

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-402

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, M.D.
Subject	Deputy Division Director Summary Review
NDA/BLA #	22-402/N000
Supplement #	
Applicant Name	Roxane Laboratories, Inc.
Date of Submission	July 2, 2008
PDUFA Goal Date	August 2, 2009
Proprietary Name / Established (USAN) Name	Codeine Sulfate Tablets/ Codeine Sulfate Tablets
Dosage Forms / Strength	Oral tablet, 15 mg, 30 mg and 60 mg
Proposed Indication(s)	The proposed indication for codeine sulfate tablets is the treatment of mild to moderately-severe acute pain in adults.
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted	
OND Action Package, including:	
CDTL Memo	Ellen Fields, M.D., M.P.H.
Medical Officer Review	Carolyn Yancey, M.D.
Statistical Review	None
Pharmacology Toxicology Reviews	Marcus Delatte, Ph.D. Dan Mellon Ph.D.
Biopharmaceutics Reviewers	Sheetal Agarwal, Ph.D. Suresh Doddapaneni, Ph.D.
CMC Reviews	Eugenia Nashed, Ph.D. Ali Al Hakim, Ph.D.
DDMAC	Mathilda Fienkeng Sangeeta Vaswani
DSI	Jacqueline A. O'Shaughnessy, Ph.D. Gopa Biswas, Ph.D.
CSS	James Hunter, R.Ph., M.P.H. Silvia Calderon, Ph.D. Michael Klein, Ph.D.
DMEPA	Kristina Armwine Carol Holquist

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

Signatory Authority Review Template

1. Introduction

As a result of recent efforts by the Office of Compliance to have manufacturers of unapproved marketed products submit NDAs or remove their product from the market, the Applicant has submitted this 505(b)(2) application for codeine sulfate.

2. Background

At the time of submission of this application, there were no approved products that contained codeine alone. There were numerous approved codeine combination products listed in the Orange Book, including a number of codeine and acetaminophen combination products indicated for the treatment of mild to moderate pain. Based on a review of the literature conducted by the Applicant, it was agreed that no clinical efficacy or safety trials would be necessary and that there appeared to be adequate evidence of efficacy and safety for use in adults based on the Agency's prior findings for the codeine acetaminophen combination products and information about codeine alone in the literature. However, there was not adequate information to support pediatric use and therefore, the applicant would need to conduct pediatric studies under the requirements of the Pediatric Research Equity Act. As the product was already on the market, and the application would be submitted in a relatively short period of time, the pediatric studies would most likely be deferred.

3. CMC/Device

The codeine drug substance is manufactured by _____ with two referenced DMFs, both of which have an adequate status. The drug product is manufactured by _____ The dosage strengths, 15 mg, 30 mg and 60 mg, are not compositionally proportional.

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As noted by Dr. Nashed, there were numerous deficiencies in the NDA application, including missing information on moisture content, hardness, and friability and an adequate method for dissolution testing of the tablets. In response to requests from the Agency, the applicant has implemented testing for the noted attributes and proposed interim acceptance criteria due to limited available data. An agreement was reached with the Applicant to collect additional data within the first 2.5 years of manufacturing and submit it in a prior approval supplement (PAS) by July 1, 2012, in order to improve the interim acceptance criteria for dissolution, hardness and friability. This will consist of dissolution profile data generated for a minimum of 20 production batches (first 10 batches for the 15 mg tablets and first 5 batches for each of the 30 mg and 60 mg tablets) during release and stability testing of commercial drug product. The dissolution profiles will include adequate number of data points to allow for comparison of the profiles, e.g., 10 min, 15 min, 30 min and 45 min. A statistical evaluation will be provided

comparing batch to batch variability, between different drug product strengths and within the same batch during stability storage, sorted by the type of container closure. Data for hardness and friability generated during release and stability testing of commercial drug product tablets will be submitted with a statistical evaluation of batch to batch variability, between different drug product strengths and within the same batch during stability storage, sorted by the type of container closure will be provided.

Dr. Nashed also notes that any extension of drug product expiry period beyond 24 months may be accomplished only *via* a prior approval supplement with adequate supporting data. The drug product expiry period may be extended to 24 months based on acceptable stability data collected according to the approved stability protocol, in accord with 21 CFR 314.70.

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. The overall EER status for this NDA is acceptable (AC) as of Mar 9, 2009. The supporting DMFs have adequate status as of Jul 7, 2009. Stability testing supports an expiry of 18 months. There are no outstanding issues that preclude approval, but additional data must be submitted following approval.

4. Nonclinical Pharmacology/Toxicology

The applicant had intended to rely on the Agency's prior findings of safety for Tylenol with Codeine No. 3 and literature and did not submit any new data from nonclinical studies. There are no novel excipients or levels of excipients that require safety qualification.

However, the proposed specification for one drug substance impurity, codeine methyl ether (CME), is NMT _____ which exceeds the ICH Q3A(R2) qualification threshold. CME is a known impurity of codeine, but has a structural alert as an α,β unsaturated ketone. No safety qualification was submitted with this application. Safety qualification will be required; however, it is likely that this substance has been present in most products for some time, and as it has no known toxicity, these data can be provided to the application following approval. Adequate safety qualification must include a minimal genetic toxicology screen consisting of two *in vitro* genetic toxicology studies with the isolated impurity, tested up to the limit dose for the assay and repeat-dose toxicology of 90-days duration to support the proposed _____ indication.

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b(4)

One degradant, codeinone, is also an α,β unsaturated ketone and exceeds the limits set by ICH guidance, Q3B(R2). The genetic toxicity of this compound has been evaluated by _____ the drug substance manufacturer. Upon initial review, concern was expressed that the *in vitro* chromosomal aberration assay considered negative by _____, was not an adequate study due to excessive chromosomal condensation at higher concentrations. However, with further review by Dr. David Jacobson-Kram, the associate Director of Pharmacology Toxicology, the studies are considered valid, as Dr. Jacobson-Kram considered the excessive chromosomal condensation to be evidence of toxicity and that the highest concentrations tested in the completed assay reflect the maximum feasible concentrations.

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b(4)

Therefore, codeinone has been adequately tested and considered to be a non-genotoxic impurity.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval and that there are studies that must be conducted following approval.

5. Clinical Pharmacology/Biopharmaceutics

Five clinical pharmacology studies were submitted in support of this application. Dose proportionality was demonstrated across the three tablet strengths. The effect of a high fat meal was assessed. There was a 50% increase in the median T_{max}, from 1.00 h to 1.54 h and an 11% decrease in C_{max}, however, the 90% confidence intervals for C_{max}, AUC(0-t), and AUC(inf) were within the 80% to 125% equivalence window. Dosing can occur without regard to the fed or fasted state. Steady state occurs after three days of dosing every four hours. A comparison of the pharmacokinetics of codeine sulfate immediate-release tablets and Tylenol #3 found the codeine levels to be bioequivalent in AUC and C_{max} under fasted conditions. No formal studies were conducted in special population in support of this NDA. However, the applicant has included language similar to that already in Tylenol #3 for the package insert.

The primary metabolic pathway for codeine is via CYP2D6 and the primary active metabolite is morphine.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics 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 first codeine-only product. Support for efficacy is based on the Agency's prior finding of efficacy for codeine in Tylenol #3 and information in the literature. Additional data beyond the finding of efficacy for codeine in combination with acetaminophen was felt to be necessary as there are no previous codeine-only products approved in the U.S. Dr. Fields has summarized the literature that was relevant to support a finding of efficacy for codeine alone. As she notes, there are limitations in using literature references to support a finding of efficacy including a lack of access to the raw data. However, there were several studies that were adequate in design to assess the efficacy of codeine and the results from the five studies highlighted in Dr. Fields' review are

consistent and demonstrate the superiority of 60 mg of codeine over placebo in a variety of clinical settings.

8. Safety

Safety is based on the Agency's prior findings of safety for codeine in Tylenol #3.

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

The following pediatric plan was submitted:

1. Objective: to evaluate the efficacy, safety, and pharmacokinetics (after single and multiple-doses) of immediate-release codeine sulfate in a pediatric population with _____ An age-appropriate formulation will be used for the younger pediatric subjects. b(4)
2. Three (3) studies will be conducted with subjects divided into the following age groups: 1 month – 2 years, 2 years – 12 years and 12 years - _____. b(4)
3. Efficacy studies will be designed as superiority trials.

A deferral for the pediatric studies was requested until after approval of codeine for the adult indication. The estimated timeline is as follows:

- Study #1 November 2009 April 2010 October 2011
- Study #2 January 2010 June 2010 December 2011
- Study #3 May 2010 October 2010 April 2012

The Pediatric Plan was presented to the Pediatric Research Committee on March 11, 2009 and concurrence was obtained from the committee at that time.

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 is in agreement that Codeine sulfate tablets should remain subject to the controls imposed by Schedule II of the Controlled Substances Act, as proposed by the Applicant.

There are no other unresolved relevant regulatory issues

12. Labeling

The label was submitted in PLR format and is under review at this time. No proprietary name was proposed for this product.

DDMAC and DMETS have reviewed the label and provided comments regarding the removal of promotional and unclear language.

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 Commitments**

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

1. 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 12 - 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 2 - 12 years old.
3. 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 following studies are required to fulfill the nonclinical pharmacology and toxicology commitment for the drug substance impurity codeine methyl ether:

4. Conduct an in vitro genetic toxicology study to detect point mutations with the isolated drug substance impurity codeine methyl ether, tested up to the limit dose for the assay.

5. **Conduct an in vitro genetic toxicology study to detect chromosome aberrations with the isolated drug substance impurity codeine methyl ether, tested up to the limit dose for the assay.**
6. **Conduct a 90-day repeat dose toxicology study in a single species with the isolated drug substance impurity codeine methyl ether.**
7. **Submit a prior approval supplement with the final, data-reflecting regulatory specifications for dissolution, hardness and friability. The supplement will include data as outlined below.**

The following data must be submitted to fulfill the CMC commitment:

- a. **Dissolution profile data generated during release and stability testing of commercial drug product, for a minimum of 20 production batches, i.e., first 10 batches of the 15 mg tablets and first 5 batches of each of the 30 mg and 60 mg tablets. The dissolution profiles will include adequate number of data points to allow comparison of the profiles, e.g., 10 min, 15 min, 30 min and 45 min. A statistical evaluation of batch to batch variability, between different drug product strengths and within the same batch during stability storage, sorted by the type of container closure, will be provided.**
- b. **Available data for hardness and friability generated during release and stability testing of commercial drug product tablets. A statistical evaluation of batch to batch variability, between different drug product strengths and within the same batch during stability storage, sorted by the type of container closure will be provided.**

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/s/

Sharon Hertz
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MEDICAL OFFICER