for Eloxatin. These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail (see below). In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

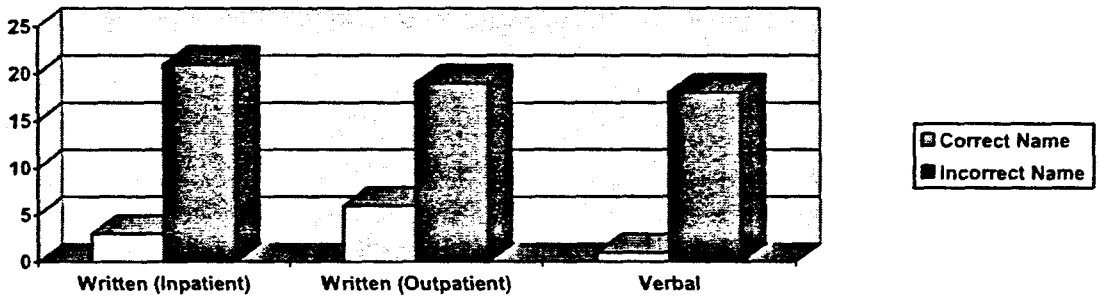
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Eloxatin 100mg 100mg IV over 2 hrs as ordered #1	Eloxatin 100 mg IV over 2 hours with Leucovorin 240 mg IV using a "Y" line.
Inpatient RX: Eloxatin 100mg in 250mL D5W IV to 2hours w/ Leucovorin 240mg IV using "Y" line	

2. Results:

The results for Eloxatin are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%) "Eloxatin"	Incorrectly Interpreted (%)
Written Inpatient	38	24 (63%)	3 (12%)	21 (88%)
Written Outpatient	36	25 (69%)	6 (24%)	19 (76%)
Verbal	32	20 (62%)	1 (5%)	19 (95%)
Total	106	69 (65%)	10 (14%)	59 (86%)



Among participants in the written prescription studies, 40 of 49 respondents (82%) interpreted the name incorrectly. The interpretations were misspelled variations of "Eloxatin". Incorrect interpretations of written prescriptions included: *Elexatim, Elexatin* (7 occurrences), *Elexetin, Elexation* (2 occurrences), *Aloxitin, Elexatrin* (2 occurrences), *Eloxatim* (2 occurrences), *Elexatain, Elaxatim, Elexatine Floxaten* (2 occurrences), *Eloxitin* (2 occurrences), *Eloxaten* (3 occurrences), *Eloxatur, Eloxater* (4 occurrences), *Elexatrim, Eloxeten, Eloxceter, Floxater, Floxitin, Eloxan, Floxatin* (2 occurrences), and *Elexative.*

Among participants in the verbal prescription studies, 19 of 20 respondents (95%) interpreted the name incorrectly. Most incorrect name interpretations were phonetic variations of "Eloxatin". Incorrect interpretations of the verbal prescription included: *Aloxapin, Zaloxator, Ilopsitin, Aloxatin* (5 occurrences), *Alloxetin* (3 occurrences), *Eloxitin, Aloxetin, Loxetin, Aloxitin,* and *Alloxatin.*

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proposed proprietary name "Eloxatin", the primary concerns raised related to look-alike, sound-alike confusion with names already in the U.S. marketplace. The products considered to have potential for name confusion with **Eloxatin** were Loxapine, Loxitane, Cefoxitin, and Enoxacin. Although the name Eloxatine had already been evaluated in DMETS consult 00-0085, the Expert Panel expressed renewed safety concerns and requested that the name be re-evaluated. The products considered to have the potential for name confusion with **Eloxatine** were Loxapine, and Loxitane.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that Eloxatin can be confused with Loxapine, Loxitane, Cefoxitin, or Enoxacin. Negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to small sample size. The majority of interpretations from the written and verbal prescription studies were phonetic/misspelled interpretations of the drug name Eloxatine.

ELOXATIN

Loxapine is a dibenzoxazepine compound from a subclass of tricyclic antipsychotic agents, chemically distinct from the thioxanthenes, butyrophenones, and phenothiazines. Loxapine is marketed under the tradename Loxitane and is also marketed generically. Loxapin is indicated for the treatment of schizophrenia. The recommended dosage of Loxapin is 60 mg to 100 mg per day by mouth and 50 mg every 4 to 6 hours by the intramuscular route of administration. Both the established name, Loxapine, and the proprietary name Loxitane may potentially be confused with Eloxatin. *Loxapine* and *Eloxatin* may sound similar when spoken. Although Eloxatin has an extra syllable compared to Loxapine (the "E" at the beginning), that syllable could be misunderstood as a separate word or as verbal hesitation during a telephone order, e.g., "eh...loxatin". In fact, one study participant responded "Loxetin" to the verbal order for Eloxatin, omitting the "E". Except for the questionably distinct "E", the two names are very similar in sound. The syllables, "loxa" are identical in both names. The syllables "tin" and "pine" start with the similar sounding plosive* consonants "t" and "p" and "in" may be pronounced the same as "ine". It is worth noting that one study participant responded "Aloxapin" to the verbal order for Eloxatin, substituting the "t" for a "p". The two drug products have additional similarities. Both are available as injectable dosage forms and the products share a common strength, 50 mg. Postmarketing experience has shown medication errors occurring as a result of common dosage forms and overlapping strengths. Differences between the drug products include different usual dosage, and different dosing intervals, however, given the similarities such as the sound-alike/ look-alike properties, the fact that these are both injectable products, and overlapping strengths. there is potential for confusion. If Loxapine was given instead of Eloxatin, the patient would not receive the benefits of chemotherapy. The patient would also be exposed to risk of Neuroleptic Malignant Syndrome as well as unnecessary side effects such as dyskinesias, drowsiness, and other unwanted anticholinergic effects. If Eloxatin was given rather than Loxapine, the patient's mental illness might not be controlled and they would be exposed to risk of allergic reactions and unwanted side effects such as thrombocytopenia, neutropenia, nausea, vomiting, and diarrhea.

* A good reference for phonetic terminology can be found at: http://www.unil.ch/ling/phonetique/api-eng.html

Loxitane is the proprietary name for Loxapine (see above). *Loxitane* and *Eloxatin* may sound similar when spoken and may look similar when written. Except for the "E" as the first syllable of Eloxatin, the names sound very much alike ("loxitane" vs. "loxatin"). When written the names look very much alike (see writing sample below). The two drug products have additional similarities. Both are available as injectable dosage forms and the products share a common strength, 50 mg. Postmarketing experience has shown medication errors occurring as a result of common dosage forms and overlapping strengths. Differences between the drug products include different usual dosage, and different dosing intervals, however, given the similarities such as the sound-alike/ look-alike properties, the fact that these are both injectable products, and overlapping strengths, there is potential for confusion. If Loxitane was given instead of Eloxatin, the patient would not receive the benefits of chemotherapy. The patient would also be exposed to risk of Neuroleptic Malignant Syndrome as well as unnecessary side effects such as dyskinesias, drowsiness, and other unwanted anticholinergic effects. If Eloxatin was given rather than Loxitane, the patient's mental illness might not be controlled and they would be exposed to risk of allergic reactions and unwanted side effects such as thrombocytopenia, neutropenia, nausea, vomiting, and diarrhea.

Cefoxitin is a semi-synthetic, broad-spectrum cepha antibiotic for intravenous administration. It is marketed under the tradename Mefoxin. Cefoxitin is indicated for the treatment of serious infections caused by susceptible strains of microorganisms in, lower respiratory tract infections, urinary tract infections, intra-abdominal infections, gynecological infections, septicemia, bone and joint infections, and skin and skin structure infections. The usual dosage is 1 g to 2 g every 4 to 8 hours. *Cefoxitin* and *Eloxatin* may sound similar when spoken. Each name has four syllables. The first syllables "Cef" vs. "El" sound similar since they share the short "e" sound. The last three syllables of each name ("oxitin" vs. "oxatin") are virtually indistinguishable, differing only in the first vowel the short "i" vs. the short "a". The two products have additional similarities. The products share a common route of administration, intravenous and both are available in vials as sterile powder for reconstitution. The products also have similar numeric strengths [1 g (Cefoxitin) vs. 100 mg, which can be written 0.1 g, (Eloxatin)]. Postmarketing experience has shown medication errors occurring as a result of a numerical similarity in strengths. The drug products differ in their dosing intervals, however, given their similarities such as the sound-alike properties, common routes of administration, dosage forms, and strengths which share the number "1", the likelihood of confusion is high. If Cefoxitin was given instead of Eloxatin, the patient would not receive the benefits of chemotherapy and would be exposed to risk of allergic reaction. If Eloxatin was given rather than Cefoxitin, the patients' infection would be untreated and they would be exposed to risk of allergic reactions and unwanted side effects such as thrombocytopenia, neutropenia, nausea, vomiting, and diarrhea.