CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

202245Orig1s000

Trade Name: Codeine Sulfate

Generic Name: Codeine Sulfate

Sponsor: Roxane Laboratories

Approval Date: 06/30/2011

Indications: for the management of mild to moderately severe pain where the use of an opioid analgesic is appropriate.

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202245

NDA APPROVAL

Roxane Laboratories
1809 Wilson Road
Columbus, Ohio 43228

Attention: Elizabeth Ernst
Director, Drug Regulatory Affairs and Medical Affairs

Dear Ms. Ernst:

Please refer to your New Drug Application (NDA) dated and received September 27, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Codeine Sulfate Oral Solution 30 mg/5mL.

We acknowledge receipt of your amendments dated October 21, 2010, and January 6 and 14, February 4 and 23, March 10, 18, and 30, April 6, 12, and 27, May 5, 12, 26 (2) and 27, and June 6, 8, 9, and 21, 2011.

This new drug application provides for the use of Codeine Sulfate Oral Solution, 30 mg/5 mL, for the management of mild to moderately severe pain when the use of an opioid analgesic is appropriate.

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

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, Medication Guide). 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/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your June 21, 2011, submission containing final printed carton and container labels.

PROPRIETARY NAME

If you intend to have 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 a request for a proposed proprietary name review. (See the guidance for industry titled, "Contents of a Complete Submission for the Evaluation of Proprietary Names", at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

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.

We are waiving the pediatric study requirement for ages 0 to 1 month because there is evidence strongly suggesting that the drug product would be ineffective or unsafe in this pediatric group because the metabolic pathway for codeine is not mature.

We are deferring submission of your pediatric study for ages one month to 17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of this postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

1784-1 Deferred pediatric study of pharmacokinetics and safety under PREA for the management 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, safety and efficacy under PREA for the management 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

Submit clinical protocols to your IND for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. Reports of this/these required pediatric postmarketing studies 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.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

1784-3 Submit a validated method for quantitative monitoring of the drug product color and update the drug product specifications with data-based acceptance criteria.

The timetable you submitted on May 27, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission: July 8, 2011

1784-4 Provide systematic release and stability data for the drug product, collected according to the updated specifications, and submit as a prior-approval supplement. Include analysis of release and stability data for color, pH, content of ascorbic acid, and the content of codeine sulfate. Provide a statistical evaluation of the observed changes for each of these attributes and propose data-reflecting acceptance criteria for drug product color, pH and the content of ascorbic acid. Submit revised drug product specifications and stability protocol with references to the validated analytical methods and corresponding, data-based acceptance criteria.

The timetable you submitted on June 6, 2011, states that you will conduct this study according to the following schedule:

Final Report Submission: September 30, 2012

Submit chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

In our letter dated December 6, 2010, we notified you that a risk evaluation and mitigation strategy (REMS) is required for Codeine Sulfate Oral Solution to ensure the benefits of the drug outweigh the risks of medication errors, which may result in life-threatening overdoses. We indicated that your REMS must include a Medication Guide and a timetable for submission of assessments of the REMS.

We acknowledge receipt of your submission dated January 6, 2011, of a proposed REMS. We have determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208.1. Therefore, it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of DRUG outweigh its risks. Therefore, a REMS for Codeine Sulfate Oral Solution is not required. We will notify you if we become aware of new safety information and make a determination that a REMS is necessary.

We remind you that the Medication Guide will be part of the approved labeling in accordance with 21 CFR 208.

PROMOTIONAL MATERIALS

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 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, 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 http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

EXPIRATION DATING PERIOD

An expiration dating period of 18 months is granted to the Codeine Sulfate Oral Solution, 30 mg/5 mL, stored at controlled room temperature, 20ºC to 25°C (68ºF to 77°F), with excursions permitted between 15°C and 30°C (between 59°F and 86°F), protected from light and moisture. The drug product must be used within 40 days from the first opening of the container closure.

METHODS VALIDATION

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

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

Sincerely,

{See appended electronic signature page}

Sharon Hertz, M.D.
Deputy Division Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

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

/s/

SHARON H HERTZ
06/30/2011