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APPLICATION NUMBER:

22-160

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	22-160
Submission Date	29 August, 2008
Drug Trade Name	Oxaliplatin Injection
Generic Name	Oxaliplatin
Formulation	Solution for Injection, 5 mg/mL (50 mg/10 mL and 100 mg/20 mL)
Indication	Colorectal Cancer
Sponsor	Teva Parental Medicines, Inc.
Reviewer	Hua Lillian Zhang, Ph.D.
Deputy Director	Brian Booth, Ph.D.
OCP Division	Division of Clinical Pharmacology 5
OODP Division	Division of Drug Oncology Products
Submission Type	NDA [505(b)(2)]

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1 EXECUTIVE SUMMARY

Oxaliplatin is a platinum-based drug used in combination with infusional 5-fluorouracil (5-FU)/leucovorin (LV), which is indicated for 1) adjuvant treatment of stage III colon cancer in patients who have undergone complete resection of the primary tumor; 2) treatment of advanced colorectal cancer. The drug product is Oxaliplatin Injection, 5 mg/mL.

The original NDA 22-160 was submitted by Sicor Pharmaceuticals Inc, a subsidiary of Teva Phamaceuticals USA, on February 9, 2007 as a 505(b)(2) application. A Clinical Pharmacology review was performed and finalized on November 30, 2007. According to the letter issued by FDA to the sponsor dated December 4, 2007, the application is approved upon the resolution of several deficiencies and labeling issues identified in the submission. This submission is a complete response to the approvable letter dated December 4, 2007, plus three additional CMC changes to the application. The following table summarizes the requests for information from FDA and their responses to each request are provided in the submission.

Date of Receipt of Request from the FDA	Types of Issues Addressed
November 6, 2007	Request for Information from the Chemistry Reviewer regarding the statistical analysis of the stability data
November 28, 2007	Telephone call from Dotti Pease requesting container and carton labels to be provided in color.
December 4, 2008	Approvable letter which includes chemistry and labeling issues
December 13, 2007	Labeling comments from DMETS
Additional Proposed Changes to the Application	Additional changes made to the application not related to questions received from the FDA

The sponsor has also revised the drug label to address the three separate deficiency letters received on November 28, 2007; December 4, 2007; and December 12, 2007, mainly with respect to the format, carton/container labels and package insert.

Overall, there is no new clinical pharmacology information in this submission. Cross-reference to NDA 22-160 was provided for the clinical pharmacology information. The current submission was reviewed for the labeling revision and format from a clinical pharmacology perspective. The new label is below in Section 1.3 Labeling.

1.1 RECOMMENDATIONS

Please see labeling below. No action is indicated.

1.2 SIGNATURES

Hua Lillian Zhang, Ph.D.
Reviewer:
Division of Clinical Pharmacology 5

Brian Booth, Ph.D.
Deputy Div Director
Division of Clinical Pharmacology 5

Cc: DDOP: CSO - A Tilley; MTL - **A Farrell**; MO – **M Brave**
DCP-5: Reviewer - **HL Zhang;** DDD & TL - **B Booth;** DD - **A Rahman**

4 Page(s) of Draft Labeling has been Withheld in Full immediately following this page as B4 (CCI/TS)

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/s/

Hua Zhang
2/23/2009 12:00:53 PM
PHARMACIST

Brian Booth
2/23/2009 12:05:55 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 22-160

Drug name:	Oxaliplatin Injection
Generic name:	Oxaliplatin
Formulation:	Solution for Injection
Indication:	Colorectal Cancer
Applicant:	Sicor Pharmaceuticals Inc 19 Hughes Irvine, CA 92618
OCP Division:	Division of Clinical Pharmacology 5
OODP Division:	Division of Drug Oncology Products
Submission Dates:	9-Feb-2007
Primary Reviewer:	Roshni Ramchandani, Ph.D.
Team Leader:	Brian Booth, Ph.D.
Type of Submission:	NDA [505(b)(2)]

This New Drug Application is for Oxaliplatin Injection, 5 mg/ml. This product has the same active ingredient, dosage form, strength, route of administration and conditions of use as the innovator drug ELOXATIN® (oxaliplatin injection).
The applicant has submitted this as a 505(b)(2) application, and identified the innovator's (Sanofi-Aventis') ELOXATIN® as the previously approved drug (under NDA 21-759 and 21-492). The applicant is relying on the findings of safety and effectiveness for ELOXATIN to support the approval of their product.

The applicant's proposed drug product contains lactose, which was present in the innovator's previously marketed lyophilized formulation of ELOXATIN. The applicant's liquid formulation was developed to match the innovator's discontinued lyophilized formulation after re-constitution (see table 1 below). In 2006, the innovator withdrew its lyophilized dosage form of ELOXATIN from the market. A citizen's petition has been filed to verify that the product was not withdrawn from sale due to safety or effectiveness reasons.

Table 1: Comparison of the Composition of SICOR's Oxaliplatin Injection and Sanofi Aventis' formulations of Eloxatin®

INGREDIENTS	SICOR's Formulation	Sanofi Aventis's Formulations	
		Liquid	Lyophilized
Each mL contains:			
Oxaliplatin	5.0 mg	5.0 mg	5.0 mg
Lactose Monohydrate, USP			
Water for Injection, USP			

(b) (4)

The applicant has requested a waiver for evidence of *in vivo* bioavailability/ bioequivalence in accordance with 21 CFR §320.22(b)(1) since this drug product meets the required criteria as follows:

- Oxaliplatin Injection, 5 mg/mL is a parenteral drug product intended for administration by intravenous infusion.

- The applicant's proposed drug product has the same active pharmaceutical moiety, dosage form, strength, route of administration, and conditions of use as the innovator's Eloxatin® Injection (oxaliplatin injection), previously approved under NDA No. 021-759.

- The only difference between the proposed drug product and Eloxatin® Injection is that the applicant's product contains lactose as an excipient. However, the innovator's formulation also contained lactose. After reconstitution the lyophilized dosage form of Eloxatin® is qualitatively and quantitatively equivalent to the applicant's Oxaliplatin Injection (see table 1 above).

- Lactose, as an excipient in drugs for parenteral use, is generally recognized as safe (GRAS).

The change in the excipient - addition of Lactose - represents a pharmaceutical change only. Both the innovator's and applicant's drug product chemical properties would be expected to be identical. This data supports that the applicant's proposed drug product is pharmaceutical equivalent to the innovator's product.

Since the dosage forms are parenteral products and the finished formulations will be pharmaceutically equivalent, SICOR's Oxaliplatin Injection, 5 mg/mL is expected to be bioequivalent to the innovator's Eloxatin® Injection (oxaliplatin injection).

Thus, the biowaiver for the applicant's product is acceptable, from the clinical pharmacology perspective. No additional biopharmaceutics or clinical pharmacology studies are needed.

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/s/

Brian Booth
11/30/2007 11:16:06 AM
BIOPHARMACEUTICS