

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022396Orig1s000**

**OTHER ACTION LETTERS**



NDA 022396

**COMPLETE RESPONSE**

Javelin Pharmaceuticals, Inc.  
c/o Hospira, Inc.  
275 North Field Dr.  
Dept. 0392, Bldg. H2-2  
Lake Forest, IL 60045

Attention: Steven Townsend  
Associate Director, Global Regulatory Affairs

Dear Mr. Townsend:

Please refer to your New Drug Application (NDA) dated December 2, 2009, received December 3, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Dyloject (diclofenac sodium) Injection 37.5 mg/mL.

We acknowledge receipt of your amendments dated November 8, 2011, June 28, July 30, August 26, October 31, November 20, and December 17, 2013.

The June 28, 2013, submission constituted a complete response to our October 1, 2010, action letter.

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

**FACILITY INSPECTIONS AND ASSESSMENT**

1. During a recent inspection of the [REDACTED] <sup>(b) (4)</sup> manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

**LABELING**

2. Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated content of labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

### **SAFETY UPDATE**

When you respond to the above deficiencies, 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/clinical trials 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 trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial 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

### **ADDITIONAL COMMENTS**

We acknowledge the submission of your revised pediatric plan dated October 31, 2013. Your pediatric plan was reviewed by the Pediatric Research Committee (PeRC), and we have the following recommendation:

Amend the pediatric plan to request a deferral of studies for pediatric patients aged birth through 16 years of age. Include proposed dates for protocol submission, study completion, and final report submission.

Revise your pediatric plan to incorporate this recommendation and include it with any resubmission.

### **OTHER**

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. 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 Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

If you have any questions, call Swati Patwardhan, Regulatory Project Manager, at (301) 796-4085.

Sincerely,

*{See appended electronic signature page}*

Rigoberto A. Roca, MD  
Deputy Director  
Division of Anesthesia, Analgesia, and  
Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE:  
Draft Labeling

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RIGOBERTO A ROCA  
12/23/2013



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 022396

**COMPLETE RESPONSE**

Hospira, Inc.  
125 Cambridge Park Drive  
Cambridge, MA 02140

Attention: Roberta Tucker, R.Ph.  
Regulatory Affairs

Dear Ms. Tucker:

Please refer to your New Drug Application (NDA) dated December 2, 2009, received December 3, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Dyloject (diclofenac sodium) Injection.

We acknowledge receipt of your amendments dated December 22, 2009, January 14, March 8, 18 and 23, April 8, 23, 27 and 28, May 6, 25 and 26, June 1, 2, 10 (2), 16 and 17 (2), July 8 (2), 12, 19 and 28, August 11, 19 and 25, September 9, 20, 21 (2), 23, and 27, 2010.

We also acknowledge receipt of your amendments dated September 28 and 29, 2010, which were not reviewed for this action. You may incorporate applicable sections of the amendments by specific reference as part of your response to the deficiencies cited in this letter.

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

**CLINICAL**

1. Data submitted do not support the proposed (b) (4)



**CHEMISTRY, MANUFACTURING AND CONTROLS**

2. [REDACTED] (b) (4)

[REDACTED] (b) (4)

Based on the currently available data provided in the amendment dated September 23, 2010, we are recommending a “For Cause Inspection” of the drug product manufacturer’s facility

[REDACTED] (b) (4)

An inspection must be performed and a satisfactory recommendation issued for all manufacturing sites by the Office of Compliance prior to marketing of this product.

**LABELING**

3. Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

4. Submit draft carton and container labeling revised as follows:

A. Container Labels

i. Ensure the established name is printed in letters that are at least half as large as the letters comprising the proprietary name and has commensurate prominence with the proprietary name taking into consideration typography factors such as the font weight, pursuant to 21 CFR 201.10(g)(2).

- ii. Remove the (b) (4) information, (b) (4) from the principal display panel, as it is not required by small label regulations and crowds the label, making it difficult to read other required product information.
- iii. Revise and increase the prominence of the route of administration statement, 'For IV Use', to read, 'For Intravenous Use Only'.

#### B. Carton Labeling

- i. Ensure the established name is printed in letters that are at least half as large as the letters comprising the proprietary name and has commensurate prominence with the proprietary name taking into consideration typography factors such as the font weight, pursuant to 21 CFR 201.10(g)(2).
- ii. Revise and increase the prominence of the route of administration statement, 'For IV Use', to read, 'For Intravenous Use Only'.
- iii. Remove the statement (b) (4) from the principal display panel as it is duplicative and crowds the principal display panel.
- iv. Include the statement, 'Single-Use Vials, Discard Unused Portion' on the principal display panel.
- v. Relocate the net quantity statement, '25 x 1 mL Vials', to appear away from the strength statement.

#### **SAFETY UPDATE**

When you respond to the above deficiencies, 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:
  - a. Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
  - b. Present tabulations of the new safety data combined with the original NDA data.

- c. Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - d. 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 trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
  4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial 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**

In your Environmental Assessment, the Estimated Introductory Concentrations (EIC) for diclofenac was calculated with the assumption that no diclofenac solution will be wasted because of the discrepancy between the proposed dosing and the proposed formulation. A Finding of No Significant Impact (FONSI) was granted based on your calculated EIC and the above described assumption. At this time, the proposed formulation for your product is a 37.5 mg/mL solution per 2mL glass vial. If you pursue another dosing regimen that results in excessive overage, a new environmental assessment would be required.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. 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's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

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 Kathleen Davies, Senior Regulatory Project Manager, at (301) 796-2205.

Sincerely,

*{See appended electronic signature page}*

Larissa Lapteva, MD MHS  
Deputy Director for Safety  
Division of Anesthesia and Analgesia Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE:  
Labeling

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

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

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/s/

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LARISSA LAPTEVA  
10/01/2010