

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-160

PHARMACOLOGY REVIEW(S)



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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22-160
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: February 9, 2007 (with amendments dated August 29, 2008, and February 11, 18, 25, and February 27, 2009)
PRODUCT: Oxaliplatin Injection
INTENDED CLINICAL POPULATION: Colon/colorectal cancer
SPONSOR: Teva Parenterals Medicines
DOCUMENTS REVIEWED: Electronic submission
REVIEW DIVISION: Division of Drug Oncology Products
PHARM/TOX REVIEWER: Margaret Brower, Ph.D.
PHARM/TOX SUPERVISOR: Haleh Saber, Ph.D.
DIVISION DIRECTOR: Robert Justice M.D.
PROJECT MANAGER: Amy Tilley

Date of review submission to Division File System (DFS): Amended Review:

Amendment to Review

The amended review of March 4, 2009 stated the following nonclinical safety issues which were conveyed to the sponsor in the Complete Response Letter of March 2, 2009:

Your proposed acceptance criteria for (b) (4) (Impurity A) and the (b) (4) (Impurity B) currently exceed ICH Q3B(R2) for the 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.

Response from Sponsor:

On March, 25, 2009, Teva accepted our requirement to lower release and shelf-life acceptance criteria for impurities A and B to meet ICH Q3B(R2) of 0.2% (as stated above). In addition, Teva is currently conducting a pre-clinical bridging study for impurity qualification.

Recommendations:

There are no additional pharmacology/toxicology concerns at this time.

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/s/

Margaret Brower
5/7/2009 02:12:48 PM
PHARMACOLOGIST

Haleh Saber
5/22/2009 09:11:26 AM
PHARMACOLOGIST



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
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PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

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SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: February 9, 2007 (with amendments dated August 29, 2008, and February 11, 18, 25, and February 27, 2009)
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INTENDED CLINICAL POPULATION: Colon/colorectal cancer
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DOCUMENTS REVIEWED: Electronic submission
REVIEW DIVISION: Division of Drug Oncology Products
PHARM/TOX REVIEWER: Margaret Brower, Ph.D.
PHARM/TOX SUPERVISOR: Haleh Saber, Ph.D.
DIVISION DIRECTOR: Robert Justice M.D.
PROJECT MANAGER: Amy Tilley

Date of review submission to Division File System (DFS): Amended Review: March 4, 2009

PHARMACOLOGY/TOXICOLOGY REVIEW

NDA number: 22-160

Review number: 1

Sequence number/date/type of submission: 000/February 9, 2007/505(b)(2) NDA

Information to sponsor: Yes (X) No () *Communicated on March 2, 2009 as part of the CR Letter*

Sponsor and/or agent: Teva Parenterals Medicines, Inc., Irvine, CA

Reviewer name: Margaret Brower, Ph.D.

Office/Division: OODP/DDOP

Review completion date: March 3, 2009 (Amended Review)

Drug:

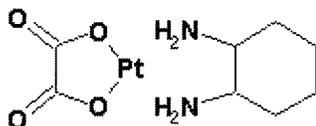
Trade name: Oxaliplatin Injection

Generic name: oxaliplatin

Chemical name: 1, 2-cyclohexanediamine, platinum complex, (1R-trans)-; platinum, (1,2-cyclohexanediamine-N, N')(ethanedioato(2-)-O, O'-, (SP-4-2-(1R-trans))-; Trans-1-diaminocyclohexane oxalatoplatinum

Molecular formula/molecular weight: C₈H₁₄N₂O₄Pt/397.29

Structure:



Relevant NDAs: NDA 21,759, NDA 21,492

Pharmacologic class: Platinum-based drug

Combination therapy: Used in combination with infusional 5-fluorouracil (5-FU)

Indication: Adjuvant treatment of Stage III colon cancer in patients who have undergone complete resection of primary tumor, and treatment of advanced colorectal cancer

Clinical formulation:

Formulation components	Teva/Sicor
Oxaliplatin	5.0mg/mL
Lactose monohydrate, USP	(b) (4)
Water for injection, USP	(b) (4)

Route of administration: intravenous

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Toxicology Issues and Recommendations:

The Teva/Sicor NDA 22,160 differs from the current reference listed drug (RLD) formulation by an addition of (b) (4) of lactose monohydrate/mL. The original Sanofi-Aventis oxaliplatin formulation (RLD) was a lyophilized formulation containing lactose (NDA 21,492, marketed 2002-2004) to be administered in combination with 5-FU/LV. Thousands of patients were treated with the oxaliplatin/lactose formulation in clinical trials at doses ranging from 0.45-200 mg/m². The Sanofi Aventis formulation changed to an aqueous solution (N21,759) in 2005; the lactose formulation was discontinued at this time.

In 2006/2007, Sanofi-Aventis petitioned that the Agency require all applicants for approval of generic and 505(b)(2) formulations referencing Eloxatin solution, containing an acid (other than oxalic acid), a conjugate base, or added sugars such as lactose, to demonstrate that any new compound or impurity resulting from such formulations, do not compromise the safety or efficacy of the drug product.

If impurities are identified which are not within the qualification limit (0.2% for drug product), as described in ICH Q3B(R), or within the end-of-shelf-life specification levels for these impurities in the RLD, the impurities will require further qualification using preclinical studies, or reduction to below qualification limits.

The following impurities of concern were identified in NDA 21,492/21,759 (Sanofi Aventis) and NDA 22,160 (Teva/Sicor):



The chemistry review team has provided a comparison of the end-of-shelf-life specifications of these impurities from the current NDA at [redacted] (b) (4), and the Sanofi Aventis specification for the same impurity profile for Eloxatin (see below). The reference citation for these Eloxatin impurity limits was not documented.

Comparative specifications for impurities:

Impurity	Teva/Sicor NDA 22-160	Sanofi Aventis NDAs 21-492/21-759
(b) (4)		

(b) (4)

All other impurities are within the qualification threshold, as described in ICH Q3B(R), or within the end-of-shelf-life specification levels for these impurities in the RLD.

March 3, 2009 Amendment: FDA General counsel has designated that this 505(b)(2) application cannot refer to impurity specification limits of the RLD, unless these data were included in the product label, or the 505(b)(2) applicant has right of reference. Since these data were not included in the label of the RLD, and Teva does not have right of reference, Teva must either lower the specifications for (b) (4) (Impurity A) and the (b) (4) (Impurity B) to meet ICH Q3B(R2), qualify the impurities preclinically, or provide justification for their levels based on appropriate literature citations.

The following deficiency was added to the CR letter which was conveyed to the sponsor on March 2, 2009:

Your proposed acceptance criteria for (b) (4) (Impurity A) and the (b) (4) (Impurity B) currently exceed ICH Q3B(R2) for the 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.

Labeling: Labeling for a 505(b)(2) must resemble the label of the innovator drug (in this case, Sanofi Aventis's Eloxatin). Changes were made to Teva's PLR to provide information comparable to that presented in the innovator's label. Pharmacology/toxicology changes were incorporated into the Teva PLR in Highlights, and Sections 5.5, 8.1, 12.1, 12.2, and 15, to comply with the label of the RLD.

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/s/

Margaret Brower
3/5/2009 12:13:19 PM
PHARMACOLOGIST

Haleh Saber
3/6/2009 08:48:18 AM
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: **22-160**
SERIAL NUMBER: **000**
DATE RECEIVED BY CENTER: **September 2, 2008**
PRODUCT: **Oxaliplatin Injection**
INTENDED CLINICAL POPULATION: **Colon/colorectal cancer**
SPONSOR: **Teva Parenterals Medicines**
DOCUMENTS REVIEWED: **Electronic submission**
REVIEW DIVISION: **Division of Drug Oncology Products**
PHARM/TOX REVIEWER: **Margaret Brower, Ph.D.**
PHARM/TOX SUPERVISOR: **Haleh Saber, Ph.D.**
DIVISION DIRECTOR: **Robert Justice M.D.**
PROJECT MANAGER: **Amy Tilley**

Date of review submission to Division File System (DFS): February 24, 2009

PHARMACOLOGY/TOXICOLOGY REVIEW

NDA number: 22-160

Review number: 1

Sequence number/date/type of submission: 000/September 2, 2008/505(b)(2) NDA

Information to sponsor: Yes () No (X)

Sponsor and/or agent: Teva Parenterals Medicines, Inc., Irvine, CA

Reviewer name: Margaret Brower, Ph.D.

Office/Division: OODP/DDOP

Review completion date: February 19, 2009

Drug:

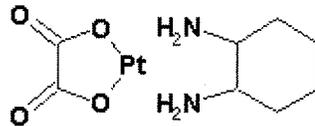
Trade name: Oxaliplatin Injection

Generic name: oxaliplatin

Chemical name: 1, 2-cyclohexanediamine, platinum complex, (1R-trans)-; platinum, (1,2-cyclohexanediamine-N, N')(ethanedioato(2-)-O, O'-, (SP-4-2-(1R-trans))-; Trans-1-diaminocyclohexane oxalatoplatinum

Molecular formula/molecular weight: C₈H₁₄N₂O₄Pt/397.29

Structure:



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Pharmacologic class: Platinum-based drug

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In 2006/2007, Sanofi-Aventis petitioned that the Agency require all applicants for approval of generic and 505(b)(2) formulations referencing Eloxatin solution, containing an acid (other than oxalic acid), a conjugate base, or added sugars such as lactose, to demonstrate that any new compound or impurity resulting from such formulations, do not compromise the safety or efficacy of the drug product.

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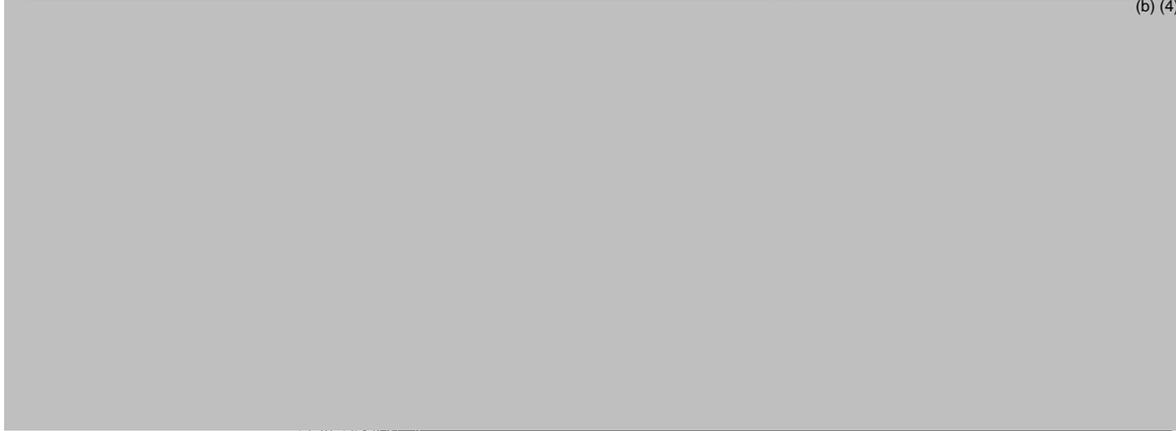
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(b) (4)



(b) (4)

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/s/

Margaret Brower
2/25/2009 09:36:12 AM
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Haleh Saber
2/25/2009 09:44:52 AM
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