CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-160

CHEMISTRY REVIEW(S)

Memorandum

To: Division of Drug Oncology Products (DDOP)

Through: Sarah C. Pope, Ph.D., Haripada Sarker, Ph.D.

From: Josephine Jee, Chemistry Reviewer

Date: 5/14/2009

Re: NDA 22-160/0015 – Oxaliplatin Injection - 505(b)(2)

Teva submitted the referenced submission dated 20-MAR-2009 to respond to the Agency's Action (Complete Response) Letter dated 02-MAR-2009. The following Pharmacology/Toxicology deficiency was specified in the 02-MAR-2009 letter:

> *Your proposed acceptance criteria for* (b) (4) *(Impurity A) and the* (b) (4) (b) (4) *(Impurity B) currently exceed ICH Q3B(R2) for Oxaliplatin Injection drug product. The proposed acceptance criteria for these impurities must be lowered to meet the current ICH Q3B (R2) guidance.*
> *If these impurity specifications exceed the qualification limits, the impurities will need to be qualified preclinically or justifications for their levels should be provided based on appropriate literature citations.*

In the current submission, Teva proposes to lower the release and stability acceptance criteria for Impurity A and Impurity B to meet the current ICH Q3B (R2) criteria. The proposed specifications are as follows:

Impurity A NMT (b) (4)
Impurity B NMT (b) (4)

Based on the previous stability data package and the new proposals for acceptance criteria, the Agency can now grant a 12-month expiration dating period for the drug product (Oxaliplatin Injection). This expiration dating period is consistent with the observed levels for Impurity A and Impurity B, which both occur at levels o (b) (4) at the 12-month time point under long term conditions (25°C/60% RH). These levels exceed the proposed specifications at the (b) (4) time point under the same conditions. Refer to the previous Chemistry Review by Josephine Jee, dated 24-FEB-2009 for additional information.

The carton and vial labels are found adequate by CMC and DMEPA. Refer to the 24-FEB-2009 Chemistry Review for additional information.

Based on the provided data at 25°C/60% RH of Oxaliplatin Injection, an expiration dating period of 12 months is the maximum that can be granted.

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

/s/

Josephine Jee
5/14/2009 11:12:54 AM
CHEMIST

Sarah Pope
5/14/2009 11:43:51 AM
CHEMIST

OFFICIAL MEMORANDUM

To: NDA 22-160

From: Terrance Ocheltree, Ph.D., R.Ph. acting for Sarah C. Pope, Ph.D.

CC: Sarah Pope, Ph.D., Haripada Sarker, Ph.D., Josephine Jee, Amy Tilley, Robert Justice, M.D.

Re: NDA 22-160

Date: 02-MAR-2009

This memorandum serves to update the Chemistry, Manufacturing and Controls (CMC) Review dated 24-FEB-2009. At the time of this review, an official consult review from DMEPA had not yet been received with respect to the container/carton labeling. All other CMC issues were resolved, and there were no additional CMC deficiencies noted.

The requested DMEPA consult review was finalized on 25-FEB-2009. The review contained several recommendations regarding to the container/carton labeling. Two of these recommendations were already covered as part of the previous CMC review. These duplicate recommendations included the font size of the dosage form, and a language revision to the dilution statement included in the container/carton labeling. These issues have already been resolved and reviewed as part of the CMC review and therefore, they were not re-conveyed to the Applicant.

The remaining recommendations received from DMEPA were conveyed to the Applicant on 26-FEB-2009, and the Applicant submitted acceptable container/carton labeling that incorporated these revisions on 27-FEB-2009. There are no other outstanding CMC deficiencies for this NDA.

All CMC deficiencies have been resolved for NDA 22-160, and approval is recommended from a CMC perspective.

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

/s/

Terrance Ocheltree
3/2/2009 02:06:38 PM
CHEMIST

CMC REVIEW OF NDA 22-160
Amendments
(25-JUN-2008 & 29-AUG-2008)

REVIEW # 1

OXALIPLATIN INJECTION, 5 MG/ML
50 mg/10 mL and 100 mg/20 mL

JOSEPHINE M. JEE
CMC REVIEWER

OFFICE OF NEW DRUG QUALITY ASSESSMENT
DIVISION OF PREMARKETING ASSESSMENT AND MANUFACTURING SCIENCE (BRANCH V)

FOR THE DIVISION OF DRUG ONCOLOGY PRODUCTS (HFD-150)

Table of Contents

Table of Contents 2

Chemistry Review Data Sheet 3

The Executive Summary 7

I. Recommendations 7

A. Recommendation and Conclusion on Approvability 7

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 7

II. Summary of Chemistry Assessments 7

A. Description of the Drug Product(s) and Drug Substance(s) 7

B. Description of How the Drug Product is Intended to be Used 9

C. Basis for Approvability or Not-Approval Recommendation 9

III. Administrative 9

A. Reviewer's Signature 10

B. Endorsement Block 10

C. CC Block 10

Chemistry Assessment 11

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data 11

S DRUG SUBSTANCE [Name, Manufacturer] 11

P DRUG PRODUCT [Name, Dosage form] 20

A APPENDICES 40

R REGIONAL INFORMATION 40

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 40

A. Labeling & Package Insert 40

B. Environmental Assessment Or Claim Of Categorical Exclusion 43

III. List Of Deficiencies To Be Communicated 43

Chemistry Review Data Sheet

1. NDA 22-160 Amendment

2. REVIEW: # 1

3. REVIEW DATE: 24-FEB-2009

4. REVIEWER: Josephine M. Jee

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Review #1	09-FEB-2007
Oxaliplatin	
NDA 21-801 - (Rolling Submission - CMC)	09-FEB-2007
Amendment	01-MAY-2007
Amendment	04-MAY-2007
Amendment	11-MAY-2007
Amendment	23-MAY-2007
Amendment	17-SEPT-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 22-160 Amendment/ Sequence 0010 – Complete Response to AP letter and Additional Changes	29-AUG-2008 02-SEP-2008 – Stamped Date
NDA 22-160/Sequence 006 (Intent to respond to Deficiencies)	14-DEC-2007
NDA 22-160/Sequence 009 (Response to CMC deficiencies)	25-JUN-2008
NDA 22-160/Sequence 010 (Complete Response to Approvable Letter and Additional Changes)	29-AUG-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Teva Parenteral Medicines, Inc.

Address: 19 Hughes
Irvine, CA 92618-1902

8. DRUG PRODUCT NAME/CODE/TYPE: **Oxaliplatin**

a) Proprietary Name: None Proposed

b) Non-Proprietary Name (USAN): Oxaliplatin
International Nonproprietary Name (INN): Oxaliplatin

c) Code Name/# (ONDC only): None provided.
Internal Codes: None provided.

d) CAS Registry Number: None provided.

e) Laboratory Codes: None provided.

f) Chemical Name (IUPAC): *SP*-4-2)-[(1*R*,2*R*)-Cyclohexane-1,2-diamine-κ*N*, κ*N*'] [ethanedioato(2-)-κ*O1*,κ*O2*]platinum

Alternative names: None provided.

g) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 505(b)(2)
- Submission Priority: **S**

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2) - Reference: **Eloxatin®** (oxaliplatin Injection), approved under **NDA 21-759** (Lyophilized form) and **NDA 21-492** (Solution form)

10. PHARMACOL. CATEGORY: Treatment of Advanced Colorectal Cancer

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: **5 mg/mL**
10 mL (50mg/10 mL), and 20 mL (100 mg/20 ml) vials

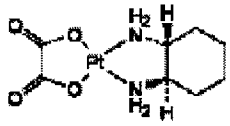
13. ROUTE OF ADMINISTRATION: Intravenously

14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): N/A

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

(*SP*-4-2)-[(1*R*,2*R*)-Cyclohexane-1,2-diamine-κ*N*, κ*N*'] [ethanedioato(2-)-κ*O1*,κ*O2*]platinum



Molecular Formula: $C_8H_{14}N_2O_4Pt$ Molecular Weight: 397.3

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS [2]	DATE REVIEW COMPLETED	COMMENTS
DMF 19559	II	Sicor de México, S.A. de C.V.	Oxaliplatin DS	1	Adequate	20-FEB-2009	Reviewed by J.Jee
(b) (4)	III		(b) (4)	3	Adequate	22-APR-2002	Review conducted by Yvonne Yang, Ph.D.
	III			3	Adequate	19-APR-2002	Review conducted by Yvonne Yang, Ph.D.
	III			3	Adequate	10-OCT-2002	Review conducted by Elsbeth Chikhale, Ph.D.

[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)

Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	None	

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			
EES	Site inspections	15-DEC-2008	S. Adams	Overall acceptable recommendation received on 05-FEB-2009.
Pharm/Tox	Drug substance, drug product impurity	09-FEB-2007	Dr. M. Brower	Satisfactory on 05-FEB-2009

	qualification (organic and inorganic)			
Biopharm	N/A			
ODS/DMEPA	Carton, Container, and Package Insert	21-JAN-2009	Dr. Raichell Brown	Met w/ Drs. Todd Bridges, Raichell Brown, and Hari Sarker and J. Jee – All agreed with comments. Final review still pending as of 24-FEB-2009.
Methods Validation	To be submitted post-approval			
EA	N/A	N/A	J.Jee	Categorical exclusion granted (see attached review).
Microbiology	Consulted to the Office of Microbiology	01-MAR-2007	Dr. Bryan Riley	Recommended Approval on 04-DEC-2007.

The Chemistry Review for NDA 22-160

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing and Controls standpoint, this New Drug Application is recommended for approval pending acceptable submission of acceptable carton and container labeling. Also note that the review from DMEPA, OSE is still pending. On 24-FEB-2009, applicant agreed to have an (b) (4) expiration date for the Oxaliplating Injection as supported by their updated stability data and they have provided updated container/carton labeling. The package insert was found acceptable on 17-FEB-2009. Microbiology review recommended approval on 04-DEC-2007. The Office of Compliance recommended an overall acceptable on 05-FEB-2009. The responses to our comments for DMF 19,559 (Oxaliplatin, Sicor de Mexico) were determined to be acceptable on 20-FEB-2009.

SICOR Pharmaceuticals, Inc. requests a waiver for evidence of bioavailability/bioequivalence in accordance with 21 CFR §320.22(b)(1). SICOR's drug product meets the required criteria:

1) Oxaliplatin Injection, 5 mg/mL is a parenteral drug product intended for administration by intravenous infusion.
2) SICOR's proposed drug product has the same active pharmaceutical moiety, dosage form, strength, route of administration, and conditions of use as Sanofi Aventis' Eloxatin® Injection (oxaliplatin injection), previously approved under NDA No. 21-759.
3) The only difference between the proposed drug product and Eloxatin® Injection is that SICOR's product contains lactose as an excipient. However, Sanofi Aventis' Eloxatin® for Injection also contained lactose.

From a CMC standpoint, waiver for evidence of bioequivalence is recommended. Also refer to the Clinical Pharmacology review dated 30-NOV-2007 for further information.

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

There are no Phase 4 CMC commitments.

II. Summary of Chemistry Assessments

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

Drug Product:

Oxaliplatin injection is formulated as 5 mg/mL sterile, preservative-free aqueous solution. This concentrate solution is further diluted in an infusion solution of 250 -500 mL of 5% Dextrose Injection, USP for intravenous administration. The concentrate formulation includes lactose monohydrate.

The concentrate solution is manufactured by (b) (4)

(b) (4)

The NDA submission included a batch analysis for **Sanofi Aventis' Eloxatin® Injection (oxaliplatin injection)** for the purpose of comparison. The test results obtained from Eloxatin Injection are very similar to the ones obtained for batches manufactured by SICOR.

The applicant proposed Pharmachemie B.V., Swensweg 5, 2031GA Haarlem, The Netherland as the drug product manufacturing site. An acceptable EES recommendation by the Office of Compliance was received on 05-FEB-2009.

The applicant provided long term (25°C ± 2°C/60% RH ± 5% RH, **24** months) stability data for three commercial-scale batches of oxaliplatin Injection, 5 mg/mL (50 mg /10 mL Vial) and three batches of oxaliplatin Injection, 5 mg/mL (100 mg /20 mL Vial) stored in an inverted and upright positions. Photostability conditions were studied using one of the primary stability batches and found that the drug product is photostable. In addition, the applicant provided accelerated (40°C ± 2°C/75% RH ± 5% RH, **6** months) stability data in all batches submitted. All three primary stability batches were manufactured using the proposed commercial process. All batch analysis and stability data were all within the proposed drug product specification.

The applicant proposed a (b) (4) expiration dating period for the drug product, when stored under room temperature condition (25°C ± 2°C/60% RH ± 5% RH), they submitted up to 24 months of long term and 6 months at accelerated storage conditions. However, the results of the long term stability study in three of the batches submitted do not meet the drug product specification for Total of Impurities after 18 months. The same three batches do not meet Impurity C specification after 2 months and Total of Impurities after three months at accelerated conditions. Based on these results, an (b) (4) expiration dating is recommended.
The applicant proposed to have acceptance criteria for related substances at release different from those for the shelf life or stability specification. After discussion with the Pharmacology Team, the related substances should be maintained at the following levels: Impurity A: NMT (b) (4) Impurity B: NMT (b) (4) Impurity C: NMT (b) (4) Any other Related Substance: NMT (b) (4) and Total of Impurities: NMT (b) (4).

On 23-FEB-2009, the following deficiency was emailed to Teva:

1. We recommend that you maintain the currently-proposed drug product release specifications for related substances (Impurity A: NMT (b) (4) Impurity B: (b) (4), Impurity C: (b) (4) Any Other Related Substance: NMT (b) (4), and Total of Impurities: NMT (b) (4) to be the same as those proposed in the drug product shelf life specifications.

In a 24-FEB-2009 teleconference and subsequent official submission, Teva agreed to reduce their proposed (b) (4) expiration dating to (b) (4) In addition, Teva have provided the requested changes for the carton and container labels. A final review is still pending from DMEPA, OSE.

Drug Substance:
Oxaliplatin is an organoplatinum complex in which the platinum atom is complexed with 1,2 diamino-cyclohexane(DACH) and with an oxalate ligand as a leaving group. It is a white or almost white crystalline powder. Oxaliplatin is slightly soluble in water, very slightly soluble in methanol, and practically insoluble in ethanol and acetone. There is no polymorphism. The Differential Scanning Calorimetry shows an exotherm at about 300°C followed by decomposition.

The control of starting materials and the synthesis are described in DMF 19,559, SICOR de Mexico.

The drug substance is tested by SICOR for description, identification (IR and HPLC), appearance of solution (clarity and color) <USP and EP>, acidity <USP and EP>, specific rotation (USP <781>, assay (HPLC), related substances (HPLC), residual solvents (b) (4) , bacterial endotoxins (USP <85>), microbial purity (USP <61>) (b) (4) r <USP and EP>.

Oxaliplatin was accepted as a United States Adopted Name (USAN) in 1998.

SICOR submitted batch analyses for eight (8) batches of oxaliplatin drug substance, but no stability data was provided in NDA 22-160. Since, the DMF Holder is one of their subsidiaries, they rely on the DMF Holder stability data. See DMF 19559 Reviews dated on 30-OCT-2007 and 20-FEB-2009 for stability data.

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

Oxaliplatin is indicated for the adjuvant treatment of stage III colon cancer patients and treatment of advanced colorectal cancer. The recommended dose of Oxaliplatin is 85 mg/m^2 intravenous (IV) infusion in 250 – 500 mL 5% Dextrose in combination with infusional 5-fluorouracil (5-FU) and leucovorin (LV) every two (2) weeks.

After Oxaliplatin Injection dilution with 250-500 mL of 5% Dextrose Injection, USP, the shelf life is **6 hours at room temperature [20-25°C (68-77°F)] or up to 24 hours under refrigeration [2-8°C (36-46°F)].** Oxaliplatin is incompatible in solution with alkaline medications or media (such as basic solutions of 5-FU) and must not be mixed with these or administered simultaneously through the same infusion line. **The infusion line should be flushed with D5W prior to administration of any concomitant medication.** Oxaliplatin is not light sensitive.

The marketed drug product would be supplied in clear, glass, single-use vials with gray elastomeric stoppers and aluminum flip-off seals containing 50 mg or 100 mg of oxaliplatin as a sterile, preservative-free aqueous solution at a concentation of 5 mg/mL. Lactose monohydrate is present as an inactive ingredient at 450 mg and 900 mg in the 50 mg and 100 mg dosage strengths, respectively.

The NDC 1234-5678-90: 50 mg single-use vial with flip-off seal individually packaged in a carton. The NDC 1234-5678-90: 100 mg single-use vial with flip-off seal individually packaged in a carton. The recommended storage condition is at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP controlled room temperature].

The recommended handling and disposal statement is included in detail together with the applicable references.

C. Basis for Approvability or Not-Approval Recommendation

This NDA is recommended for Approval from a Chemistry, Manufacturing, and Controls standpoint pending on satisfactory carton and container labels. The stability updates (SICOR) for the drug product are acceptable in support of an (b) (4) expiration dating period, the responses to our comments to DMF 19,559, SICOR de Mexico, S.A. de C.V. are satisfactory, the microbiology consult recommended approval on 04-DEC-2007, and an overall acceptable recommendation was issued by the Office of Compliance on 05-FEB-2009.

III. Administrative

This NDA was submitted electronically as a 505(b)(2) application. A Quality Overall Summary is included in the application. Although, Sanofi Aventis' Eloxatin® for Injection was withdrawn from the US market, a Citizen's Petition was filed requesting that the Commissioner make a determination that this product was not voluntarily withdrawn from sale due to safety or effectiveness reasons (refer to docket 2006P-0291/CP1).

SICOR Pharmaceuticals, Inc. requests a waiver for evidence of bioavailability/bioequivalence in accordance with 21 CFR §320.22(b)(1). The drug product met all the criteria under 21 CFR §320.22(b)(1); therefore, the waiver is recommended from a CMC standpoint.

A. Reviewer's Signature

See electronic signatures in Division File System (DFS).

B. Endorsement Block

See electronic signatures in DFS

C. CC Block

See DFS

33 Page(s) has been Withheld in Full immediately following this page as B4 (CCI/TS)

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

/s/

Josephine Jee
2/24/2009 05:13:31 PM
CHEMIST

Haripada Sarker
2/24/2009 05:15:22 PM
CHEMIST

Sarah Pope
2/25/2009 11:15:48 AM
CHEMIST

DMF REVIEW Number: 19,559 DMF Type: II

Title: **Oxaliplatin** **DMF No. 19,559**

1. CHEM REVIEW AMENDMENT No. 1

2. REVIEW DATE: **20-FEB-2009**

3. ITEM REVIEWED

A. IDENTIFICATION

USAN:

rINN: Oxaliplatin

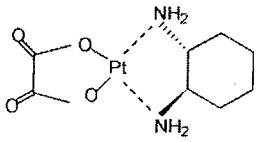
Chemical Name: (SP-4-2)-((1 R,2R)-Cyclohexane-1 ,2-diamine-κN, κN') (ethanedioato (2-)-κO^1, κO^2) platinum

Trade Name: N/A

CAS Number: 61825-94-3

Other Names: None provided.

Chemical Name:



Molecular Weight: 397.3 **Molecular Formula:** $C_8 H_{14} N_2 0_4 Pt$

4. DOCUMENTS

Type of Document	Date of Document	Location
Original	07-AUG-2006	Vol. 1.1, Vol., 1.2, (Reviewed on 10/30/07)
Amend.	20-FEB-2008	Vol. 1.3
Amend.	31-AUG-2008	Vol. 2.1

5. NAME & ADDRESS OF DMF HOLDER REPRESENTATIVE(S):

Name (Holder): TEVA Pharmaceutical – API Division (Sicor de México, S.A. de C.V.)

Address: 5 Bazel St.
P.O. B. 3190 Petah
Tiqva 49131, Israel

Responsible Agent: Hana Shahar, Regulatory Affairs Manager
TEVA Group, API Division

REPRESENTATIVE or U.S. AGENT: NAME: N/A
PHONE: N/A

CONTACT PERSON NAME: Hana Shahar, Regulatory Affairs Manager
Teva Pharmaceuticals – API Division
Teva Pharamceuticals
5 Bazel St,, P.O.B. 3190
Petah Tiqva 49131, israel

6. DMF REFERENCED FOR:

NDA: 22-160
PRIMARY DMF: Yes
APPLICANT NAME: Teva Parenteral Medicines, Inc.
LOA DATE: 14-AUG-2006

DRUG PRODUCT NAME: Oxaliplatin
DOSAGE FORM: Injection
CODE:
STRENGTH: 5 mg/mL (**50 mg/10 mL** and **100 mg/ 20 mL**)
ROUTE OF ADMINISTRATION: Intravenous by Infusion

7. SUPPORTING DOCUMENTS: NDA 22-160

8. CURRENT STATUS OF DMF:

DATE OF LAST UPDATE OF DMF: 07-AUG-2006 (Original submission)
Date of most recent List of Companies for which LOA's Have Been Provided: August 7, 2007

9. CONSULTS: None

10. COMMENTS: DMF 19,559 Amendments submitted on 20-FEB-2008 and 31-AUG-2008 by Sicor de Mexico in response to comments submitted on Nov 7, 2007 have provided adequate information to support oxaliplatin API to be used for NDA 22-160.

11. CONCLUSIONS: Adequate.

cc:
Orig. DMF 19,559
DDOP DMF File
DDOP/J.Jee/20-FEB-2008
DDOP/H. Sarker
DDOP/S. Pope
DDOP/A.Tilley
Doc: DMF 19559 Oxaliplatin.AMD

Josephine Jee
Review Chemist, CMC Branch V (Pre-Marketing)
Division of Pre-Market Assessment III &
Manufacturing Science, ONDQA

Sarah C. Pope, Ph. D.
Chief, CMC Branch V (Pre-Marketing)
Division of Pre-Market Assessment III &
Manufacturing Science, ONDQA.

11 Page(s) has been Withheld in Full immediately following this page as B4 (CCI/TS)

Linked Applications	Sponsor Name	Drug Name / Subject
MF 19559	SICOR DE MEXICO SA DE CV	OXALIPLATIN AS MANUFACTURED IN ESTADO DE MEXICO, MEXICO.

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

/s/

JOSEPHINE M JEE
02/24/2009

SARAH C POPE
02/25/2009
Concur

HARIPADA SARKER
02/25/2009

MEMORANDUM

Date : November 1, 2007
From: Ravi S. Harapanhalli, Ph.D., Branch Chief, ONDQA 12/4/07
To: Robert Justice, M.D.
Through: Rik Lostritto, M.D. 12/4/07
Subject: NDA 22-160 Oxaliplatin Injection, Applicant: SICOR Pharmaceuticals, Inc.
Reference: Impact of Sanofi-Aventis' Citizen Petition and Citizen Petition Supplement for Oxaliplatin on the approval of NDAs

Background:

SICOR's Formulation:

Oxaliplatin Injection, 5 mg/ml contains the same active ingredient in the same concentration as the innovator drug product Eloxatin Injection, 5 mg/ml marketed by Sanofi Aventis. The only difference is that the innovator formulation contains oxaliplatin in water for injection whereas SICOR's formulation contains an additional (b) (4) of lactose monohydrate per ml along with 5 mg of oxaliplatin. It should be noted that Sanofi Aventis marketed (NDA 21-492 and 21-759) a lyophilized oxaliplatin formulation containing lactose during 1993 to 2004 and switched the formulation to an aqueous solution as mentioned above.

Impurities of concern:

The following impurities are identified and are described in both NDAs.

(b) (4)

[redacted]

Comparative specifications for impurities:

Impurity	SICOR NDA 22-068	Sanofi Aventis NDAs 21-492/21-759
[redacted]		

(b) (4)

(b) (4)

SICOR's Stability data (12 Months at room temperature storage):

Impurity	SICOR NDA Specification	10-ml Vials 25°C/60% RH	20-ml Vials 25°C/60% RH
(b) (4)			

Observations and Results:

- (b) (4) not found in the RLD is specified a (b) (4) n SICOR's NDA and is within the qualification threshold according to ICH Q3B® since the maximum daily dose (MDD) is (b) (4)
- Assay range is tighter in SICOR's specifications than it is in the RLD
- Total impurities range in SICOR's NDA may be tightened to NMT (b) (4) % and SICOR may be asked to submit stability updates if they expect an expiration dating period beyond 12 months.

Conclusion:

The Sanofi-Aventis petitioned that the Agency require all applicants for approval of generic formulations referencing Eloxatin solution (ANDAs and also 505(b)(2) applications), containing an acid other than oxalic acid or a conjugate base thereof, or solutions containing added sugars such as lactose, to demonstrate through sufficient preclinical and/or clinical testing that any new compound resulting from such formulations do not compromise the safety or efficacy of the drug product. As seen above, SICOR's specifications are within the specification limits for all Pt-containing degradation products listed in Sanofi-Aventis' NDA. These impurities are known and identified impurities described in SICOR's as well as Sanofi-Aventis' NDAs. Also, none of them exceeds the qualification threshold (which is NMT 0.2% in this case). Therefore, from the CMC view point, the approval of SICOR's NDA is not impacted by Sanofi-Aventis' CP.

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

/s/

Ravi Harapanhalli
12/4/2007 04:27:55 PM
CHEMIST
Impact of Sanofi-Aventis' CP on NDA approval

CMC REVIEW OF NDA 22-160

REVIEW # 1
OXALIPLATIN INJECTION, 5 MG/ML
50 mg/10 mL and 100 mg/20 mL

JOSEPHINE M. JEE
CMC REVIEWER

OFFICE OF NEW DRUG QUALITY ASSESSMENT
DIVISION OF PREMARKETING ASSESSMENT AND MANUFACTURING SCIENCE
(BRANCH V)

FOR THE DIVISION OF DRUG ONCOLOGY PRODUCTS (HFD-150)

Table of Contents

Table of Contents 2

Chemistry Review Data Sheet 3

The Executive Summary 6

I. Recommendations 6

A. Recommendation and Conclusion on Approvability 6

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 6

II. Summary of Chemistry Assessments 6

A. Description of the Drug Product(s) and Drug Substance(s) 6

B. Description of How the Drug Product is Intended to be Used 7

C. Basis for Approvability or Not-Approval Recommendation 8

III. Administrative 8

A. Reviewer's Signature 8

B. Endorsement Block 8

C. CC Block 8

Chemistry Assessment 9

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data 9

S DRUG SUBSTANCE [Name, Manufacturer] 9

P DRUG PRODUCT [Name, Dosage form] 20

A APPENDICES 56

R REGIONAL INFORMATION 56

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 57

A. Labeling & Package Insert 57

B. Environmental Assessment Or Claim Of Categorical Exclusion 61

III. List Of Deficiencies To Be Communicated 63

Chemistry Review Data Sheet

1. NDA 22-160

2. REVIEW: # 1

3. REVIEW DATE: 05-NOV-2007

4. REVIEWER: Josephine M. Jee

5. PREVIOUS DOCUMENTS:

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 21-801 - (Rolling Submission - CMC)	09-FEB-2007
Amendment	01-MAY-2007
Amendment	04-MAY-2007
Amendment	11-MAY-2007
Amendment	23-MAY-2007
Amendment	17-SEPT-2007

7. NAME & ADDRESS OF APPLICANT:

Name: SICOR Pharmaceuticals, Inc.

Address: 19 Hughes
Irvine, CA 92618-1902

8. DRUG PRODUCT NAME/CODE/TYPE: **Oxaliplatin**

a) Proprietary Name: None Proposed

b) Non-Proprietary Name (USAN): Oxaliplatin
International Nonproprietary Name (INN): Oxaliplatin

c) Code Name/# (ONDC only): None provided.
Internal Codes: None provided.

d) CAS Registry Number: None provided.

e) Laboratory Codes: None provided.

f) Chemical Name (IUPAC): *SP*-4-2)-[(1*R*,2*R*)-Cyclohexane-1,2-diamine-κ*N*, κ*N*'] [ethanedioato(2-)-κ*O1*,κ*O2*]platinum

Alternative names: None provided.

g) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 505(b)(2)
- Submission Priority: **S**

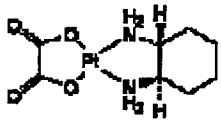
9. LEGAL BASIS FOR SUBMISSION: 505(b)(2) - Reference: **Eloxatin®** (oxaliplatin Injection), approved under **NDA 21-759** (Lyophilized form) and **NDA 21-492** (Solution form)

10. PHARMACOL. CATEGORY: Treatment of Advanced Colorectal Cancer
11. DOSAGE FORM: Injection
12. STRENGTH/POTENCY: **5 mg/mL**
10 mL (50mg/10 mL), and 20 mL (100 mg/20 ml) vials
13. ROUTE OF ADMINISTRATION: Intravenously

14. Rx/OTC DISPENSED: __X_Rx ___OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): N/A

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

(SP-4-2)-[(1*R*,2*R*)-Cyclohexane-1,2-diamine-κ*N*, κ*N*'] [ethanedioato(2-)-κ*O1*,κ*O2*]platinum



Molecular Formula: $C_8H_{14}N_2O_4Pt$ Molecular Weight: 397.3

17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
DMF 19559	II	Sicor de México, S.A. de C.V.	Oxaliplatin DS	1	Inadequate	30-OCT-2007	Reviewed by J.Jee
(b) (4)	III		(b) (4)	3	Adequate	22-APR-2002	Reviewed by Yvonne Yang, Ph.D.
	III			3	Adequate	19-APR-2002	Reviewed by Yvonne Yang, Ph.D.
	III			3	Adequate	10-OCT-2002	Reviewed by Elsbeth Chikhale, Ph.D.

[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)

Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	None	

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			
EES	Site inspections	21-FEB-2007	S.Adams	Acceptable on 27-NOV-2007
Biopharm	N/A			
ODS/DMETS	N/A			Consult pending
Methods Validation	Pharm. Eur. & Proposed USP			No validation is needed
EA	N/A	N/A	J.Jee	Categorical exclusion granted (see attached review).
Microbiology	Consulted to the Office of Microbiology	01-MAR-2007	Dr. S. Langille	Acceptable recommendation provided on 03-DEC-2007.

The Chemistry Review for NDA 22-160

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Office of Compliance deemed all facilities acceptable for cGMP Compliance on 27-NOV-2007. The Product Quality Microbiology recommended approval on 03-DEC-2007. However, from a Chemistry, Manufacturing and Controls standpoint, this New Drug Application is approvable, pending the resolution of the CMC issues listed at the end of the review, acceptable responses to our comments for DMF 19,559 (Oxaliplatin, Sicor de Mexico).
SICOR Pharmaceuticals, Inc. requests a waiver for evidence of bioavailability/bioequivalence in accordance with 21 CFR §320.22(b)(1). SICOR's drug product meets the required criteria:

1) Oxaliplatin Injection, 5 mg/mL is a parenteral drug product intended for administration by intravenous infusion.
2) SICOR's proposed drug product has the same active pharmaceutical moiety, dosage form, strength, route of administration, and conditions of use as Sanofi Aventis' Eloxatin® Injection (oxaliplatin injection), previously approved under NDA No. 21-759.
3) The only difference between the proposed drug product and Eloxatin® Injection is that SICOR's product contains lactose as an excipient. However, Sanofi Aventis' discontinued formulation, Eloxatin® for Injection also contained lactose.

From a CMC standpoint, waiver for evidence of bioequivalence is recommended.

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

There are no Phase 4 CMC commitments.

II. Summary of Chemistry Assessments

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

Drug Product:

Oxaliplatin injection is formulated as 5 mg/mL sterile, preservative-free aqueous solution. This concentrate solution is further diluted in an infusion solution of 250 -500 mL of 5% Dextrose Injection, USP for intravenous administration. The concentrate formulation includes lactose monohydrate.

The concentrate is manufactured by (b) (4)

(b) (4) The NDA submission included a batch analysis for **Sanofi Aventis' Eloxatin® Injection (oxaliplatin injection)** for the purpose of comparison. The test results obtained from Eloxatin Injection are very similar to the ones obtained for batches manufactured by SICOR.

The applicant proposed Pharmachemie B.V., Swensweg 5, 2031GA Haarlem, The Netherland as the drug product manufacturing site. An EES recommendation by the Office of Compliance is pending.

The applicant provided long term (25°C ± 2°C/60% RH ± 5% RH, **12** months) stability data for three commercial-scale batches of oxaliplatin Injection, 5 mg/mL (50 mg /10 mL Vial) and one batch of oxaliplatin Injection, 5 mg/mL (100 mg /20 mL Vial) , and two batches of oxaliplatin Injection, 5 mg/mL (100 mg /20 mL Vial) at (25°C ± 2°C/60% RH ± 5% RH, **9** months)when stored in an inverted and upright positions. Photostability conditions were studied using one of the primary stability batches. In addition, the applicant provided accelerated (40°C ± 2°C/75% RH ± 5% RH, **6** months) stability data for all submitted batches. All three primary stability batches were manufactured using the proposed commercial process. All batch analysis and stability data were all within the proposed drug product specification.

The applicant proposed a (b) (4) expiration dating period for the concentrate, when stored under room temperature conditions (25°C ± 2°C/60% RH ± 5% RH), however, they submitted only up to twelve months of data and are expected to submit additional update.

Drug Substance:

Oxaliplatin is an organoplatinum complex in which the platinum atom is complexed with 1,2 diamino-cyclohexane(DACH) and with an oxalate ligand as a leaving group. It is a white or almost white crystalline powder. Oxaliplatin is slightly soluble in water, very slightly soluble in methanol, and practically insoluble in ethanol and acetone. There is no polymorphism. The differential Scanning Calorimetry shows an exotherm at about 300°C followed by decomposition. The control of starting materials and the synthesis are described in DMF 19,559, SICOR de Mexico.

The drug substance is tested by SICOR for description, identification (IR and HPLC), appearance of solution (clarity and color) <USP and EP>, acidity <USP and EP>, specific rotation (USP <781>, assay (HPLC), related substances (HPLC), residual solvents (b) (4) , bacterial endotoxins (USP <85>), microbial purity (USP <61>), (b) (4) <USP and EP>.

Oxaliplatin was accepted as a United States Adopted Name (USAN) in 1998.

SICOR submitted batch analyses for eight (8) batches of oxaliplatin drug substance, but no stability data was provided in NDA 22-160. Since, the DMF Holder is one of their subsidiaries, they rely on the DMF Holder stability data. Up to 12 months of long-term stability data and 6 months of accelerated stability data are submitted for 6 batches of oxaliplatin drug substance by the DMF Holder. The stability data obtained from batches tested by SICOR de Mexico conform with the Oxaliplatin Drug Substance specification.

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

Oxaliplatin is indicated for the adjuvant treatment of stage III colon cancer patients and treatment of advanced colorectal cancer. The recommended dose of Oxaliplatin is 85 mg/m^2 intravenous (IV) infusion in 250 – 500 mL 5% Dextrose in combination with infusional 5-fluorouracil (5-FU) and leucovorin (LV) every two (2) weeks.

After Oxaliplatin Injection dilution with 250-500 mL of 5% Dextrose Injection, USP, the shelf life is **6 hours at room temperature [20-25°C (68-77°F)] or up to 24 hours under refrigeration [2-8°C (36-46°F)].** Oxaliplatin is incompatible in solution with alkaline medications or media (such as basic solutions of 5-FU) and must not be mixed with these or administered simultaneously through the same infusion line. **The infusion line should be flushed with D5W prior to administration of any concomitant medication.** Oxaliplatin is not light sensitive.

The marketed drug product will be supplied in clear, glass, single-use vials with gray elastomeric stoppers and aluminum flip-off seals containing 50 mg or 100 mg of oxaliplatin as a sterile, preservative-free aqueous solution at a concentration of 5 mg/mL. Lactose monohydrate is present as an inactive ingredient at 450 mg and 900 mg in the 50 mg and 100 mg dosage strengths, respectively.
The NDC 1234-5678-90: 50 mg single-use vial with flip-off seal individually packaged in a carton.
The NDC 1234-5678-90: 100 mg single-use vial with flip-off seal individually packaged in a carton.
The recommended storage condition is at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP controlled room temperature].
The recommended handling and disposal statement is included in detail together with the applicable references.

C. Basis for Approvability or Not-Approval Recommendation

This NDA is approvable from a Chemistry, Manufacturing, and Controls standpoint pending satisfactory responses to the deficiencies in DMF 19,559.
Acceptable cGMP recommendation from the Office of Compliance was dated 27-NOV-2007.
Acceptable recommendation from the Product Quality Microbiology on 03-DEC-2007.

III. Administrative

This NDA was submitted electronically as a 505(b)(2) application. A Quality Overall Summary is included in the application. Although, Sanofi Aventis' Eloxatin® for Injection was withdrawn from the US market, a citizen petition has been filed requesting the Commissioner to make a determination that this product was not voluntarily withdrawn from sale due to safety or effectiveness reasons (refer to docket 2006P-0291/CP1).

SICOR Pharmaceuticals, Inc. requests a waiver for evidence of bioavailability/bioequivalence in accordance with 21 CFR §320.22(b)(1). The drug product met all the criteria under 21 CFR §320.22(b)(1); therefore, the waiver is recommended from a CMC standpoint.

A. Reviewer's Signature

See electronic signatures in Division File System (DFS).

B. Endorsement Block

See electronic signatures in DFS

C. CC Block

See DFS

62 Page(s) has been Withheld in Full immediately following this page as B4 (CC /TS)

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

/s/

Josephine Jee
12/3/2007 03:08:58 PM
CHEMIST

Ravi Harapanhalli
12/3/2007 03:12:02 PM
CHEMIST
AE recommendation

INITIAL QUALITY ASSESSMENT

OFFICE OF NEW DRUG QUALITY ASSESSEMNT
DIVISION OF PREMARKETING ASSESSMENT AND MANUFACTURING SCIENCE (BRANCH V)
CMC REVIEW OF NDA 22-160
FOR THE DIVISION OF ONCOLOGY DRUG PRODUCTS (HFD-150)

OND Division:	Division of Drug Oncology Products
NDA:	22-160
Applicant:	**SICOR Pharmaceuticals, Inc.**
Assigned Date:	20-FEB-2007
Stamp date:	09-FEB-2007
PDUFA Date:	09-DEC-2007
Proposed Trade Name:	None proposed.
Established Name:	Oxaliplatin Injection
Laboratory Code:	None
Dosage Form:	**Oxaliplatin Injection, 5 mg/mL in 10 mL (50mg/10 mL), and 20 mL (100 mg/20 ml) vials**
Route of Administration:	Intravenously.
CMC Reviewer:	Josephine Jee

	YES	NO
ONDQA Fileability:	√	___
Draft Comments for 74-Day Letter:	√	___

Summary, Critical Issues and Comments

A. Summaries

Background Summary

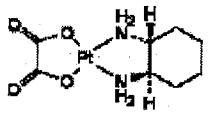
NDA 22-160 has been submitted under Section 505(b)(2) for Oxaliplatin Injection, 5 mg/mL, intended for treatment of advanced colorectal cancer. Reference is made to Eloxatin® (oxaliplatin injection), as approved under NDA 21-759 and NDA 21-492. The basis for NDA 22-160 is a formulation revision to the reference listed drug Eloxatin (oxaliplatin injection). The approved and proposed products have the same active ingredient, dosage form, strength, route of administration, and conditions of use as the innovator drug Eloxatin® (oxaliplatin injection). However, the proposed drug product also contains lactose, which was present at the same concentration in Sanofi-Aventis's previously marketed lyophilized dosage form of Eloxatin® (oxaliplatin injection). SICOR's liquid formulation of the drug was developed to match the assay and impurity profiles of the innovator's discontinued lyophilized drug after reconstitution.

A full comparison of SICOR's proposed drug to the innovator's drugs is provided in the NDA.

Drug Substance Summary

Oxaliplatin is a white to almost white crystalline powder, which is slightly soluble in water, very slightly soluble in methanol, and practically insoluble in ethanol. Oxaliplatin thermally decomposes at 300°C, is isomorphic (confirmed by X-ray diffraction), and the specific optical rotation is 74.5° – 78.0°.

The chemical structure of Oxaliplatin is as follows:



Chemical Name: (*SP*-4-2)-[(1*R*,2*R*)-Cyclohexane-1,2-diamine-κ*N*, κ*N*'] [ethanedioato(2-)-κ*O1*,κ*O2*]platinum

Molecular Formula: $C_8H_{14}N_2O_4Pt$

Molecular Weight: 397.3

The Chemistry, Manufacturing and Controls information for oxaliplatin is cross-referenced to DMF 19,559 (Sicor de México, S.A. de C.V). DMF 19,559 was filed with the Agency on 16-JUN-2006..
The active substance will be re-tested at Pharmachemie after (b) (4).

The proposed manufacturing site is listed below:

Site(s) of Drug Substance Manufacturing:
Sicor de México, S.A. de C.V.,
Av. San Rafael No. 35
Parque Industrial Lerma
Lerma, Estado de México,
C.P. 52000
México

Drug Product Summary

The formulation is a sterile, preservative-free solution for parenteral administration via intravenous infusion. Two fill volumes are proposed: a 10-mL (50 mg) fill volume and a 20-mL (100 mg) fill volume. Both vials contain the same 5 mg/mL solution. The drug product also includes the following compendial inactive ingredients: lactose monohydrate and water for injection.
The proposed batch size is (b) (4).

Composition:

Composition, unit formula per vial

Component	Unit formula per vial	
	10 mL[1]	20 mL[1]
Drug substance		
Oxaliplatin	50 mg	100 mg
Excipients		
Lactose monohydrate	450 mg	900 mg
Water for Injection	(b) (4)	
Primary packaging		
Container	Colorless glass vial (b) (4) (b) (4) (b) (4)	Colorless glass vial (b) (4) (b) (4) (b) (4)
Closure	(b) (4)	
Snap-cap	Aluminum seal (b) (4)	Aluminum seal (b) (4) (b) (4)

B. Preliminary Comments and Recommendations

Drug Substance Section
All drug substance information has been cross-referenced to DMF 19,559 (see Letter of Authorization dated 07-AUG-2006).

Drug Product Section
The Sponsor has provided three pilot batches for the 10 mL fill volume (two batches (b) (4)) and three batches for the 20 mL fill volume (b) (4)). The proposed commercial batch size is (b) (4) Twelve (12) months of long-term (25°C ± 2°C/60% ± 5% RH) stability data and six (6) months of the corresponding accelerated (40°C ± 2°C/75% ± 5% RH) stability data. The proposed marketed stability protocol are:

Long-term testing conditions
Storage conditions: 25°C ± 2°C/60% RH ± 5% RH.
Testing frequency: 0, 3, 6, 9, 12, 18, 24 and 36 months.
Accelerated testing conditions
Storage conditions: 40°C ± 2°C/75% RH ± 5% RH.
Testing frequency: 0, 3 and 6 months.

The Sponsor has proposed a (b) (4) expiration dating period for the drug product, when stored at 25°C ± 2°C/60% RH ± 5% RH.

C. Critical issues for review and recommendation

Drug Substance

a. DMF 19559 was received by the Agency (29-JUN-2006), and it has never been formally reviewed. A thorough CMC review should be conducted for the included drug substance manufacturing information.
b. Due to the previous approval of Oxaliplatin Injection (NDA 21-759), a pharmacology/toxicology consult will not be filed for this NDA. If Pharmacology/Toxicology feedback or confirmation is necessary during the CMC review cycle, this should be obtained as soon as possible.

Drug Product

a. The proposed manufacturing process is conventional for (b) (4) injectable formulations, and compendial excipients are stated in the drug product composition. While the submitted manufacturing and compositional information should be completely assessed, there are no significant (high-risk) triggers in the provided process and compositional information.

b. Due to the injectable nature of the formulation, all sterility assurance information will also be consulted to the Office of Microbiology for review (The request for Micro. Consult is already been sent on 01-MAR-2007).
The proposed manufacturing facility is listed below:

Site(s) of Drug Product Manufacturing, Packaging, Labeling, Testing (Release and Stability), and Warehousing and Distribution of Drug Product:

Pharmachemie B.V.
Swensweg 5
NL-2031 GA Haarlem
The Netherlands

D. Comments for 74-day Letter:
Stability data analysis and the appropriate SAS transport files should be provided as soon as possible.

Updated primary stability data should be provided as soon as possible.

E. Recommendation for fileability: **Fileable**

Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	√		EES have been submitted on 21-FEB-2007
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		See DMF 19,559
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?		√	12 M long-term stab. data and 6 M acc. data submitted. Request for (b) (4) (b) (4) exp. dating.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	√		
16	Have all consults been identified and initiated? (bolded items to be handled by ONDQA PM)	√ √		**Microbiology** EES (21-FEB-2007)

Have all DMF References been identified? Yes (√) No ( )

DMF Number	Holder	Description	LOA Included
19559	Sicor de México, S.A. de C.V.	Oxaliplatin	Yes
[redacted]		(b) (4)	Yes
			Yes
			Yes

Recommendation for Team Review:
This NDA includes a significant portion of drug substance manufacturing information, as cross-referenced to a recently-filed Drug Master File (DMF 19559). However, the drug product information is conventional in nature, and the CMC review will be conducted in conjunction with a microbiological assessment/review. The majority of the critical quality attributes for the drug product are microbiological (sterility, endotoxin limits, etc.), and the CMC review for the drug product should be straightforward.

The team review approach is not recommended for this NDA.

Josephine Jee
CMC Reviewer

02-MAR-2007
Date

Ravi Haranpahalli
Branch Chief, Branch V

Date

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

/s/

Josephine Jee
4/9/2007 07:45:02 AM
CHEMIST

Ravi Harapanhalli
4/16/2007 10:53:04 AM
CHEMIST

DMF REVIEW Number: 19,559 DMF Type: II

(Non-Potable)

Title: Oxaliplatin **DMF No. 19,559**

1. CHEM REVIEW No. 1

2. REVIEW DATE: 30-OCT-2007

3. ITEM REVIEWED

A. IDENTIFICATION

USAN:

rINN: Oxaliplatin

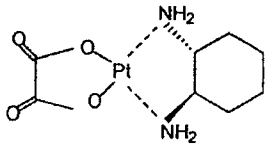
Chemical Name: (SP-4-2)-((1 R,2R)-Cyclohexane-1 ,2-diamine-κN, κN') (ethanedioato (2-)-κO^1, κO^2) platinum

Trade Name: N/A

CAS Number: 61825-94-3

Other Names: None provided.

Chemical Name:



Molecular Weight: 397.3 **Molecular Formula**: $C_8 H_{14} N_2 O_4 Pt$

4. DOCUMENTS

Type of Document	Date of Document	Location
Original	07-AUG-2006	Vol. 1.1, Vol., 1.2, Vol. 1.3

5. NAME & ADDRESS OF DMF HOLDER REPRESENTATIVE(S):

Name (Holder): Sicor de México, S.A. de C.V.

Address: Av. San Rafael 35
Parque Industrial Lerma
CP 52000 Lerma, Estado de Mexico
Mexico

Responsible Agent: Jovita Trinidad, Regulatory Manager

Name (Agent): Plantex USA, Inc
2 University Plaza, Suite 305
Hackensack, New Jersey 07601
Tel: (201) 343-4141
Fax: (201) 343-3833

REPRESENTATIVE or U.S. AGENT: NAME: N/A PHONE: N/A

CONTACT PERSON NAME: Carolyn Leitgeb
Administrative Assistant – Customer Service

ADDRESS: Plantex USA, Inc
2 University Plaza, Suite 305
Hackensack, New Jersey 07601

6. DMF REFERENCED FOR:

NDA: 22-160
PRIMARY DMF: Yes
APPLICANT NAME: Teva Parenteral Medicines, Inc.
LOA DATE: 14-AUG-2006

DRUG PRODUCT NAME:	Oxaliplatin
DOSAGE FORM:	Injection
CODE:	
STRENGTH:	5 mg/mL (50 mg/10 mL and 100 mg/ 20 mL)
ROUTE OF ADMINISTRATION:	Oral

7. SUPPORTING DOCUMENTS: NDA 22-160

8. CURRENT STATUS OF DMF:

DATE OF LAST UPDATE OF DMF: 07-AUG-2006 (Original submission)
Date of most recent List of Companies for which LOA's Have Been Provided: August 7, 2007

9. CONSULTS: None

10. COMMENTS: DMF 19,559 has not provided all required information; see pp 23-24 of this review for comments.

11. CONCLUSIONS: Inadequate.

11/5/07
Josephine Jee
Review Chemist, CMC Branch V (Pre-Marketing)
Division of Pre-Market Assessment III &
Manufacturing Science, ONDQA

11/5/07
Ravi Harapanhalli, Ph. D.
Chief, CMC Branch V (Pre-Marketing)
Division of Pre-Market Assessment III &
Manufacturing Science, ONDQA.

cc:
Orig. DMF 19,559
DDOP DMF File
DDOP/J.Jee/30-OCT-2007
DDOP/R.Harapanhalli
DDOP/D.Pease
Doc: DMF 19559 Oxaliplatin.doc

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 22160/000	Action Goal:	
Stamp:	09-FEB-2007	District Goal:	01-JAN-2009
Regulatory Due:	02-MAR-2009	Brand Name:	OXALIPLATIN INJECTION
Applicant:	TEVA PARENTERAL	Estab. Name:	
	19 HUGHES	Generic Name:	OXALIPLATIN INJECTION
	IRVINE, CA 92618		
Priority:	5S	Dosage Form:	(INJECTION)
Org Code:	150	Strength:	5.0 MG/ML

Application Comment: APPLICATION WAS RESUBMITTED ON 2-SEPTEMBER-2008, SO ESTABLISHMENTS ARE BEING RESUBMITTED. (on 09-DEC-2008 by D. MESMER (HFD-800) 301-796-4023)

PHARMACHEMIE PERFORMS THE FOLLOWING: DRUG PRODUCT MANUFACTURING, PACKAGING, LABELING, TESTING (RELEASE AND STABILITY), AND WAREHOUSING AND DISTRIBUTION OF DRUG PRODUCT. PLEASE CHECK FOR FACILITY ADEQUACY FOR THESE FUNCTIONS.

SICOR DE MEXICO IS THE MANUFACTURER OF OXALIPLATIN DRUG SUBSTANCE. CHECK FOR ADEQUACY. (on 21-FEB-2007 by J. JEE () 301-796-1375)

FDA Contacts:	D. MESMER	(HFD-800)	301-796-4023	, Project Manager
	J. JEE		301-796-1375	, Review Chemist
	H. SARKER	(HFD-150)	301-796-1747	, Team Leader

Overall Recommendation: ACCEPTABLE on 05-FEB-2009by S. ADAMS (HFD-325)301-796-3193

ACCEPTABLE on 27-NOV-2007by S. ADAMS (HFD-325)301-796-3193

Establishment: CFN 9611517 FEI 3002807910

PHARMACHEMIE BV

SWENSWEG 5

HAARLEM, , NL

DMF No: 8786 AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: (b) (4) OAI Status: NONE

Estab. Comment: APPLICATION WAS RESUBMITTED ON 2-SEPTEMBER-2008, SO ESTABLISHMENTS ARE BEING RESUBMITTED.
PHARMACHEMIE PERFORMS THE FOLLOWING: DRUG PRODUCT MANUFACTURING, PACKAGING, LABELING, TESTING (ANALYTICAL,RELEASE AND STABILITY), AND WAREHOUSING AND DISTRIBUTION OF DRUG PRODUCT. PLEASE CHECK FOR FACILITY ADEQUACY FOR THESE FUNCTIONS. (on 09-DEC-2008 by D. MESMER (HFD-800) 301-796-4023)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	21-FEB-2007				JEE
MITTED TO DO	22-FEB-2007	GMP			ADAMSS
ASSIGNED INSPECTION T	23-FEB-2007	GMP			ADAMSS
INSPECTION SCHEDULED	14-JUN-2007		05-JUL-2007		IRIVERA
INSPECTION PERFORMED	05-JUL-2007		05-JUL-2007		ADAMSS

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

INSPECTION PERFORMED 05-JUL-2007 05-JUL-2007 BRUCE.MCCUL

This was a drug CGMP and pre-approval (PDUFA) EI of a (b) (4) manufacturer, initiated by CDER/OC/DMPQ/IPCB. FACTS assignment ID: 3800173.

CGMP coverage was a full-option inspection, covering the Quality, Facilities & Equipment, Production, and Laboratory Systems. Pre-Approval coverage included: NDA 022-160 Oxaliplatin Injection, 5 mg/mL; (b) (4)

(b) (4)

The previous inspection (5/3-7/04) covered Profile Classes (b) (4) and was classified OAI. That inspection revealed CGMP deficiencies associated with: (b) (4)

s.

At the beginning of the current inspection, we identified ourselves to Jan P.P. Moors, Vice-President, Quality Assurance. The current inspection revealed corrections to the previous observations. However, the current inspection revealed other CGMP deficiencies

regarding [redacted] (b) (4) including:

- [redacted] (b) (4)

DO RECOMMENDATION	27-NOV-2007		ACCEPTABLE	ADAMSS
			ADEQUATE FIRM RESPONSE	
FIRM PROVIDED ADDITIONAL CORRECTIVE ACTIONS AS REQUESTED BY CDER/OFFICE OF COMPLIANCE.				
OC RECOMMENDATION	27-NOV-2007		ACCEPTABLE	ADAMSS
			FIRM RESPONSE TO DEFIC. ADEQUA	
SUBMITTED TO OC	09-DEC-2008			MESMERD
SUBMITTED TO DO	15-DEC-2008	GMP		ADAMSS
ASSIGNED INSPECTION T	10-JAN-2009	GMP		ADAMSS
DO RECOMMENDATION	05-FEB-2009		ACCEPTABLE	ADAMSS
			BASED ON FILE REVIEW	
AC GMP EI 7/2007				
OC RECOMMENDATION	05-FEB-2009		ACCEPTABLE	ADAMSS
			DISTRICT RECOMMENDATION	

Establishment: CFN 9616073 FEI 3002808102

SICOR DE MEXICO S.A. DE C.V.

AVENIDA SAN RAFAEL 35

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

LERMA, EDO. DE. MEXICO, MX

DMF No: 19559 AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: (b) (4) OAI Status: NONE

Estab. Comment: APPLICATION WAS RESUBMITTED ON 2-SEPTEMBER-2008, SO ESTABLISHMENTS ARE BEING RESUBMITTED.
SICOR DE MEXICO IS THE MANUFACTURER OF OXALIPLATIN DRUG SUBSTANCE. CHECK FOR ADEQUACY. (on 09-DEC-2008 by D. MESMER (HFD-800) 301-796-4023)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	21-FEB-2007				JEE
SUBMITTED TO DO	22-FEB-2007	GMP			ADAMSS
ASSIGNED INSPECTION T	23-FEB-2007	GMP			ADAMSS
INSPECTION PERFORMED	19-APR-2007		19-APR-2007		VLADA.MATUS

This pre-approval inspection of an API manufacturer was initiated in response to FACTS Assignment # 3960790, Operation ID # 3171828 and an assignment from International District Pre-Approval Manager requesting coverage of APIs used in manufacturing of (b) (4) Oxaliplatin Injection, 5 mg/ml, NDA # 22160/000 (b) (4) This inspection was conducted in accordance with C.P. 7356.002F, C.P. 7346.832 and C.P. 7352.832.

previous inspection of the firm, dated 1/12-22/04, was classified VAI. This inspection revealed the following cGMP deficiencies, which were documented on the Form FDA-483: (b) (4)

Corrections implemented by the firm in response to these deficiencies were evaluated during the current inspection.

The current inspection revealed that the firm continues as a manufacturer of API's cributed worldwide. Quality, Laboratory Control, Facilities and Equipment and Production Systems were evaluated. The following deficiencies were documented on the Form FDA-483 issued to the firm's management at the conclusion of this inspection:

(b) (4)

incomplete investigation into customer complaint, no assurance of reproducibility of HPLC instrument used in Oxaliplatin API assay testing and no record of standard weights used during related substance analysis of Oxaliplatin (b) (4) (b) (4). The firm's management promised corrections. There were no samples collected and no refusals were encountered.

INSPECTION SCHEDULED	21-MAY-2007	20-APR-2007		IRIVERA
DO RECOMMENDATION	15-AUG-2007		ACCEPTABLE	ADAMSS
			INSPECTION	
RECOMMENDATION	16-AUG-2007		ACCEPTABLE	ADAMSS
			DISTRICT RECOMMENDATION	
SUBMITTED TO OC	09-DEC-2008			MESMERD
OC RECOMMENDATION	15-DEC-2008		ACCEPTABLE	ADAMSS

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

BASED ON PROFILE
