CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-759

CHEMISTRY REVIEW(S)

NDA 21-759
ELOXATIN
(Oxaliplatin Injection)

Sanofi-Synthelabo, Inc.

Haripada Sarker, Ph.D.
HFD-150 Division of Oncology

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-759

2. REVIEW #1:

3. REVIEW DATE: 01-25-2005

4. REVIEWER: Haripada Sarker, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 41, 817	February 26, 1993
NDA 21-492	August 9, 2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA 21-759 submission	March 31, 2004
Amendment NDA 21-759 (N-000)BL	January 21, 2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Sanofi-Synthelabo, Inc.
Address:	9 Great Valley Parkway P.O. Box 3026 Malvern, PA 19355
Representative:	Mark Moyer
Telephone:	610-889-6417

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Eloxatin
b) Non-Proprietary Name (USAN): Oxaliplatin Injection
c) Code Name/#: SR96669
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 5
- Submission Priority: S

e) Proposed Trade Name: N/A

9. LEGAL BASIS FOR SUBMISSION: Fulfilled PDUFA filing requirements

10. PHARMACOL. CATEGORY: Patients previously untreated for locally Advanced or Metastatic Colorectal Cancer

11. DOSAGE FORM: Aqueous Solution

12. STRENGTH/POTENCY: 50 mg and 100 mg per vial

13. ROUTE OF ADMINISTRATION: I.V.

14. Rx/OTC DISPENSED: _X_Rx ___OTC

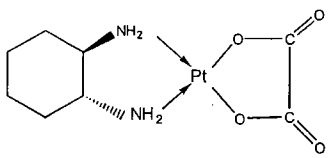
15. <u>SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):</u>

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Structure:



Name	**Oxaliplatin**
Chemical Name	[SP-4-2-(1R,2R)-(cyclohexane-1,2-diamine-κ^2N,N'(oxalato(2-)-κ^2O^1,O^2]platinum(II)
CAS number	61825-94-3
Molecular Weight	397.3
Molecular Formula	$C_8H_{14}N_2O_4Pt$
Structural formula	Page 523 USAN 2000

17. RELATED/SUPPORTING DOCUMENTS:

A. **DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	Tanaka Kikinzoku Kogyo K.K.	[redacted]	3	Adequate	Not reviewed	See review of DMF [redacted] No change
[redacted]	II	Johnson Matthey Pharmaceutical.	[redacted]	3	Adequate	See review	See review of DMF [redacted] Minor change

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: NONE

18. STATUS:

ONDC: To be filled later

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Clinical (efficacy)	Acceptable	28-FEB-02	Amana Ibrahim
EES	Acceptable	03-JAN-05	J.D. Ambrogio
Pharm/Tox	Acceptable	12-JUL-04	Margaret Bower
Biopharm	Acceptable	01-JUN-04	Angela Y. Men
DMETS	Acceptable	09-DEC-04	Kristina Arnwine
EA	Categorical Exclusion Acceptable	22-SEP-04	Haripada Sarker
Microbiology	Acceptable	20-DEC-04	Bryan Riley

The Chemistry Review for NDA 21-492

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This application is recommended for approval from CMC standpoint because all the deficiencies have been satisfactorily addressed and the office of compliance has given an overall acceptable recommendation (see attached). However, the following comment regarding the expiration date for the drug product should be included in the action letter.

(a) An expiration dating period of twenty four months for drug product will be granted based on stability data provided.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Oxaliplatin is a well-characterized drug substance, which was previously approved under NDA 21-492 for lyophilized formulation. The applicant referenced DMF [redacted] and DMF [redacted] for oxaliplatin drug substance. DMF [redacted] was previously reviewed by this reviewer for NDA 21-492. Oxaliplatin drug substances that are utilized in NDA 21-492 and in the current submission are found to be identical.

The chemical name of oxaliplatin is: [SP-4-2-(1R,2R)-(cyclohexane-1,2-diamine-κ^2N,N'(oxalato(2-)-κ^2O^1,O^2]platinum(II), and CAS registry number 61825-94-3. Oxaliplatin is a white to off-white powder. Oxaliplatin is an organometalic compound, with the platinum atom [redacted] to a 1,2-diaminocyclohexane and an oxalate group. [redacted] Absence of polymorphic form has been reported for oxaliplatin. Oxaliplatin is slightly soluble in water, very soluble in methanol, and insoluble in ethanol and acetone. The pKa study on oxaliplatin indicated that the molecule is neutral with no dissociation in solution. Multiple batch records demonstrate 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 [redacted] at 25 °C/60 RH condition using the commercial container/closure system. Oxaliplatin is found to be unstable in basic pH, [redacted]

The drug product, oxaliplatin injection is formulated as preservative free sterile aqueous solution (5 mg/mL) in two strengths, 50 mg and 100 mg/vial, which is reconstituted with 5% dextrose injection before infusion. During the manufacturing of oxaliplatin drug product, [redacted] Acceptance criteria for specified impurities in oxaliplatin injection have been broadened [redacted] when compared to approved lyophilized formulation. The proposed limits for specified impurities were found acceptable by pharmacology/ toxicology reviewer Dr. Margaret Bower (please see her review, dated July 12, 2005).

[redacted] months of primary stability data have been provided. The applicant has proposed [redacted] months of shelf-life based on the above and also based on statistical evaluation. However, based on provided stability data, 24 months of shelf-life may be granted. Validated analytical methods were provided in the submission.

The trade name Eloxatin [redacted] initially proposed by the applicant was found not acceptable by DMETS, Office of drug safety as it contained a qualifier. DMETS suggested Eloxatin Injection. This was acceptable to both the applicant and the Agency.

B. Description of How the Drug Product is Intended to be Used

Drug product should be diluted with 5% dextrose to a concentration of [redacted] and stored at 2-8°C (36-46°F) and should be used before 24 hours or used within 6 hours when stored at 20-25°C (68-77°F).

C. Basis for Approvability Recommendation

This application is recommended for approval from CMC standpoint because all the issues were resolved to our satisfaction and the office of compliance has provided an overall acceptable recommendation.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Haripada Sarker, Ph.D.
ChemistryTeamLeaderName/Date: Nallaperumal Chidambaram, Ph.D.
ProjectManagerName/Date: Christy Wilson

C. CC Block

47 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Chemistry-*1

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

/s/

Haripada Sarker
1/26/05 05:33:57 PM
CHEMIST

Nallaperumal Chidambaram
1/26/05 05:40:04 PM
CHEMIST

Categorical Exclusion for Eloxatin (oxaliplatin injection) solution (revised trade name to be determined)

Date

Name of Applicant **Sanofi-Synthelabo Inc.**

Address of Applicant **9 Great Valley Parkway**
Malvern, PA 19355

- **Claim of Categorical Exclusion from Preparation of an Environmental Assessment**

Sanofi-Synthelabo Inc. is claiming Categorical Exclusion from preparation of an Environmental Assessment per 21 CFR Part 25 for the proposed action requesting approval for use of Eloxatin (oxaliplatin injection) solution for treatment of advanced carcinoma of the colon or rectum per section 505(b) of the Food, Drug and Cosmetic Act. Please refer to NDA 21-492 and this application for specification information for the active moiety oxaliplatin drug substance.

Compliance with the categorical exclusion criteria is made pursuant to 21 CFR Part 25, Subpart C, Categorical Exclusions, Section 25.31, Human drugs and biologics, paragraph (b):

> "The classes of actions listed in this section are categorically excluded and, therefore, ordinarily do not require the preparation of an EA or an EIS: Action on an NDA if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion."

Based upon marketing estimates for the first five years of sales and environmental fate data, the estimated quantity of the active moiety oxaliplatin substance expected to enter the aquatic environment of the United States is below 1 part per billion.

Additionally, based on environmental effects and other data, to the best of the applicants knowledge, the requested action will not result in extraordinary circumstances per 21 CFR section 25.21 since no significant effect on the human environment is expected.