# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**22-402**

## OTHER REVIEW(S)

**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology**

| | |
|---|---|
| Date: | July 2, 2009 |
| To: | Bob Rappaport, M.D., Director<br>Division of Analgesia, Anesthesia and Rheumatology Products |
| Through: | Denise Toyer, Pharm.D., Deputy Director<br>Carol Holquist, R.Ph., Director<br>Division of Medication Error Prevention and Analysis |
| From: | Kristina C. Arnwine, Pharm.D., Team Leader<br>Division of Medication Error Prevention and Analysis |
| Subject: | Labeling Review |
| Drug Name: | Codeine Sulfate Tablets, USP, 15 mg, 30 mg, and 60 mg |
| Application Type/Number: | NDA 22-402 |
| Applicant: | Roxane Laboratories, Inc. |
| OSE RCM #: | 2008-1131 |

**CONTENTS**



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## EXECUTIVE SUMMARY

The results of the Label and Labeling Risk Assessment found that the similaritv of the product trade dress, lack of prominence of strength and established name, in addition to [redacted] b(4)

This risk can be addressed and mitigated prior to drug approval if corrective measures are taken prior to approval. We provide recommendations in Section 6 that aim at reducing the risk of this type of error.

## 1 BACKGROUND

### 1.1 INTRODUCTION

This review was written in response to a request from the Division of Anesthesia, Analgesia and Rheumatology Products to evaluate the proposed labels and labeling for Codeine Sulfate Tablets, USP, 15 mg, 30 mg and 60 mg.

### 1.2 REGULATORY HISTORY

This application was filed as a (505)(b)(2) standard review for the use of Codeine Sulfate Tablets, USP. The reference listed drug serving as the basis for this application is Tylenol with Codeine No. 3®, ANDA 85-055 by Ortho McNeil Janssen. This formulation is unapproved and has been marketed since the 1980's under the name Codeine Sulfate Tablets, USP, 15 mg, 30 mg and 60 mg.

### 1.3 PRODUCT INFORMATION

Codeine Sulfate Tablets, USP, are indicated for the relief of mild to moderately severe pain. The usual adult dose is 15 mg to 60 mg up to every four hours as needed. Doses above 60 mg may fail to give commensurate pain relief, and may be associated with an increased incidence of undesirable side effects.

Codeine is supplied in 15 mg, 30 mg and 60 mg tablets. The 15 mg and 30 mg tablets are supplied in unit dose with 25 tablets per card, and 4 cards per carton. The 30 mg and 60 mg tablets are available in bottles of 100 tablets.

## 2 METHODS AND MATERIALS

This section describes the methods and materials used by medication error prevention staff to conduct a label, labeling, and/or packaging risk assessment. The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis (DMEPA) defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

### 2.1 ADVERSE EVENT REPORTING SYSTEM (AERS)

On July 1, 2009, DMEPA conducted a search of the FDA Adverse Event Reporting System (AERS) database to determine if any medication errors involving Codeine Sulfate Tablets, USP have been reported. The following criteria were used: MedDRA High Level Group Term (HLGT) 'Medication Errors' and the Preferred term (PT) 'Pharmaceutical Product Complaint' with the active ingredient (codeine), and the verbatim term "Codei%". The narratives were searched electronically for the manufacturer "Roxan".

[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

The cases were manually reviewed to determine if medication errors occurred involving the label/labeling and/or nomenclature. Those cases that did not describe a medication error were excluded from further analysis. The cases that did describe a medication error were categorized by type of error. We reviewed the cases within each category to identify contributing factors.

### 2.2 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The package insert and patient package insert labeling is intended to communicate to practitioners and patients, all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because medication error prevention staff analyze reported misuse of drugs, our staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. We use FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

Roxane Laboratories submitted the following Codeine Sulfate Tablets, USP labels and labeling for the Agency's review on July 2, 2008 (see Appendices):

- Container label, 30 mg, 60 mg tablets (Appendix B)
- Blister label, 15 mg, 30 mg tablets (Appendix C)
- Carton labeling, 15 mg, 30 mg tablets (Appendix D)
- Package Insert (PI) (no image)

## 3 RESULTS

### 3.1 ADVERSE EVENT REPORTING SYSTEM (AERS)

The Adverse Event Reporting System (AERS) search retrieved 22 cases involving Codeine Sulfate Tablets, USP marketed by Roxane Laboratories. Of these 22 cases, two cases pertained to this review. Ten cases were eliminated from further analysis because they were related to intentional abuse, overdose or suicide. Another ten cases were eliminated because they related to published literature and review of 612 cited references to obtain information on fatal and tissue concentrations of more than 200 drugs including Codeine. Cause of death was inconclusive but Codeine was included as a suspect drug, and medication errors were not mentioned as being involved in the reasons for the fatalities. The two cases involving medication errors related to selection and dispensing relevant to this review are described below.

> One case was from the VA Medical Center in Portland, Oregon dated March 24, 1995. During the nursing department's review of medication errors over the previous two years, it concluded that the errors made with Roxane products occurred because "the tablets and packaging all look the

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

same." Four drugs were specifically mentioned: Morphine 1.5 mg, Codeine 30 mg, Oxycodone 5mg and Hydromorphone 4 mg. No adverse events had been reported but medication errors had occurred, although those errors were not specified.

The remaining case, dated April 2006, was from a hospital pharmacy. Morphine Sulfate was dispensed by a hospital pharmacist instead of Codeine Sulfate, picked up by a visiting nurse and delivered to the patient. The error was subsequently discovered by the nurse when the patient became lethargic and required hospitalization. The pharmacist had erroneously dispensed the Morphine from stock due to misreading the label because "the Morphine and Codeine tablets and bottle labeling looked identical and were side-by-side on the shelf". Both the Morphine and Codeine were marketed by Roxane. The two bottles looked identical having the same size, color, and label color.

### 3.2 LABEL AND LABELING RISK ASSESSMENT

The proposed container label, blister label and carton labeling for the 15 mg, 30 mg and 60 mg tablets were reviewed for areas of vulnerability that may lead to medication errors. The following observations were made:

#### *3.2.1 Container Label 30 mg and 60 mg (100 count bottle)*

The 30 mg and 60 mg tablet container labels are almost identical in appearance because they both use similar colors in the trade dress (white background with dark brown font). Additionally, the tablets are similar in appearance (white, scored tablets).

#### *3.2.2 Blister Label (15 mg and 30 mg)*

When compared side-by-side, the 15 mg and 30 mg tablet container labels are almost identical in appearance because they both use similar colors in the trade dress (white background with dark brown font). Additionally, the tablets are similar in appearance (white, scored tablets).

[ ] b(4)

The product strengths lack prominence.

#### *3.2.3 Carton Labeling (15 mg and 30 mg)*

When compared side-by-side, the 15 mg and 30 mg tablet carton labels are almost identical in appearance because they both use similar colors in the trade dress (white and purple background with dark brown font). Additionally, the tablets are similar in appearance (white, scored tablets).

## 4 DISCUSSION

The Label and Labeling Risk Assessment found that information presented in the proposed Codeine labeling submitted is vulnerable to confusion that could lead to medication errors. This vulnerability relates to the similar trade dress [redacted] nd the lack of prominence of the product strengths and established name on the on the unit-dose blisters. b(4)

### 4.1 [redacted]

[ ] b(4)

b(4)

### 4.2 SIMILAR TRADE DRESS AND LACK OF PROMINENCE OF PRODUCT STRENGTH AND NAME ON BLISTER CARDS

When comparing the 15 mg and 30 mg blister labels side-by-side they appear similar. We recognize the Applicant has tried to differentiate the strength but because of the small size of the blister, this differentiation is not effective. The boxing and contrasting color are lost to the overall trade dress similarity. Additionally, since the tablets are similar in appearance (white, scored tablets), if the strengths were to be confused with one another, it would be difficult to tell the different strengths by looking at the labels or the tablets. Since the Applicant will not revise the trade dress it is important that the product name and strength be increased in size so that they are the most prominent information on the labels.

## 5 CONCLUSIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information on the proposed Codeine labels and labeling introduces vulnerability to confusion that could lead to medication errors. DMEPA believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

## 6 RECOMMENDATIONS

### 6.1 COMMENTS TO THE DIVISION

Based upon our assessment of the labels and labeling, and the review of post-marketing medication error cases, DMEPA has identified areas of needed improvement. We have provided the following recommendations in Section 6.2 and request this information be forwarded to the Applicant.

We would be willing to meet with the Division for further discussion, if needed. Please copy us on any communication to the applicant with regard to this review. If you have further questions or need clarifications, please contact Chris Wheeler, Project Manager, at (301) 796-0151.

### 6.2 COMMENTS TO THE APPLICANT

***Blister Label 15 mg and 30 mg Tablets:***

1. b(4)

2. Increase the prominence of the established name and product strength.

[3] ISMP-Acute Care Medication Safety Alert, Volume 13, Issue 2, January 31, 2008

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_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/
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7/2/2009 03:22:23 PM
DRUG SAFETY OFFICE REVIEWER

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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DATE: March 27, 2009

TO: Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and
Rheumatology Products

FROM: Jacqueline A. O'Shaughnessy, Ph.D.
Gopa Biswas, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 22-402 Codeine Sulfate Tablets 15, 30 and 60 mg, Sponsored by Roxane Laboratories

At the request of Division of Anesthesia, Analgesia, and Rheumatology Products, the Division of Scientific Investigations conducted audits of the following bioequivalence study:

**Study# CODE-T30-PVFS-1:** "A Single Dose, 2-Period, 2-treatment, 2-Way Crossover Comparative Bioavailability Study of Codeine 30mg Tablets (investigational product/Roxane laboratories) and Tylenol#3 (acetaminophen 300 mg with codeine sulfate 30 mg) tablets (Ortho-McNeil) under fasting conditions"

The clinical and analytical portions of the study were conducted at CEDRA Clinical Research LLC, San Antonio, TX and ——————— respectively. Following the inspection of CEDRA Clinical Research (1/29-2/18/09), there were no significant findings and no FDA Form 483 was issued. Following the inspection of —— (March 3-6, 2009), Form 483 was issued (Attachment 1). The objectionable findings and our evaluation are discussed below: b(4) b(4)

**1. The basis for increasing the volume of elution solvent from 990 µL to 1050 µL for method LCMSC 396 V2 was not**

**recorded. The change was implemented during the method validation between the runs 2EKR2 and 3EKR2 (Form 483, Item 5).**

Although it is objectionable that the firm failed to document a justifiable reason for changing the extraction volume during the validation experiments, overall method performance was not affected by this change as precision and accuracy results for quality control samples using the same volume were acceptable.

**2. The validity of the stock solution stability experiment for codeine on 12/20/06 was not demonstrated in that the freshly prepared solutions used for comparison failed the stock verification check (Form 483, Item 6).**

Stability of codeine in methanol was reported for 89 days at 2-8°C. At the time of the stability assessment, the firm also compared two freshly prepared codeine stock solutions and found them dissimilar (i.e., >5% different). As one of these fresh stocks was used for the stability assessment, validity of the 89 day stability result was not assured. Notwithstanding this finding, the firm provided additional stock solution stability for 35 days to cover the period of use in the Roxane study.

**3. The final report did not include all samples reassayed for incurred sample reproducibility (ISR). Five of 153 samples reassayed for morphine-6β-glucuronide were rejected for aberrant internal standard response and were excluded from the final report (Form 483, Item 7).**

The firm should report all reassay results obtained during ISR testing to assess overall method performance. Since the number of rejected samples not included in the final report was only 3% of the total samples reassayed (5 of 153), there is no impact on study outcome or the reproducibility of the analytical results.

**4. The firm's procedures do not include documentation to confirm the condition of reference standards upon receipt (Form 483, Item 8).**

For example, following receipt, codeine phosphate and morphine-3β-glucuronide required refrigeration and morphine-6β-glucuronide required frozen conditions. The firm should

establish procedures to document that shipping conditions were appropriate for subsequent storage requirements.

**Conclusion:**

Following the above inspections, the Division of Scientific Investigations concludes the following:

- [redacted] needs to improve their record keeping and reporting practices for analytical study conduct. b(4)
- The clinical and analytical portions of Study CODE-T30-PVFS-1 can be accepted for review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Jacqueline A. O'Shaughnessy, Ph.D.

Gopa Biswas, Ph.D.

**Final Classification:**

**NAI** - CEDRA Clinical Research LLC, San Antonio, TX b(4)
**VAI** - [redacted]

cc: DFS
DSI/Vaccari
DSI/Viswanathan/O'Shaughnessy/Biswas
DSI/Patague/Rivera-Lopez/CF
OND/ODEII/DAARP/Sullivan/Agarwal/Doddapaneni

cc: email
HFR-SW1540/Joel Martinez (BIMO)
HFR-CE250/Shapley (BIMO)/Milazzo/McNew

Draft: GB/JAO
Edit: MFS 3/23/09
DSI: [redacted] O:\BE\eircover\22402rox.cod.doc b(4)
FACTS: [redacted]

# Attachment 1

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✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

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**Date:** March 12, 2009

**To:** Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology Products

**Through:** Michael Klein, Ph.D, Director
Controlled Substance Staff,

**Through:** Silvia Calderon, Ph.D, Team Leader
Controlled Substance Staff

**From:** James R. Hunter, R.Ph., MPH
Controlled Substance Staff

**Subject:** NDA 22-402, Codeine Sulfate Tablets, USP, 15mg, 30mg, and 60mg for the relief of mild to moderate severe pain.
*Sponsor*: Roxane Laboratories, Inc.
*Materials Reviewed*: 505(b)(2) NDA package, including product labeling

This memorandum responds to the Division of Anesthesia, Analgesia and Rheumatology Products consult regarding the Sponsor's submission dated July 02, 2008.

**Summary:** Roxane Laboratories submitted an NDA for its currently marketed, but unapproved products, Codeine Sulfate Tablets, USP, 15mg, 30mg, and 60mg, to bring them into voluntary regulatory compliance. The NDA is submitted as a 505(b)(2) application citing the listed drug Tylenol with Codeine No.3 (NDA 85-055) as the reference drug. Therefore, the sponsor is relying on FDA's previous finding of safety and efficacy for this comparator product as the basis for NDA 22-402. A biopharmaceutics study bridging the Roxanne 30mg codeine formulation to Tylenol with Codeine No. 3 demonstrates bioequivalence with respect to codeine. Other pharmacokinetic characterization studies support consistency in performance and dose linearity between the three dosage strength formulations of codeine sulfate.

**Background:** Codeine sulfate has a century-long history of use as an analgesic. As a derivative of opium, codeine is a selective mu receptor agonist, but with weaker affinity than morphine. Although less potent than morphine, codeine sulfate has a high potential for abuse and is controlled in Schedule II of the U.S. Controlled Substances Act.

While there are numerous FDA approved oral combination codeine sulfate products, no immediate-release single drug oral products are FDA approved. Therefore, the sponsor is seeking approval for codeine sulfate immediate release 15mg, 30mg, and 60mg oral tablets. The sponsor has marketed this tablet formulation since the 1980's, under the brand name

Codeine Sulfate Tablets, USP. The proposed tablet strengths under NDA 22-402 have the same indication, dosage, and route and dosing interval of administration as the currently marketed, but unapproved drugs.

There were no specific questions from the sponsor for CSS. CSS reviewed the submitted product labeling and the development plan for these products. The following sections include the current abuse/misuse profile of codeine containing drug products, drug use data and emergency visits (ED) captured by SAMSHA's Drug Abuse Warning Network (DAWN). DAWN ED numbers were compared for currently marketed narcotic analgesics containing codeine, hydrocodone, oxycodone, and propoxyphene.

**Conclusions and Recommendations:**

1) CSS agrees with the sponsor that Codeine Sulfate Tablets U.S.P. should remain subject to the controls imposed by Schedule II of the Controlled Substances Act.

2) The proposed drug abuse and dependence section of the label is acceptable.

**CSS Review:**

*Abuse and Misuse of Codeine Containing Drug Products*

The following subsections summarize data from the Drug Abuse Warning Network (DAWN) which contributes to the abuse potential evaluation of codeine as compared to three other narcotic analgesic drug substances, specifically by the number of emergency department visits related to abuse and misuse.

**1. Drug Abuse Warning Network (DAWN)**

DAWN is a public health surveillance system that monitors drug-related visits to hospital emergency departments (ED) and drug related deaths reported to DAWN by participating medical examiners and coroners (ME/Cs) to track the impact of drug use, misuse, and abuse in the U.S. The Substance Abuse and Mental Heath Administration (SAMHSA) is the agency responsible for DAWN operations. DAWN relies on a national sample of general, non-Federal hospitals operating 24-hour EDs. The sample is national in scope, with oversampling of hospitals in selected metropolitan areas. In each participating hospital, ED medical records are reviewed retrospectively to find the ED visits that were related to recent drug use. All types of drugs- illegal drugs, prescription and over-the-counter (OTC) pharmaceuticals, dietary supplements, and nonpharmaceutical inhalants- are included. Alcohol, when it is the only drug implicated in a visit, is included for patients younger than age 21; alcohol, when it is present in combination with another drug, is included for patients of all ages.

DAWN not only captures ED visits associated with substance abuse/misuse, both intentional and accidental, but includes ED visits related to the use of drugs for legitimate therapeutic purposes.

Eight case types are defined in the new DAWN and each case is assigned into one and only one case type, the first that applies from the following hierarchy: "suicide attempt", "seeking detox", "alcohol only (age <21)", "adverse reaction", "overmedication", "malicious poisoning", "accidental ingestion", and "other."

The "other" grouping as reported in DAWN, includes the nonmedical use of pharmaceuticals which captures the following:

- Taking more than the prescribed dose of a prescription pharmaceutical or more than the recommended dose of an OTC pharmaceutical or supplement
- Taking a pharmaceutical prescribed for another individual
- Deliberate poisoning with a pharmaceutical by another person, and
- Documented misuse or abuse of a prescription or OTC pharmaceutical or dietary supplement.

Nonmedical use of pharmaceuticals may involve pharmaceuticals alone or pharmaceuticals in combination with illicit drugs or alcohol.

DAWN estimates overall totals of 536, 247 ED visits in 2004, 669,214 ED visits in 2005 and 741,425 in 2006 involved nonmedical use of prescription or OTC pharmaceuticals or dietary supplements.

As shown in **Table 1**, the number of estimated visits associated with the nonmedical use and the projected prescription dispensed of codeine containing products remained relatively consistent over the years 2004 (7,171), 2005 (6,180), and 2006 (6,928). In contrast, estimated ED mentions and projected prescriptions dispensed for both hydrocodone and oxycodone containing products showed an increase over this same time interval. Estimated ED mentions in DAWN for propoxyphene containing products increased between 2004 (6,744) and 2005 (7,648), then decreased in 2006 (6,220). Projected prescriptions filled for these products remained relatively constant over this same time period.

The number of estimated nonmedical ED visits for codeine products decreased 3 percent from 2004 to 2006. During this same time period (2004-2006), the number of associated nonmedical ED visits rose 44 percent for hydrocodone products, 56 percent for oxycodone products, and decreased 8 percent for propoxyphene products. The number of prescriptions sold between the years 2004-2006 ——— for oxycodone and hydrocodone products, and ——— for codeine and propoxyphene products. In 2006, more than ——— prescriptions for codeine containing products were dispensed in the United States[1], representing a ——— decrease in the number of prescriptions dispensed from 2004. b(4)

[1] Verispan's Vector One™: National VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. The

To account for differences in the availability of each product to patients, estimates of the nonmedical ED mentions per 100,000 prescriptions sold[1] were calculated. As seen in **Table 1**, the rate for ED mentions for codeine products rose slightly from [redacted] per 100,000 prescriptions sold in 2004 to [redacted] per 100,000 prescriptions sold in 2006. The rate for the non-medical use-related ED visits per 100,000 prescriptions dispensed for oxycodone products increased at a much steeper rate and ranged from [redacted] in 2004 to [redacted] in 2006 per 100,000. The rate for hydrocodone products increased from [redacted] in 2004 to [redacted] in 2006 per 100,000. Non-medical use related ED visits per 100,000 for propoxyphene remained unchanged between 2004 and 2006 at [redacted] per 100,000.

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[1] Vector One™ database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups.

**Table 1**: Calculated Rates of Nonmedical ED Mentions in DAWN (2004-2006) per 100,000 Dispensed Prescriptions.

| DRUGS[1] | 2004 | 2005 | 2006 |
|---|---|---|---|
| | DAWN TOTAL NONMEDICAL USE ED MENTIONS[2] | | |
| Codeine/combinations | 7171 | 6180 | 6928 |
| Hydrocodone/combinations | 39844 | 47192 | 57550 |
| Oxycodone/combinations | 41701 | 52943 | 64888 |
| Propoxyphene/combinations | 6744 | 7648 | 6220 |
| | PROJECTED PRESCRIPTIONS DISPENSED[3] | | |
| Total Codeine | [redacted] | | |
| Total Hydrocodone | | | |
| Total Oxycodone | | | |
| Total Propoxyphene | | | |
| | RATES OF NONMEDICAL ED MENTIONS IN DAWN PER 100,000 PRESCRIPTIONS[4] | | |
| Codeine | [redacted] | | |
| Hydrocodone | | | |
| Oxycodone | | | |
| Propoxyphene | | | |

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[1] Mentioned drugs are placed in various control schedules of the Federal Controlled Substances Act. Codeine products may include some products in CII, but primarily include CIII, CIV and CV products, hydrocodone products are CIII, oxycodone products are CII, and propoxyphene products are CIV. [2] Source: SAMHSA, Office of Applied Studies, 2004-2006 DAWN-ED. Nonmedical use cases include the following types of case: Overmedication, malicious poisoning, and other. [3]Verispan, LLC: Vector One™: National VONA. [4] [DAWN Nonmedical Use ED Mention for specific year X 100,000] / Yearly Projected Prescriptions Dispensed

In conclusion, the number and rate of nonmedical codeine related ED mentions in DAWN remained relatively consistent from 2004 to 2006. The number of dispensed prescriptions containing codeine has remained relatively constant over this same period of time. The rate of nonmedical use ED mentions per 100,000 prescriptions dispensed for codeine products for 2004-2006 is lower than that of hydrocodone and oxycodone products, and comparable to propoxyphene products.

**2. Labeling:**

The proposed "Drug Abuse and Dependence" section of the codeine sulfate label is similar to the same section of the recently approved NDA for Morphine Sulfate Tablets label. This text in the codeine label is acceptable.

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/s/
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