



NDA 202245/S-005

**SUPPLEMENT APPROVAL  
RELEASE FROM POSTMARKETING REQUIREMENTS  
NEW POSTMARKETING REQUIREMENT**

West-Ward Pharmaceuticals Corp.  
1809 Wilson Road  
Columbus, OH 43228

Attention: Sarah A. Smith  
Director, Drug Regulatory Affairs and Labeling

Dear Ms. Smith:

Please refer to your Supplemental New Drug Application (sNDA) dated and received May 18, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Codeine Sulfate Oral Solution.

We also refer to our letter April 20, 2017, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Codeine Sulfate Oral Solution. This information pertains to the risk of life-threatening respiratory depression in children associated with use of codeine-containing products and the risk of life-threatening respiratory depression in breastfed infants whose mothers were treated with codeine-containing products.

This supplemental new drug application provides for revisions to the labeling for Codeine Sulfate Oral Solution, consistent with our April 20, 2017, letter, as well as additional revisions to the Package Insert.

**APPROVAL & LABELING**

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

**WAIVER OF HIGHLIGHTS SECTION**

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

## **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. 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 provide appropriate annotations, including supplement number(s) and annual report date(s).

## **RELEASE FROM POSTMARKETING REQUIREMENT**

FDA previously determined that you were required to conduct the following postmarketing studies in our letter dated June 30, 2011:

- 1784-1      Deferred pediatric study of pharmacokinetics and safety under PREA for the treatment of mild to moderately severe pain when the use of an opioid analgesic is appropriate in pediatric patients ages 2 to 17 years.

Final Protocol Submission:              December 2011  
Final Report Submission:                 March 2014

- 1784-2      Deferred pediatric study of pharmacokinetics and safety under PREA for the treatment of mild to moderately severe pain when the use of an opioid analgesic is appropriate in pediatric patients ages one month to 2 years.

Final Protocol Submission:              September 2014  
Final Report Submission:                 December 2016

We have determined that you are released from the above postmarketing requirements because, with the approval of this supplement, Codeine Sulfate Oral Solution is contraindicated in children less than 12 years old, and the use of Codeine Sulfate Oral Solution should be avoided in 12 to 18 year old patients who have risk factors that may increase their sensitivity to the respiratory depressant effects of Codeine Sulfate Oral Solution.

The above postmarketing requirements will be replaced by the new postmarketing requirement as described below:

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Your deferred pediatric study required under section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81(b)(2)(vii) and section 505B(a)(3)(C) of the FDCA. This required study is listed below.

1784-5            To study the pharmacokinetics and safety of codeine for the management of mild to moderate pain where treatment with an opioid is appropriate and for which alternative treatments are inadequate in pediatric patients ages 12 to less than 17 years.

Final Protocol Submission: 02/2018  
Study Completion: 05/2020  
Final Report Submission: 11/2020

For the required PK and safety studies in pediatric patients 12 to less than 17 years of age, you must modify the enrollment criteria to exclude patients in that age range who have risk factors that may increase their sensitivity to the respiratory depressant effects of codeine such as obesity, obstructive sleep apnea, and other respiratory conditions, as described in the prescribing information.

Submit the protocol(s) to your IND 075764, with a cross-reference letter to this NDA.

Reports of this required pediatric postmarketing study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

## **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager  
FDA/CDER  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

## **REPORTING REQUIREMENTS**

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 Mark Liberatore, PharmD; Safety Regulatory Project Manager, at (301) 796-2221.

Sincerely,

*{See appended electronic signature page}*

Judith A. Racoosin, M.D., M.P.H.  
Deputy Director for Safety  
Division of Anesthesia, Analgesia, and  
Addiction Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE:  
Content of Labeling

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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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JUDITH A RACOOSIN  
08/29/2017