CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-160

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	August 7, 2009
From	Robert L. Justice, M.D., M.S.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	22-160
Applicant Name	Teva Parenteral Medicines, Inc.
Date of Current Submission	June 30, 2009, received July 1, 2009
PDUFA Goal Date	September 1, 2009
Proprietary Name / **Established (USAN) Name**	Oxaliplatin Injection/ oxaliplatin
Dosage Forms / Strength	50 mg/10 mL and 100 mg/20 mL
Proposed Indication(s)	1. Adjuvant treatment of stage III colon cancer patients in patients who have undergone complete resection of the primary tumor 2. Treatment of advanced colorectal cancer
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	N/A
Statistical Review	N/A
Pharmacology Toxicology Review	X
CMC Review/OBP Review	X
Microbiology Review	X
Clinical Pharmacology Review	X
DDMAC	N/A
DSI	N/A
CDTL Review	N/A
OSE/DMEPA	X
OSE/DDRE	N/A
OSE/DSRCS	N/A
Other	N/A

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Errors Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

Signatory Authority Review

1. Introduction

This 505(b)(2) application seeks approval of Oxaliplatin Injection, 50 mg/10 mL and 100 mg/20 mL. The application was tentatively approved on May 22, 2009. The current submission was received on July 1, 2009 and requests final approval of the application. The submission states the following:

> On June 30, 2009, we received the final judgment for the entry of an Order of Summary Judgment on non-infringement of U.S. Patent No. 5,338,874. This final judgment disposes of and is final with respect to Sanofi-Aventis' claims of infringement of the '874 patent. In accordance with CFR 314.107(b)(3)(B)(iv), final approval can be granted before the expiration of the 30 month stay if the court decides that the patent is invalid, unenforceable or not infringed. The approval may be made effective on the date the court enters a final order or judgment that the patent is invalid, unenforceable or not infringed. Therefore, we are notifying your office that the final judgment has been entered and we expect to receive the approval letter on the day the final judgment was entered or as soon as administratively possible.

This review will summarize the previous reviews of the application and resolution of the deficiencies.

2. Background

This product differs from Eloxatin (oxaliplatin injection), the reference listed drug, by the addition of (b) (4) of lactose monohydrate/mL. The original Eloxatin formulation was a lyophilized formulation containing lactose but is no longer marketed. This 505(b)(2) application was originally submitted on February 9, 2007. The deficiencies in the December 4, 2007 action letter were as follows:

1. DMF 19,559 was deemed inadequate to support this NDA. A Letter of Deficiencies was sent to the DMF Holder on November 6, 2007. Satisfactory resolution of the Letter of Deficiencies is required for approval of this NDA.

2. Propose specifications for (b) (4), individual and total metallic impurities derived from platinum for the drug substance testing.

3. Reconcile a discrepancy in the proposed acceptance criteria for Impurity C in the drug product listed in "SPECIFICATION SHEET – CHECK USA", NMT (b) (4) to be consistent with the acceptance criteria for Impurity C at NMT (b) (4) in the "SPECIFICATION SHEET – RELEASE USA" and submit the revision to the NDA.

Regarding the carton/container labels:

4. Increase the prominence of the name of the drug "OXALIPLATIN INJECTION."

5. Provide a cautionary statement "Caution: contains cytotoxic agent" in the container and carton labels.

6. Provide separate NDC numbers for each of the vial configurations.

7. Submit a revised package insert identical to the attached version with the following additional revisions:

   a. Remove the capitalization from all the "Oxaliplatin"s.

   b. Provide separate NDC numbers for each of the vial configurations.

The applicant submitted a complete response to the action letter on August 29, 2008. The complete response letter of March 2, 2009 identified the following remaining deficiencies.

Your proposed acceptance criteria for (b) (4) (Impurity A) and the (b) (4) (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.

3. CMC/Device

The Chemistry Review of the first complete response was signed on 2/24/09 and made the following recommendation and conclusion on approvability.

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.

In an update of the Chemistry Review dated 3/2/09 it was noted that all of the DMEPA comments regarding container and carton labeling have been addressed by the applicant and that "approval is recommended from a CMC perspective."

The Chemistry Review of the previous submission provides the following summary of the complete response to our March 2, 2009 action letter.

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

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 of (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.

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

Comment: I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. With an expiration dating period of 12 months the impurity levels are acceptable and do not require further qualification (see below).

4. Nonclinical Pharmacology/Toxicology

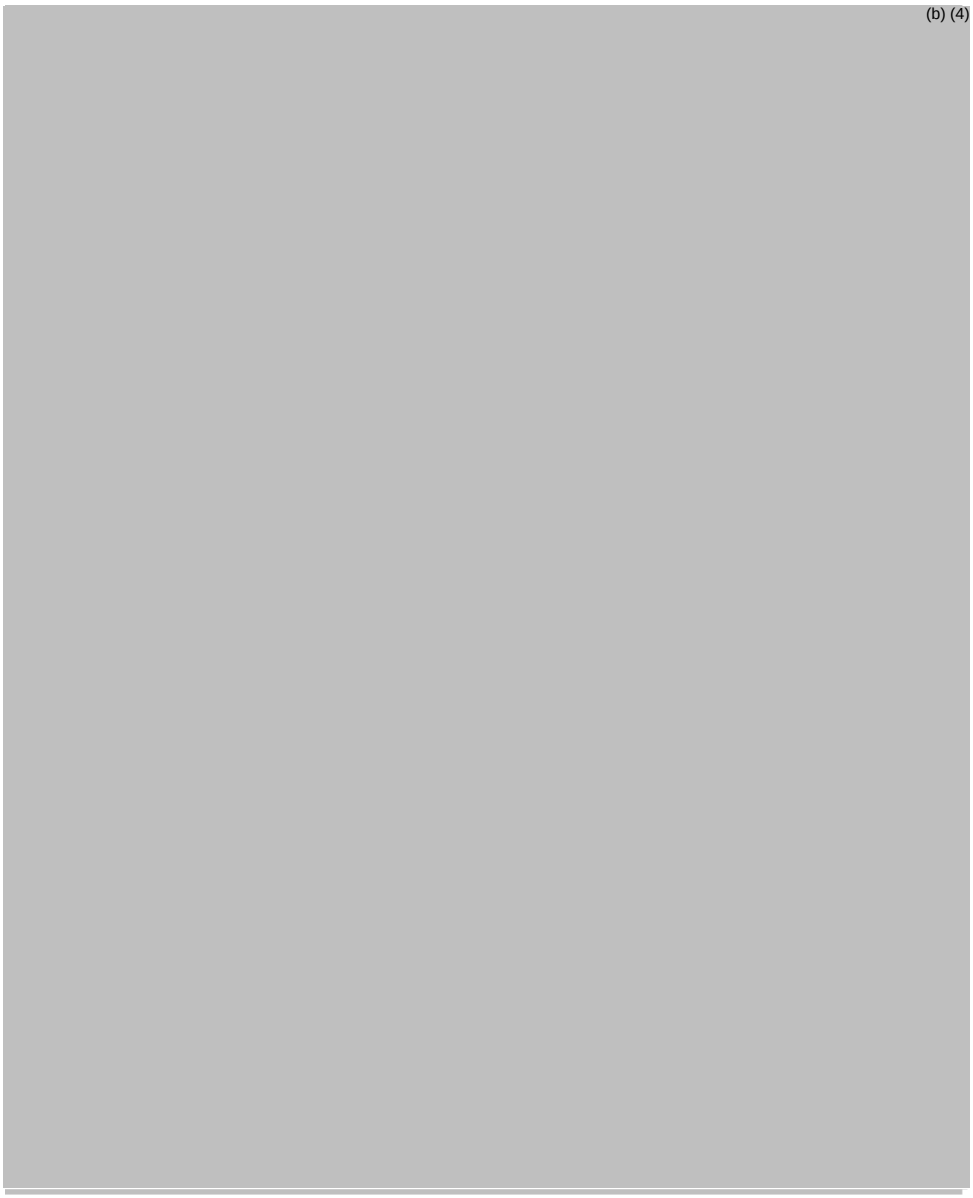
The Pharmacology/Toxicology Review signed 2/25/09 addressed the issues of impurities.

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 (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
[redacted] (b) (4)		
[redacted] (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.

The amended pharmacology/toxicology review of March 4, 2009 concluded the following.

Nonclinical Safety Issues Relevant to Clinical Use: The proposed acceptance criteria for [redacted] (b) (4) (Impurity A) and the [redacted] (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.

Adverse clinical reactions associated with Oxaliplatin Injection are expected to be comparable to those reported for Eloxatin.

The pharmacology toxicology review of the second complete response stated the following.

> **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.

Comment: I concur that the impurity issue has been resolved by the change in release and shelf-life acceptance criteria for impurities A and B and that there are no other pharmacology/toxicology issues that would preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review of this complete response dated 2/23/09 noted that there is no new clinical pharmacology information in this submission.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Not applicable. No clinical efficacy data were submitted.

8. Safety

Not applicable. No clinical safety data were submitted.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

A full pediatric waiver was granted by the PeRC.

11. Other Relevant Regulatory Issues

The following issue related to patent infringement litigation that resulted in the previous tentative approval has been addressed by FDA's Office of General Counsel:

> Whether, under section 505(j)(5)(B)(iii)(I) of the Federal Food, Drug, and Cosmetic Act (the Act), the district court's entry of judgment that the '874 patent is not infringed permits FDA to approve ANDAs that are otherwise eligible for final approval notwithstanding a subsequent stay of the judgment by the Federal Circuit.

Their conclusion is as follows and is documented in a memo by OGD:

> The district court has decided that the '874 patent is not infringed by certain oxaliplatin drug products proposed for approval in ANDAs, and has entered judgment reflecting this decision. Therefore, paragraph IV certifications and litigation associated with the '874 patent are no longer a barrier to approval of these ANDAs.

There are no other unresolved relevant regulatory issues that would preclude approval.

12. Labeling

- Proprietary name: Oxaliplatin Injection
- Physician labeling: The package insert was reviewed for consistency with the RLD label.
- Carton and immediate container labels: On 2/25/09 DMEPA made recommendations for revisions to the carton and container labels. The applicant submitted revised labels which were found to be acceptable to the chemistry reviewers.
- Patient labeling: The patient labeling was reviewed for consistency with the RLD label.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

The risk benefit relationship for Oxaliplatin Injection is the same as that for the RLD.

- Recommendation for Postmarketing Risk Management Activities

None

- Recommendation for Other Postmarketing Study Commitments

None

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

/s/

ROBERT L JUSTICE
08/07/2009