CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202245Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, M.D.
Subject	Deputy Division Director Summary Review
NDA/BLA # **Supplement #**	202245/N-000
Applicant Name	Roxane Laboratories, Inc.
Date of Submission	September 27, 2010
PDUFA Goal Date	July 27, 2011
Proprietary Name / **Established (USAN) Name**	Codeine Sulfate Oral Solution
Dosage Forms / Strength	Oral Solution 30 mg/5 mL
Proposed Indication(s)	Codeine sulfate is an opioid analgesic indicated for the management of mild to moderately severe pain where the use of an opioid analgesic is appropriate.
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Elizabeth Kilgore, M.D.
Statistical Review	None
Pharmacology Toxicology Reviews	Marcus Delatte, Ph.D., Dan Mellon Ph.D.
Clinical Pharmacology Reviewers	Sheetal Agarwal, Ph.D., Yun Xu, M.D., Ph.D.
CMC Reviews	Eugenia Nashed, Ph.D., Prasad Peri, Ph.D.
DDMAC	Mathilda Fienkeng, Twyla Thompson
CSS	Alicja Lerner, M.D., Michael Klein, Ph.D.
DMEPA	Richard Abate, R.Ph, M.S, Melina Griffis, R.Ph., Carol Holquist, R.Ph.
DRISK	Steve L. Morin, R.N., MSN, CWOCN, LaShawn Griffiths, R.N., MSHS-PH, BSN
DSI, Bioequivalence Branch	Charles R. Bonapace, Pharm.D., Michael Skelly, Ph.D.

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication ErrorsPrevention
DRISK = Division of Risk Management
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader

1. Introduction

This is an application for a new codeine sulfate oral solution, 30 mg/5 mL. No new clinical efficacy or safety studies were submitted; the application relies the Agency's prior findings of safety and efficacy for NDA 085055, Tylenol with Codeine, on published literature and information used to support another of the applicant's products, NDA 22-402 codeine sulfate tablets. One new pharmacokinetic study was submitted in support of this application.

2. Background

NDA 022-402 was the first single ingredient codeine sulfate, approved in 2009 based on the Agency's prior findings of efficacy for NDA 085055, Tylenol with Codeine, and based on a review of studies of codeine in the literature.

3. CMC/Device

Drug Substance

Codeine sulfate trihydrate is manufactured by Covidien/Mallinckrodt St. Louis, Missouri, with two referenced DMFs, both of which have an adequate status.

As described by Dr. Peri, the drug substance specifications have "acceptable controls for description, identification (ID), specific rotation, acidity, (b) (4) (b) (4) readily carbonizable substances, (b) (4), limits on morphine, heavy metals, microbial limits, residual solvents, related compounds, and assay. Note that (b) (4) is controlled at NMT (b) (4) which was found to be acceptable by the Pharm Tox team."

Drug Product

The drug product is an oral solution of codeine sulfate with (b) (4) and manufactured by Boehringer Ingelheim Roxane, Inc. in Columbus, OH.. The formulation contains approximately (b) (4) sorbitol, (b) (4) glycerine, (b) (4) (b) (4) ascorbic acid, (b) (4) citric acid, (b) (4) sucralose, sodium benzoate and EDTA as (b) (4) There is also artificial coloring (FD&C Yellow #6 and Red #40) and orange flavoring.

The product is packaged in 500 mL PET amber bottles with a child resistant closure. Five oral calibrated syringes (5 mL) and 5 mL measuring cup are co-packaged in the same carton.

An acceptable EER is available for the manufacturing facilities as of Jan 24, 2011.

There were numerous deficiencies in the NDA application, addressed over the review cycle in a series of information requests as noted by Dr. Nashed. Dr. Nashed concluded that the deficiencies were resolved adequately except for a change in color and pH during storage conditions. These changes do not impact the assay of the active drug and do not result in a safety concern. The applicant has agreed to the following post marketing commitment to address this issue.

- A validated method for quantitative monitoring of the drug product color and update the drug product specifications with data-based acceptance criteria by July 8, 2011.

- Adequate systematic release and stability data for the drug product, according to the updated specifications, and submit in a prior-approval supplement by September 30, 2012. The submission will include analysis of release and stability data for color, pH, content of ascorbic acid, and the content of codeine sulfate. Additionally, the applicant committed to providing a statistical evaluation of the observed changes for each of these attributes and proposes data-reflecting acceptance criteria for drug product color, pH and the content of ascorbic acid. They will also revise, as needed, drug product specifications and stability protocol with detailed references to the validated analytical methods.

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. An expiration dating period of 18 months is established based on the provided stability data. There are no outstanding issues that preclude approval.

4. Nonclinical Pharmacology/Toxicology

The applicant has not conducted any new nonclinical pharmacological or toxicological studies in support of this application and is relying on similar material used to support NDA 022-402 which includes published nonclinical studies. There are no novel excipients or levels of excipients that require safety qualification. Although the daily exposure to several excipients is greater than the Maximum Potency Listed in the Inactive Ingredient Database (IID), adequate coverage for the MTDD was identified via cross reference with the Drug Product Reference File.

For this drug product, it was determined that a reasonable MDD is 360 mg/day. With the exception of one impurity, (b) (4) all specifications for the drug substance are in accordance with ICHQ3A(R2), including (b) (4) an impurity that contains (b) (4). The impurity (b) (4) was previously qualified as non-genotoxic by the Applicant and therefore can be regulated as per ICHQ3A(R2). Adequate safety justification for the (b) (4) specification was provided in this NDA with studies originally submitted to NDA 022-402, and reviewed by Dr. Delatte who found the proposed specification of NMT (b) (4) to be acceptable. Drug product specifications were also deemed acceptable from a safety perspective, as they were in accordance with ICHQ3B(R2).

Dr. Delatte reviewed the results of extractable and leachable studies using the container closure system. While several peaks were detected in the extractable studies, none were detected in the leachables study. Therefore, there are no nonclinical safety concerns with the proposed drug product container closure system.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology

One clinical pharmacology study was submitted in support of this application, a relative bioavailability study compared to codeine sulfate tablets, NDA 22-402, that demonstrated bioequivalence. As noted by Dr. Agarwal, the formulation has less than (b) (4) sorbitol, an amount not expected to have an interaction with food, and so a food effect study was not performed. Moreover, since the test product is bioequivalent to the reference product under fasted conditions, food effect from the reference product codeine sulfate tablets can be extrapolated to the test product codeine sulfate solution. As indicated in the labeling of the reference product, codeine sulfate tablets, (b) (4)

The primary metabolic pathway for codeine is via CYP2D6 and the primary active metabolite is morphine. The labeling for this product reflects the labeling for NDA 22-402.

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

NA

7. Clinical/Statistical-Efficacy

Codeine is a drug substance that has been present in analgesics in combination with a non-narcotic analgesic for decades. This application represents the second single entity codeine product submitted for FDA approval. Support for efficacy is based on the Agency's prior finding of efficacy for codeine sulfate oral tablets (NDA 022-402) which referenced the prior findings for Tylenol #3 (ANDA 085-055) and information in the literature.

8. Safety

Safety is based on the Agency's prior findings of safety for NDA 022-402. Dr. Kilgore reviewed the safety data from the pharmacokinetic study and found nothing unexpected.

9. Advisory Committee Meeting

No advisory committee was convened for this application as the drug is not a new molecular entity and there were no novel questions or problems.

10. Pediatrics

In order to comply with the Pediatric Research Equity Act (PREA), the Applicant submitted a pediatric plan. The plan is identical to that submitted with NDA 022-402 (codeine tablets). The plan includes PK, safety and efficacy studies in pediatric patients from age one month to two years, and PK and safety in pediatric patients ages 2 to 17 years. As per the current Division policy, efficacy findings from adults may be extrapolated to pediatric patients over the age of two years. Studies in pediatric patients under the age of one month are waived due to the timing of the development of the metabolic pathway for codeine, and the inability of patients less than one month of age to metabolize codeine.

The Applicant requested deferral of pediatric studies for Codeine Sulfate Oral Solution 30 mg/5mL for the following pediatric populations because the product was ready to be approved in adults:

- Infant (1 month to 2 years)
- Children (2 to 12 years)
- Adolescent (12 years to < 16 years)

The Applicant's proposed pediatric plan with timelines is shown below:

Table 1. Proposed Codeine Pediatric Assessment Timelines

Codeine	Final Protocol	FDA Comments	First Patient In	Last Subject Out	Final Report
Safety and PK Study for peds from 2 to 17	1 Dec 2011	1 Mar 2012	1 Sep 2012	1 Sep 2013	1 March 2014
Safety and PK Study for peds under 2	1 Dec 2011	1 Mar 2012	1 Sep 2012	1 Sep 2013	1 March 2014
Safety and Efficacy Study for peds under 2	1 Sept 2014[1]	1 Dec 2014	1 Jun 2015	1 Jun 2016	1 Dec 2016

[1]We will require FDA's comments on the results of the under 2 year old PK/Safety study before this protocol (under 2 year old Safety and Efficacy study) can be finalized. If greater review time is required by the agency, remaining dates for the Safety and Efficacy Study for the under 2 year olds would shift accordingly.

(Source: Applicant's Table, 9//27/10 cover letter)

The Applicant's proposed pediatric plan was presented to the Agency's Pediatric Review Committee (PeRC) on 5/11/11 and was found to be acceptable.

11. Other Relevant Regulatory Issues

There are no outstanding regulatory issues. The regulatory requirements to support this 505(b)(2) application have been adequately addressed.

The Controlled Substance Staff will follow standard databases for any evidence of abuse and diversion of this product

There are no other unresolved relevant regulatory issues.

12. Labeling

No proprietary name was proposed for this product.

DDMAC and DMEPA have reviewed the label and provided comments regarding the removal of promotional and unclear language. Agreement has been reached with the Applicant on the PI, carton and container labels, and on the inclusion of an oral syringe for accurate measuring of the dose. Final labeling was submitted on June 21, 2011.

This product will have a Medication Guide and a Medication Guide-only REMS. However, Although, (b) (4) as the Medication Guide alone is sufficient to address concerns about medication errors and proper dosing of this oral solution opioid.

The Controlled Substance Staff is in agreement with the proposed drug abuse and dependence section of the label.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval

- Risk Benefit Assessment

There is adequate evidence of efficacy and safety to support approval of codeine sulfate immediate-release tablets.

- Recommendation for Postmarketing Risk Management Activities

None

- Recommendation for other Postmarketing Study Requirements

  The following studies are required to fulfill the requirements under the Pediatric Research Equity Act:

  1. Deferred safety and pharmacokinetic (single and multiple dose) study under PREA for codeine sulfate in pediatric patients with mild to moderately severe pain in pediatric patients 2 - 17 years old.

  2. Deferred efficacy, safety and pharmacokinetic (single and multiple dose) study under PREA for codeine sulfate in pediatric patients with mild to moderately severe pain in pediatric patients 1 month - 2 years old.

The Applicant has agreed to the following CMC commitments:

1. To develop a validated method for quantitative monitoring of the drug product color and update the drug product specifications with data-based acceptance criteria by July 8, 2011.

2. 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.

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/s/

SHARON H HERTZ
06/30/2011