CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
NDA 21-492

Chemistry Review(s)

NDA 21-492

Eloxatin®
(Oxaliplatin for Injection)
Colorectal Cancer Drug

Sanofi-Synthelabo, Inc.

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

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-492

2. REVIEW #1:

3. REVIEW DATE: 07-18-2002

4. REVIEWER: Haripada Sarker, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND [redacted]	February 26, 1993
NDA 21-063	July 22, 1999

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA 21-492 submission	April 15, 2002
IND [redacted] Serial 351	April 09, 2001

7. NAME & ADDRESS OF APPLICANT:

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

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Oxaliplatin for Injection
b) Non-Proprietary Name (USAN): Oxaliplatin
c) Code Name/#: SR96669
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
- Submission Priority: S

e) Proposed Trade Name: Eloxatin®

9. LEGAL BASIS FOR SUBMISSION: Fulfilled PDUFA filing requirements

10. PHARMACOL. CATEGORY: Colorectal Cancer

11. DOSAGE FORM: Lyophilized Powder

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

13. ROUTE OF ADMINISTRATION: I.V.

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

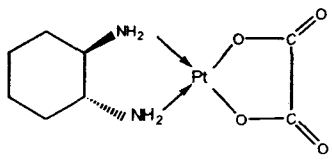
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____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 COM-PLETED	COMMENTS
[redacted]	II	[redacted]	Oxaliplatin drug substance	1	Adequate	20-MAR-00	None
[redacted]	III	[redacted]	Glass vials (USP Type I)	3	Adequate	Not reviewed	See review of NDA 21-063 No change
[redacted]	III	[redacted]	Stopper	3	Adequate	Not reviewed	See review of NDA 21-063 No 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	30-JUN-02	
Pharm/Tox	Acceptable		Wendely Schmidt
Biopharm	Acceptable	28-FEB-02	Brian Booth
LNC	Acceptable	24-JAN-02	
Methods Validation	Acceptable		
OPDRA	Acceptable		
EA	Categorical Exclusion Acceptable	22-MAR-02	Haripada Sarker
Microbiology	Acceptable		Bryan Riley

The Chemistry Review for NDA 21-492

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC perspective, this Fast Track Priority application may be approved. Applicant addressed all the deficiencies related to drug substance, drug product, and labeling. It is known from the Medical Officer's efficacy review that the action to be taken on this application will be to recommend approval.

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

Sanofi-Synthelabo Inc. commits to provide the [redacted] data update by annual report. Thereafter at least one production batch of each dose, manufactured by the proposed manufacturer and packaged in the proposed package configuration will be placed on stability at [redacted] annually.

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 first reported in Gann 67, 921-922, 1976, and subsequently co-developed by Senofi and Debiopharm to market the drug in 1996 (France).

The USAN 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) with CAS registry number 61825-94-3 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. It is an enantiomer (enantiomeric purity 99.5%) and is optically active with two chiral centers. Four disteriomers are possible but only the drug substance with the enantiomer (1S, 2S) is observed in the finished drug substance. No inter-conversion among the isomers is observed or expected. 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, 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%

dextrose injection for the infusion. During the manufacturing of oxaliplatin drug product, [redacted] is performed prior to lyophilization followed by sealing and capping of the vial. Since oxaliplatin degrades in solution when held for longer times, the compounded solution holding time needed to be controlled to keep the degradation level within specifications. Even though some updates are performed in specification monographs between pre-clinical/clinical batches and the proposed drug product batches, the overall oxaliplatin drug products are comparable. 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.

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

The infusion solution is prepared by reconstituting DP lyophilized powder with Water for Injection, USP, or 5% dextrose injection USP to give a concentration of 5 mg oxaliplatin/mL, which is further diluted in an infusion solution of 250-500 mL with Water for Injection, USP, or 5% Dextrose Injection, USP. The reconstituted oxaliplatin will be administered at a dosing of 85 mg/m^2 IV infusion in 250-500 mL 5% dextrose solution in water over 120 minutes. Administration of reconstituted oxaliplatin drug product changes according to the clinical protocols.

C. Basis for Approvability Recommendation

There are no remaining deficiencies in the drug substance and drug product. This application may be approved from a CMC perspective

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Haripada Sarker, Ph.D.
ChemistryTeamLeaderName/Date: Richard T. Lostritto, Ph.D.
ProjectManagerName/Date: Christy Wilson

C. CC Block

Redacted 39 pp. (9-47)

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secret and/or

confidential

commercial

information

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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.

/s/

Haripada Sarker
7/19/02 05:42:54 PM
CHEMIST

Richard Lostritto
7/22/02 05:23:42 PM
CHEMIST

Christy Wilson
7/23/02 08:46:35 AM
CSO