# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**22-160**

# OTHER ACTION LETTER(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-160

**SUSPENSION OF APPROVAL**

Teva Parenteral Medicines, Inc.
Attention: Susan O'Brien
Director, Regulatory Affairs
19 Hughes
Irvine, CA 92618-1902

Dear Ms. O'Brien:

Please refer to your new drug application dated February 9, 2007, received February 9, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) for Oxaliplatin Injection, 50 mg/10 mL and 100 mg/20 mL.

We refer to our August 7, 2009 Approval letter, which approved Oxaliplatin Injection, 50 mg/10 mL and 100 mg/20 mL for adjuvant treatment of stage III colon cancer in patients who have undergone complete resection of the primary tumor and for treatment of advanced colorectal cancer.

The Food and Drug Administration (FDA) is hereby notifying you that approval of this NDA is suspended in accordance with the order issued on August 13, 2009 by the United States Court of Appeals for the District of Columbia Circuit. Approval of this NDA will not become effective until FDA issues a letter lifting the suspension of approval, which is dependent on further order of the court.

Please note that, pursuant to section 505(a) of the Act, no person "shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of the application filed pursuant to subsection 505(b) or (i) [of the Act] is effective with respect to such drug." Also, until the approval is no longer suspended, this drug product will not be listed in the "Orange Book."

If you have any questions, call Amy Tilley, Regulatory Project Manager, at (301) 796-3994.

Sincerely,

*{See appended electronic signature page}*

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

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ROBERT L JUSTICE
08/14/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-160 **NDA APPROVAL**

Teva Parenteral Medicines, Inc.
Attention: Susan O'Brien
Director, Regulatory Affairs
19 Hughes
Irvine, CA 92618-1902

Dear Ms. O'Brien:

Please refer to your new drug application (NDA) dated February 9, 2007, received February 9, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Oxaliplatin Injection, 50 mg/10 mL and 100 mg/20 mL.

We also acknowledge receipt of your submissions dated June 18 and June 30, 2009.

The June 30, 2009 submission constituted a complete response to our May 22, 2009 action letter.

This new drug application provides for the use of Oxaliplatin Injection, 50 mg/10 mL and 100 mg/20 mL for adjuvant treatment of stage III colon cancer in patients who have undergone complete resection of the primary tumor and treatment of advanced colorectal cancer.

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format submitted on March 20, 2009.

We acknowledge your March 20, 2009, submission containing final printed carton and container labels.

If you choose to use a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit any proprietary name to the Agency for our review prior to its implementation.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the

proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Amy Tilley, Regulatory Project Manager, at 301-796-3994**.**

Sincerely,

*{See appended electronic signature page}*

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure: Labeling

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/s/

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ROBERT L JUSTICE
08/07/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-160

Teva Parenteral Medicines, Inc.
Attention: Susan O'Brien
Director, Regulatory Affairs
19 Hughes
Irvine, CA 92618-1902

Dear Ms. O'Brien:

Please refer to your new drug application (NDA) dated February 9, 2007, received February 9, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Oxaliplatin Injection, 50 mg/10 mL and 100 mg/20 mL.

We also acknowledge receipt of your Class 1 Complete Response submission dated March 20, 2009, received March 23, 2009, and your amendment dated April 1, 2009.

Your submission of March 20, 2009 constituted a complete response to our March 2, 2009 action letter.

This NDA provides for the use of Oxaliplatin Injection, 50 mg/10 mL and 100 mg/20 mL for adjuvant treatment of stage III colon cancer in patients who have undergone complete resection of the primary tumor and treatment of advanced colorectal cancer.

We completed our review of this application. It is tentatively approved under 21 CFR 314.105 for use as recommended in the enclosed agreed upon package insert and carton and container labels submitted on March 20, 2009. This determination is contingent upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices of the facilities used in manufacturing and testing of the drug product) and is, therefore, subject to change on the basis of any new information that may come to our attention.

Your application contains certifications to each of the patents under section 505(b)(2)(A)(iv) of the Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of, this drug product under this application ("Paragraph IV certifications"). Section 505(c)(3)(C) of the Act provides that approval of a new drug application submitted pursuant to section 505(b)(2) of the Act shall be made effective immediately, unless an action is brought for infringement of one or more of the patents that were the subject of the paragraph IV certifications. This action must be taken prior to the expiration of forty-five days from the date the notice provided under section 505(b)(3) is received by the patent owner/approved application holder. You notified us that you complied with the requirements of section 505(b)(3) of the Act. In addition, you have notified the Agency that the patent owner and/or approved application holder has initiated a patent infringement suit against you with respect to patents 5290961, 5338874, 5716988, and 5420319 in the United States District Court for the District of New Jersey, and Sanofi-Aventis and Debiopharm, S.A. (collectively, "sanofi-aventis") vs.

Teva Parenteral Medicines, Inc., Teva Pharmaceuticals USA, Inc. and Teva Industries, Ltd., [Civil Action Case No. 3:07-cv-02837]).

Therefore, final approval cannot be granted until:

1. a. expiration of the 30-month period provided for in Section 505(c)(3)(C) beginning on the date of receipt of the 45-day notice required under Section 505(b)(3), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or

   b. the date the court decides that the patent(s) is/are invalid or not infringed as described in section 505(c)(3)(C)(i), (ii), (iii,) or (iv) of the Act, or,

   c. the listed patent(s) has/have expired, and

2. We are assured there is no new information that would affect whether final approval should be granted.

The listed reference drug product upon which you based your application is subject to a period of patent protection and therefore final approval of your application under section 505(c)(3) of the Act (21 U.S.C. 355(c)(3)) may not be made effective until the following patent periods have expired:

| US Patent Numbers | Expiration Date |
|---|---|
| 5290961 | July 12, 2013 |
| 5338874 | October 7, 2013 |
| 5716988 | February 7, 2016 |
| 5420319 | February 9, 2017 |

An expiration dating period of 12 months will be granted for the drug product, when stored under room temperature conditions (25°C ± 2°C/60% RH ± 5% RH).

No more than 60 days prior to August 9, 2016 or when requested, submit an amendment to this application identifying changes, if any, in the conditions under which your product was tentatively approved. This information should include updated labeling, chemistry, manufacturing and controls data, and a safety update.

Failure to submit this amendment will prompt a review of the application that may result in rescission of the tentative approval letter.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

Any significant change in the conditions outlined in this NDA requires our review before final approval may be granted.

Before we issue a final approval letter, this NDA is not deemed approved. If you believe that there are grounds for issuing the final approval letters before August 9, 2016, you should amend your application accordingly.

This product may be considered misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before final approval.

If you choose to use a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit any proprietary name to the Agency for our review prior to its implementation.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

If you have any questions, call Amy Tilley, Regulatory Project Manager, at 301-796-3994.

Sincerely,

*{See appended electronic signature page}*

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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

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/s/
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Robert Justice
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-160

**COMPLETE RESPONSE**

Teva Parenteral Medicines, Inc.
Attention: Rosalie A. Lowe
Director, Regulatory Affairs
19 Hughes
Irvine, CA 92618-1902

Dear Ms. Lowe:

Please refer to your new drug application (NDA) dated February 9, 2007, received February 9, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Oxaliplatin Injection, 50 mg/10 mL and 100 mg/20 mL.

We acknowledge receipt of your amendments dated August 29, 2008, February 11, 18, 25, and 27, 2009.

The August 29, 2008, amendment constituted a complete response to our December 4, 2007, action letter.

We have completed the review of your application, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

## NONCLINICAL

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

Submit your labeling previously submitted on February 18, 2009, per 21 CFR 314.50(l)(1)(i) in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

Your draft carton/container labeling submitted February 27, 2009, is acceptable.

**SAFETY UPDATE**

When you respond to the above deficiency, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

**OTHER**

The listed drug referenced in your application Oxaliplatin Injection of Teva are subject to periods of patent protection. The following patents and expiration dates are currently listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"):

| U.S. Patent Number | Expiration Date |
|---|---|
| 5290961 | January 12, 2013 |
| 5338874 | April 7, 2013 |
| 5716988 | August 7, 2015 |
| 5420319 | August 9, 2016 |

Your application contains certifications to each of the patents under section 505(b)(2)(A)(iv) of the Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of, this drug product under this application ("Paragraph IV certifications"). Section 505(c)(3)(C) of the Act provides that approval of a new drug application submitted pursuant to section 505(b)(2) of the Act shall be made effective immediately, unless an action is brought for infringement of one or more of the patents that were the subject of the paragraph IV certifications. This action must be taken prior to the expiration of forty-five days from the date the notice provided under section 505(b)(3) is received by the patent owner/approved application holder. You notified us that you complied with the requirements of section 505(b)(3) of the Act. In addition, you have notified the Agency that the patent owner and/or approved application holder has initiated a patent infringement suit against you with respect to patent numbers, 5,290,961, 5,420,319, 5,716,988, and 5,338,874 in the United States District Court for the District of New Jersey, and Sanofi-Aventis U.S., LLC, Sanofi-Aventis, and Debiopharm, S.A. (collectively, "sanofi-aventis") vs. Teva Parenteral Medicines, Inc., Teva Pharmaceuticals USA, Inc., and Teva Industries, Ltd., [Civil Action Case No. 3:07-cv-02837]).

Therefore, final approval cannot be granted until:

1. a. expiration of the 30-month period provided for in Section 505(c)(3)(C) beginning on the date of receipt of the 45-day notice required under Section 505(b)(3), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or
   b. the date the court decides that the patent(s) is/are invalid or not infringed as described in section 505(c)(3)(C)(i), (ii), (iii,) or (iv) of the Act, or
   c. the listed patent(s) has/have expired, and

2. We are assured there is no new information that would affect whether final approval should be granted.

In addition, the listed reference drug product upon which you base your application is subject to a period of exclusivity protection and therefore, final approval of your application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective until the period has expired, i.e., November 07, 2009.

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved.

If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (http://www.fda.gov/cder/guidance/2125fnl.htm).

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Amy Tilley, Regulatory Project Manager, at (301) 796-3994.

Sincerely,

*{See appended electronic signature page}*

Robert Justice, M.D.
Division Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

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/s/

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Robert Justice
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-160

Teva Parenteral Medicines, Inc.
19 Hughes
Irvine, CA 92618-1902

Attention: Rosalie A. Lowe
Director, Regulatory Affairs

Dear Ms. Lowe:

Please refer to your new drug application (NDA) dated February 9, 2007, received February 9, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for oxaliplatin 5 mg/mL, 50 mg/10 mL, and (b) (4).

We acknowledge receipt of your submissions dated May 4, 11, and 23, 2007; September 17, 2007; and November 7, 2007.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following:

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.

Regarding the package insert:

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.

Additionally, we refer to your September 17, 2007 submission in which you notified us that Sanofi-Aventis has filed suit against you under 21 CFR 314.107(f)(2), having received your Notice of Certification on May 7, 2007. Therefore, no approval of this application may be effective until November 7, 2009 unless the court extends or reduces the 30 month stay of approval.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Dotti Pease, Regulatory Project Manager, at (301) 796-1434.

Sincerely,
*{See appended electronic signature page}*

Ann Farrell, M.D.
Deputy Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

ENCLOSURE: FDA version package insert

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/s/
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Ann Farrell
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