

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-402

MEDICAL REVIEW(S)

NDA 22-204
Addendum Regarding Financial Disclosures

Reviewer: Ellen Fields, MD, MPH
Clinical Team Leader
DAARP

The Sponsor included form 3454 in the NDA submission that stated they have not entered into any financial arrangement with the listed clinical investigators, and certified that each investigator had no financial interests disclosed to the Sponsor.

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/s/

Ellen Fields
7/15/2009 02:35:50 PM
MEDICAL OFFICER

NDA 22-402 Codeine Sulfate Tablets: 15, 30, and 60 mg
Boehringer Ingelheim, Inc.; Roxane Laboratories

**Food and Drug Administration, FDA
Center for Drug Evaluation and Research, CDER
Division of Anesthesia, Analgesia and Rheumatology Products, DAARP**

Clinical Review NDA 22-402

Date: December 22, 2008

From: Carolyn L. Yancey, MD, Medical Officer, DAARP
Through: Ellen Fields, MD, Clinical Team Leader, DAARP, and
Sharon Hertz, MD, Deputy Director, DAARP

NDA: 22-402
Type NDA: 505(b)(2)
Applicant: Boehringer Ingelheim, Inc., Roxane Laboratories, Inc.

Letter Date: July 1, 2008
Received: September 10, 2008
PDUFA Goal Date: May 2, 2009

Proprietary Name: Codeine Sulfate Tablets, USP
Established name: Codeine Sulfate Tablets, USP
Dosage strength: Oral Tablets 15 mg, 30 mg and 60 mg
Indication: Relief of mild to moderately severe pain in adult patients

RECOMMENDED REGULATORY ACTION

Approval.

The literature regarding the efficacy of oral codeine sulfate submitted in NDA 22-402, 505(b)(2) supports the approval of codeine sulfate oral tablets (15 mg, 30 mg and 60 mg) for the relief of mild to moderately severe pain in adults. The safety of codeine sulfate is based on the previous findings of safety for Tylenol® with Codeine No. 3 under NDA 85-055.

INDICATION

The proposed clinical indication for codeine sulfate oral tablets (15, 30, and 60 mg) is for the relief of mild to moderately severe pain in adult patients.

INTRODUCTION

Currently, Roxane Laboratory, Inc. (Roxane Labs) is marketing an unapproved codeine sulfate oral tablet for the treatment of acute pain in adults. The Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) met with Roxane Labs to discuss a regulatory pathway forward by which the sponsor could obtain approval for their

NDA 22-402 Codeine Sulfate Tablets: 15, 30, and 60 mg
Boehringer Ingelheim, Inc.; Roxane Laboratories

marketed but unapproved oral codeine tablet product. The sponsor proposed submission of a 505(b)(2) NDA application that would rely upon the Agency's previous findings of safety for the codeine combination product, Tylenol® with Codeine No. 3 (acetaminophen and codeine phosphate), and upon the published clinical literature to support efficacy.

Therefore, in accordance with 21 CFR 314.50, Roxane Lab is submitting a 505(b)(2) New Drug Application (NDA) for codeine sulfate oral tablets, USP (15, 30, and 60 mg). The sponsor proposes to achieve approval for the use of codeine sulfate oral tablets for the relief of mild to moderately severe pain in adults. Under the regulations of 21 CFR 314.54, the sponsor referenced the listed drug under NDA 85-055 (Tylenol® with Codeine No. 3) as the basis for NDA 22-402 clinical safety. The bioavailability bridging studies to support Roxane Labs' 30 mg codeine formulation were performed with Tylenol® with Codeine No. 3. The pharmacokinetic (PK) characterization studies for the proposed codeine formulation (15, 30, and 60 mg) are also included for support of this NDA.

The drug product will be manufactured, tested, labeled, packaged, and released by Boehringer Ingelheim Roxane, Inc. No other contract manufacturers or packagers will be used for the proposed drug product.

OVERVIEW OF CODEINE

Codeine is an orally absorbed, naturally occurring opioid alkaloid: 7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-morphinan-6-ol monohydrate. It is an analgesic agent believed to mediate its effect through interference with opioid receptors. Although codeine has been in clinical use for approximately 150 years, the pharmacokinetic (PK) properties have only recently been investigated. Like morphine, codeine is a constituent of the opium poppy plant, *Papaver somniferum*.

Codeine is prepared from morphine by methylation (addition of a methyl group to the 3-carbon hydroxyl group of morphine) of the phenolic hydroxyl group, specifically, from an -OH to -OCH₃. Codeine and its metabolites are thought to act via binding to opioid receptors in the central nervous system. The precise mechanism of action of codeine phosphate, an opioid agonist, in relieving pain has not been established. The binding of codeine phosphate to mu, delta, and kappa opioid receptors in the central nervous system (CNS) may change the perception of pain.

Morphine is metabolized to the M6G, a potent analgesic estimated to be 50 times more potent than morphine. Codeine's main metabolite is C6G, similar in structure to the active receptor agonist M6G. Codeine is a weak analgesic with a weak affinity to the μ receptor, 300 times less than morphine. The precise mechanism of action of codeine phosphate, an opioid agonist, in relieving pain has not been established. The binding of codeine phosphate to μ , delta, and kappa opioid receptors in the central nervous system (CNS) may change the perception of pain. The analgesic activity of codeine phosphate is probably due to its conversion to morphine.

NDA 22-402 Codeine Sulfate Tablets: 15, 30, and 60 mg
Boehringer Ingelheim, Inc.; Roxane Laboratories

The cytochrome (CYP) 450 2D6 enzyme is responsible for the conversion of codeine to morphine. It is also recognized that human genetic polymorphisms result in different CYP2D6 phenotypes which are directly responsible for the *O*-demethylation of codeine to morphine. A total dose of codeine is metabolized by 2D6 into morphine.

Between individuals and across diverse ethnic groups there are differences in the ability to metabolize codeine to morphine via *O*-demethylation. A significant degree of unpredictability, variable, or poor response to treatment with codeine has been reported in many human and animal studies. Inhibition, induction or altered enzyme genotypes appear to alter codeine's effectiveness. More definitive studies of codeine are needed to better define these issues in order to make more definitive predictions about the potential of codeine as a prodrug and for drug-drug interactions with codeine.

REGULATORY BACKGROUND

The 505(b)(2) NDA 22-402 for Codeine Sulfate Tablets was submitted to the Agency on July 1, 2008. This submission consists of fifty-three (53) volumes in hard copy. The only electronic portions of this submission include the bioequivalency data tables, FDA Form 356H, Table of Contents, the cover letter, and the proposed labeling.

- **1980s:** Roxane has marketed the brand name formulation of Codeine Sulfate Tablets, USP, 15 mg, 30 mg, and 60 mg for the relief of mild to moderate severe pain since the early 1980's.
- **December 15, 2006. Meeting Package:** Roxane Labs submitted a meeting package with 7 questions for response from the Agency. A Type-B meeting, recorded as a Pre-IND meeting, was scheduled for January 24, 2007.
- **January 24, 2007. Type-B Meeting:** The FDA agreed that a 505(b)(2) application could be submitted for Codeine Sulfate Tablets, USP, 15 mg, 30 mg, and 60 mg. For additional details, see the meeting minutes including the Agency responses to the sponsor's questions under IND 75,764 as of February 8, 2007. The sponsor agreed to submit a background meeting package including the published literature proposed to support the efficacy of codeine in mild to moderately severe acute pain in adults and the non-clinical pharmacology toxicology literature to support the product safety. The division's rationale for requesting an early submission of the clinical literature was to permit a preliminary evaluation by the division of whether or not the literature would be adequate to support the proposed clinical indication. The safety of Roxane's codeine sulfate tablets would be supported by the Agency's finding of safety for Tylenol® with Codeine No. 3. The division responded to Roxane Labs that Tylenol® with Codeine No. 3 may be an acceptable reference to support the safety as long as 1) the codeine doses used in the combination product are the same or higher doses than used in the proposed doses of the codeine sulfate oral tablets, and 2) as long as the pharmacokinetics of codeine in the reference product are similar to those of Roxane Labs' codeine.
- **Proposed Pediatric Study. Type B meeting January 24, 2007:** The division noted that literature regarding the efficacy of oral codeine in pediatric patients was also included in the clinical literature package. The division stated that the sponsor could use extrapolation of efficacy from adults with mild to moderately severe

pain to children with similar pain conditions and this approach may be considered for the proposed _____ application.

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- Nonclinical Pharmacology/Toxicology, January 24, 2007: Roxane Labs proposed

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b(4)

- A Pre-NDA meeting would be scheduled *after* the review of the submitted clinical literature. Roxane Labs proposed to submit their NDA by 1Q08 and requested a response from the Agency about the adequacy of the submitted clinical literature by July 1, 2007.
- April 13, 2007, Pre-NDA Meeting Package: The meeting package contained the clinical and the pharmacology-toxicology information.
- July 1, 2008: Roxane Labs submitted the 505(b)(2) NDA 22-402 application for Codeine Sulfate Tablets, USP 15 mg, 30 mg, and 60 mg. This application includes a complete Chemistry, Manufacturing and Controls (CMC) submission with supportive data.
- July 14, 2008 Teleconference: The division requested the following: 1) certification of the requested pediatric deferral; 2) an overview efficacy table clarifying the submitted clinical literature references with the published study number in the submission; and 3) an Integrated Summary of Efficacy for the published clinical trials. These documents were submitted to the Agency on July 23, 2008.
- July 17, 2008, Response Letter: The sponsor will rely on the published literature for the non-clinical pharmacology and toxicology (Pre-NDA package submitted April 13, 2007) aspects of the application.
- July 24, 2008: Telephone conference, the sponsor notified the Agency of a forthcoming submission of an amendment to NDA 22-402 containing a revised Package Insert with supportive literature.
- July 30, 2008: _____

b(4)

- October 17, 2008: The division requested missing clinical literature references, # 66 through # 71. The sponsor provided these references in a timely manner.
- October 2008: the pharmacology-toxicology review team requested that the _____

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The sponsor concurred.

See the Pharmacology Toxicology review by Marcus Delatte, PhD.

COMBINATION PRODUCTS WITH CODEINE

NDA 22-402 Codeine Sulfate Tablets: 15, 30, and 60 mg
Boehringer Ingelheim, Inc.; Roxane Laboratories

Codeine and its' phosphate or sulfate salts are used in a variety of pharmaceutical products as an analgesic, sedative, hypnotic, anti-peristaltic, and anti-tussive therapeutic agent. The Agency has approved 62 combination products with codeine across 56 NDAs. The potential advantage of combining two analgesics, which act by different mechanisms of action, is the increased analgesic efficacy. Examples of these approved combination products with codeine as a tablet or capsule include:

- 200 mg mg aspirin, 325 mg carisoprodol and 16 mg codeine phosphate as an oral tablet (Capital with Codeine, NDA 083-543);
- 50 mg butalbital, 325 mg acetaminophen, 40 mg caffeine and 30 mg codeine phosphate as an oral capsule (Fioricet with Codeine, NDA 020-232);
- 325 mg aspirin, 50 mg butalbital, 40 mg caffeine and 30 mg codeine phosphate as an oral capsule (Fiorinal with Codeine, NDA 019-429);
- 300 mg acetaminophen and 30 mg codeine phosphate as an oral tablet (Tylenol with Codeine, NDA 085-055); and
- 325 mg aspirin, 200 mg carisoprodol, and 16 mg codeine phosphate oral tablet (Soma Compound with Codeine, NDA 012-366).

Fewer combination products with codeine as an oral solution, suspension, and or syrup are available and approved. Examples of such approved formulations include:

- 10 mg/5 mL codeine phosphate, 30 mg/5 mL pseudoephedrine hydrochloride; 1.25 mg/5 mL triprolidine hydrochloride as an oral syrup (Actifed with Codeine, NDA 012-575);
- 10 mg/5 mL codeine phosphate, 30 mg/ 5 mL pseudoephedrine hydrochloride and 1.25 mg/5 mL triprolidine hydrochloride as an oral syrup (Triacin, NDA 088-704);
- 10.5 mg/5 mL codeine phosphate, 6.25 mg/ 5 mL promethazine hydrochloride as an oral syrup (Promethazine with Codeine, NDA 040-650) and
- 120 mg/5 mL acetaminophen and 12 mg/5 mL codeine as an oral suspension (Capital and Codeine, ANDA 085-883);

As noted in the introduction of this review, codeine, alone, is not an approved product; however, the proposed formulation has been marketed as a single entity since the early 1980s by Roxane Labs.

DEFERRED PEDIATRIC STUDIES AND PEDIATRIC WAIVER

In accordance with 21 CFR 314.55(b) *Deferred Submission*, Roxane Labs is requesting a deferral of pediatric studies for codeine sulfate tablets, USP, 15 mg, 30 mg, and 60 mg NDA until after approval has been granted for codeine sulfate products in adult patients. This pediatric deferral is requested for the following pediatric populations: infants (≥ 1 month to < 2 years), children (≥ 2 years to < 12 years) and adolescent (≥ 12 years to _____).
Roxane commits to conduct Phase 4 pediatric trials as discussed in the Pre-IND 75,764 meeting with the Agency on January 24, 2007. The sponsor requests deferral of all pediatric ages until after the approval has been granted for oral codeine sulfate tablets, after which, the sponsor proposes _____.

Thus far, a pediatric waiver has not been submitted to the Agency by the sponsor.

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NDA 22-402 Codeine Sulfate Tablets: 15, 30, and 60 mg
Boehringer Ingelheim, Inc.; Roxane Laboratories

The sponsor proposes that _____

b(4)

The sponsor proposes _____

_____ The following is a summary of the sponsor's planned pediatric development program as explained in their July 23, 2008 submission:

b(4)

Summary of Recent Literature for Codeine Use in Pediatrics

Codeine combination products are approved for use in pediatric population ages ≥ 3 years of age. As example, NDA 085-861 for 120 mg/mL acetaminophen and 12 mg/5mL codeine phosphate oral solution (Atlantic Mid-Atlantic) was approved January 1982, and NDA 088-764 for 10 mg/5 mL codeine phosphate, 5 mg/5 mL phenylephrine hydrochloride, 6.25 mg/ mL promethazine hydrochloride oral syrup was approved October 1981 for pediatric patient age ≥ 3 years. The pediatric literature reports that codeine is frequently recommended for pediatric use. A reported survey of pediatric anesthesiologists in the United Kingdom showed that alongside morphine and fentanyl, codeine is the most widely prescribed opioid analgesic in pediatric anesthesia practice.¹ The reportedly lower incidence of opioid-related side effects has made codeine popular for the younger age groups including neonates and especially in situations where airway management and neurological assessment are critical.

There are few clinical trials of the analgesic efficacy or side effects of codeine in children, and although the incidence of side effects may be low, analgesia may be inadequate for post-operative pain in some circumstances. In children, codeine is generally given in doses of 1 mg/kg up to a maximum of 3 mg/ kg/day; however, larger doses have been used.^{3,4} Pediatric use of codeine may be in combination with other drugs, for example, aspirin, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), and diphenhydramine in the treatment of mild to moderate pain. It is reported that in neonates and children, codeine has been used in both acute and chronic pain conditions and for post-operative and cancer pain.²

Briefly, the pediatric codeine PK and PD data reported in the literature are limited. In addition, the literature suggests that age specific differences in the PK of codeine may be significant.

Pediatric References

1. de-Lima J, Lloyd-Thomas AR, Howard RF, Summer E Quinn TM. Infant and Neonatal Pain: anesthesiologists perceptions and prescribing patterns. *BMJ* 1996; 313: 787.
2. Williams DG, Hatch DJ, Howard RF. Codeine phosphate in pediatric medicine. *BJA* 2001; 86 (3): 413-21.
3. British National Formulary, 40th Edn. British Medical Association and Royal Pharmaceutical Society of Great Britain. September 200; 211-212.
4. Semple D, Russell S, Doyle E, Aldridge LM, Comparison of morphine sulphate and codeine phosphate in children undergoing adenotonsillectomy. *Paediatric Anesth* 1999; 9, 135-8.
5. Moodenaar F, Grosmeijer G, Visser J, Meijer DK, Rectal versus oral absorption of codeine phosphate in man. *Biochem Drug Dispos* 1983; 4: 195-9.

CONCLUSIONS AND RECOMMENDATIONS:

PEDIATRIC DEFERRED STUDIES AND PEDIATRIC WAIVER

The Agency concludes that the sponsor's proposed pediatric deferral request, as submitted, is inadequate based on the three following issues and concerns.

1) A proposed _____ is not appropriate for the proposed indication for oral codeine sulfate. The pediatric patient population should include patients with mild to moderately severe acute pain. b(4)

2) The proposed _____ is not appropriate to demonstrate the effectiveness of the proposed oral codeine sulfate tablet formulation. A superiority clinical trial design will be required to demonstrate the efficacy of codeine sulfate in pediatric patients. The sponsor proposes _____ b(4)

3) The proposed _____ of the Agency concludes that _____ of the appropriate pediatric population of ≥ 1 month to ≤ 17 years based on the clinical use of codeine for mild to moderate pain. In consideration that it takes approximately 2 weeks for CYP2D6 to mature in newborns, the Agency concludes that clinical study in infants ≥ 1 month would be appropriate. b(4)

Though further internal Agency discussion will occur, the following recommendations and issues are being considered by the division for communication to the sponsor:

1) Characterize the single- and multiple-dose PK/PD parameters of codeine sulfate for the pediatric population ages ≥ 1 month to ≤ 17 years of age.

2) Conduct a randomized, double-blind, adequately controlled, superiority design clinical trial for effectiveness, comparing codeine with either placebo or an active comparator. This clinical trial must include a pediatric population with the age range noted in #2 above. This clinical trial must include blinded data collection rather than the proposed open-label data collection and include the appropriate pediatric patient population with mild to moderately severe acute pain. The safety and PK/PD clinical trials of the pediatric development program *do not* have to be randomized, double-blinded or controlled.

3) Timelines for completion would need to be submitted to reflect initiation of the clinical trial, the estimated enrollment period for the clinical trial, when the first expected study report would be submitted to the Agency, and when the final study report would be submitted to the Agency.

4) Propose a codeine solution, suspension or syrup formulation for oral administration to patients unable to swallow a oral codeine sulfate tablet.

5) The final protocols for pediatric PK/PD parameters, effectiveness, and safety must be submitted to the Agency for review and approval prior to initiating any investigation in human subjects.

6) If the sponsor does not agree to study infants and young children < 3 years to 0 days of age, a pediatric waiver request must be submitted to the Agency by the sponsor with the

NDA 22-402 Codeine Sulfate Tablets: 15, 30, and 60 mg
Boehringer Ingelheim, Inc.; Roxane Laboratories

appropriate rationale for not including young children < 3 years of age in the proposed pediatric safety and PK/PD clinical trials.

CHEMISTRY, MANUFACTURING AND CONTROLS (CMC)

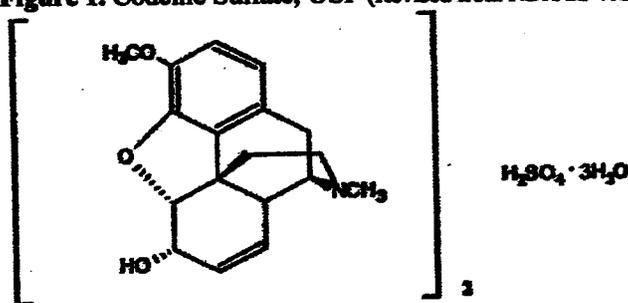
Codeine is an alkaloid from the juice of the poppy plant *Papaver somniferum*.

Chemically, codeine sulfate is 7,8-didehydro-4,5-epoxy-3-methoxy-17methylmorphinan-6-ol sulfate (2:1)(salt), trihydrate. See Figure 1. Codeine is extracted from opium in amounts described by the sponsor as too small to be of commercial importance.

Therefore, commercial codeine is prepared from morphine by methylation of the phenolic hydroxyl group.

b(4)

Figure 1. Codeine Sulfate, USP (Revised from NDA 22-402 submission.)



Note:

Based on the mid-cycle presentation from the CMC reviewer, Eugenia M. Nashed, PhD, there are outstanding CMC review issues including:

- 1) No dissolution profiles have been submitted for review;
- 2) Manufacturing was evidently changed for the codeine sulfate, 15 mg oral tablet; impurities must be defined and reviewed;
- 3) There appear to be degradation issues with _____, this must be defined and review;
- 4) Only one DMF file was submitted to the Agency for review; two additional DMF files have not yet been submitted for review;
- 5) CMC support for the _____ of the proposed formulation has not been submitted to the Agency for review;
- 6) Only 6-month data rather than the required 1-year data for the current batches have been submitted to the Agency for review; the inadequacy of the 6-month data was communicated to the sponsor in the 74-Day letter.

b(4)

b(4)

See the CMC comments by Eugenia M. Nashed, PhD, CMC reviewer.

CLINICAL PHARMACOLOGY/ BIOAVAILABILITY STUDIES

Under NDA 22-402, Roxane Labs conducted five clinical trials to investigate the PK of codeine sulfate oral tablets (Studies CODE-T60-PLFS-1; CODE-T15-PVFS-1; CODE-T30-PVFS-1; CODE-T60-PVFS/FD-1; CODE-T15-30-60-PVFS-1). Four of these five studies are single-dose studies, fasting, and or fed, and one is a steady-state bioavailability study of codeine sulfate 15 mg tablets under steady-state conditions.

As reported in this submission, Study T60-PLFS-1, was a single-dose, three-period, three-treatment, six-sequence crossover PK and comparative bioavailability clinical trial of codeine sulfate tablet formulations (15 mg, 30 mg, and 60 mg) under fasting conditions conducted in August 2006 and provided to the Agency January 24, 2007. In summary, this study demonstrated that the C_{max} and AUC appear to increase in a dose proportional manner.

As a result of the January 24, 2007 meeting, the division requested Roxane Labs to conduct four clinical trials to develop the descriptive PK section for the proposed codeine sulfate (15, 30, and 60 mg oral tablet) labeling. A brief description of each trial design, the enrollment, and the results/summary of the four new clinical pharmacology trials is reported below.

1) Study T15-PVFS-1 is reported as a steady state, 1-period, 1-treatment clinical trial of codeine sulfate 15 mg tablets under steady state conditions. The PK parameters C_{max}, AUC(0-4), and AUC(0-24) for codeine, morphine, morphine-3-glucuronide (M3G), and morphine-6-glucuronide (M6G) were determined.

Patients received a dose of 15 mg every 4 hours for a total daily dose of 90 mg for 5 days. A total of 36 subjects were enrolled and 32 subjects completed the study. The reported results appear to demonstrate that steady-state plasma concentrations of codeine, morphine, M3G and M6G were reached in 48 hours. The mean plasma concentration-time profiles were consistent across the 6 doses administered on Day 5. Codeine and M3G, 55% and 36%, respectively, represented the largest percentages of total circulating study treatment. Morphine was reported to represent 2% which most likely represents its rapid conversion to the glucuronide conjugates. The remaining 7% of the circulating material was M6G. Clinical pharmacology requested the sponsor to explain their rationale for not measuring C3G, C6G, norcodeine and NC6G.

See Clinical Pharmacology review by Sheetal Agarwal, PhD.

2) Study T30-PVFS-1 is reported as a pivotal bioavailability clinical trial designed to assess the comparative bioavailability codeine from Roxane Labs' codeine sulfate 30 mg tablets to that of Tylenol® #3 (APAP 300 mg/codeine phosphate 30 mg) under fasting conditions. Comparison of the PK parameters for C_{max}, AUC(0-t), and AUC(inf) for codeine, morphine, M3G, and M6G among the formulation was completed.

A total of 36 subjects were enrolled and 34 subjects completed both periods of the study. The reported results demonstrated that codeine sulfate tablets 30 mg was bioequivalent to Tylenol #3 (codeine phosphate 30 mg) with respect to codeine, M3G and M6G but not to morphine. The sponsor reports that there were essentially no differences in the AUC ratios for morphine-to-codeine, M3G-to-morphine, and M6G-to-morphine after administration of two formulations, indicating that the extent of metabolism of codeine to morphine and of morphine to the two glucuronides was not affected by either the formulation or the salt form.

NDA 22-402 Codeine Sulfate Tablets: 15, 30, and 60 mg
Boehringer Ingelheim, Inc.; Roxane Laboratories

In summary, this clinical pharmacology trial appears to support comparability of codeine sulfate and codeine phosphate. This conclusion supports the use of published clinical trials in which either agent was employed, as comparable, to support the efficacy for codeine sulfate.

3) Study T60-PVFS/FD-1 is reported as a clinical trial designed to evaluate the effect of food on the absorption of codeine from Roxane Labs' codeine sulfate 60 mg tablets. A total of 36 subjects were enrolled and all subjects completed both periods of the clinical trial. Comparison of the PK parameters C_{max}, AUC (0-t), and AUC(inf) for codeine, morphine, M3G and M6G between fasting and fed treatments was completed.

In summary, the reported results demonstrate that administration of Roxane Labs' codeine sulfate tablet 60 mg under fed conditions resulted in no change in the rate of the excretion of absorbed codeine. There were reported decreases in the rate of formation of morphine from codeine and M3G and M6G from morphine under fed conditions but no change in the extent of conversion. There were no reported differences in the AUC(inf) ratios for morphine-to-codeine, M3G-to-morphine, and M6G-to-morphine after oral administration under fed and fasted conditions, indicating that the extent of metabolism of codeine to morphine and then morphine to two glucuronides was not affected by food.

4) Study T15-30-60-PVFS-1 is reported as a clinical trial designed to evaluate the dose linearity of Roxane Labs' 15 mg, 30 mg, and 60 mg codeine sulfate tablets under fasted conditions. A total of 34 subjects were enrolled into the study. A total of 33 subjects were reported to have completed all three treatments and one subject completed two or three treatments. Comparison of the PK parameters for C_{max}, AUC_{90-t}, and AUC(inf) for codeine, morphine, M3G, and M6G was completed.

In summary, the reported results demonstrate that after oral administration of Roxane Labs' codeine sulfate tablets 15 mg x 1, 30 mg x 1, and 60 mg x 1, mean plasma concentrations and mean values for codeine C_{max}, AUC_{90-t}, and AUC(inf) increased in proportion to the increase in dose. The 90% confidence intervals for the geometric means for the dose-normalized C_{max}, AUC_{90-t}, and AUC_{90-t}(inf) were all within 80% to 125% indicating linearity with respect to codeine. The comparisons of the metabolites, morphine, M3G, and M6G support the linearity of the three tablet strengths demonstrated with respect to codeine.

In summary, the clinical pharmacology studies appear adequate to describe the PK parameters of the proposed formulation of codeine sulfate 15, 30, and 60 mg oral tablets.

The DSI inspection is pending for the study site in San Antonio, Texas and the analytical site in ~~_____~~

See the comments in the Clinical Pharmacology review by Sheetal Agarwal, PhD.

b(4)

LITERATURE SEARCH for EFFICACY of CODEINE

This 505(b)(2) NDA efficacy submission is based on a PubMed literature search. The sponsor proposed a literature search from 2003 to 2007. The division requested that the

literature search begin from 1960 through 2007 and include human clinical trials with randomized, controlled clinical trial design. There were a total of 430 articles identified by the sponsor from which 159 articles were submitted as specifically supportive to the proposed efficacy of codeine sulfate oral tablets. As noted in the regulatory history section of this review, the division requested early submission of the proposed clinical literature to permit a preliminary assessment for adequacy to support the proposed efficacy of codeine sulfate. This internal assessment was completed under Pre-IND 75,764 (The Pre-IND number was established by the DAARP project manager for oral codeine sulfate tablets, alone, which did not have an existing IND number) on December 15, 2006 and it was reported that the literature submitted appeared to be adequate for a 505(b)(2) application.

A total of 6 published articles were identified from 159 articles to support the efficacy of the codeine sulfate for the proposed indication. There are limitations in all of the published clinical trials reviewed in this application. Specifically, these limitations include:

- Since all the clinical trials are from published literature, the details of each clinical trial protocol, the adherence to the protocol or lack thereof to the protocol and any reported deviations, including integrity and reliability of data, are unknown.
- It appears that none of the published clinical trials included statistical analyses which would include correction for multiplicity of efficacy endpoints employed in the trial designs.
- Baseline data is frequently summarized in general terms without data specific to individual treatment groups.
- There was no accountability for differences across individual patients' ability to metabolize codeine. This would have been specifically useful in the studies with high PBO response rates, even higher than what is generally reported in the analgesia literature.

SUMMARY OF EFFICAY RESULTS

The efficacy studies reviewed in this application include three major clinical trials, literature references Study #20 (30 mg codeine, single-dose), Study #69 (60 mg codeine, single-dose) and Study #56 (60 mg codeine, multiple-dose). In addition, brief summaries of three supportive clinical trials include literature reference Study #78 (30 mg codeine [single-dose] and 60 mg codeine [multiple-dose]), Study #24 (60 mg codeine, multiple-dose) and Study #65 (65 mg codeine, multiple-dose). See the **Appendix, Literature References**, for each study publication.

In summary, the three major clinical trials and the three supportive clinical trials appear adequate to support the proposed claim for efficacy of codeine oral tablets in adults with mild to moderately severe acute pain. Collectively, these six trials appear adequate to support single- and multiple-dose codeine (15 mg, 30 mg, and 60 mg) for the proposed efficacy claim. The rationale for this conclusion is discussed in each study summary as well as the limitations specific to the individual study.

NDA 22-402 Codeine Sulfate Tablets: 15, 30, and 60 mg
Boehringer Ingelheim, Inc.; Roxane Laboratories

The pain models, patient populations, and study designs across the three major clinical trials include: a randomized, double-blind, placebo-controlled, single-dose trial with 30 mg codeine in patients with episiotomy pain (Study #20); a randomized, double-blind, placebo-controlled, single-dose, 60 mg codeine trial in post oral surgery patients (Study #69); and a randomized, double-blind, placebo-controlled, multiple-dose trial with 60 mg codeine in post oral surgery patients (Study #56). In the supportive clinical trials, the pain models, patient populations, and study designs include: a randomized, double-blind, placebo-controlled, crossover trial with 30 mg codeine (single-dose phase) and 60 mg codeine (multiple-dose phase) in patients with diverse chronic pain conditions (Study #78); a randomized, double-blind, placebo-controlled, multiple-dose trial with 60 mg codeine in patients with episiotomy (Study #24); and a randomized, double-blind, placebo controlled, crossover trial with 65 mg codeine in post orthopedic surgery patients.

The efficacy endpoints included standard measures of patient reported pain assessment including pain intensity (0-100 mm on a visual analogue scale/VAS), pain intensity difference (PID), the largest PID (PEAKPID) score, and the sum of pain intensity (SPID), as well as pain relief, total pain relief (TOPAR), and the largest pain relief (PEAKREL) score, and the time to remedication in the multiple-dose trials. In each of the individual trials reviewed, codeine demonstrated superiority over placebo in relieving mild to moderately severe pain. The well-known placebo effect reported in analgesia clinical trials was also reported in several of these trials, specifically, in the post oral surgery pain populations.

The combination products, such as acetaminophen and codeine, which were employed in several of these trials, demonstrated better analgesia than codeine alone. This was not an unexpected outcome in these published analgesia clinical trials. Several trials reviewed included active comparators such as the new molecular entity (NME), Z.424 (in Study #78), described as a new oral analgesic compound with analgesic activity of central origin not structurally related to narcotic or non-narcotic agents. The analgesic efficacy of 60 mg Z.424 appeared to be comparable to 60 mg codeine in Study #78. Another example of a NME investigated is Ro 4-1778/1 (in Study #56), [1(p-chlorophenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline]. This product is reported to have analgesic properties similar to codeine phosphate when administered to mice. There was no statistically significant difference between 60 mg codeine and 60 mg Ro 4-1778/1 in pain relief in Study # 56.

Codeine 30 mg (2 capsules, each 15 mg Codeine)
Single-Dose/ Acute Pain, Patients with Episiotomy
Study # 20
Levin et al. 1974

Study Design. Objectives

NDA 22-402 Codeine Sulfate Tablets: 15, 30, and 60 mg
Boehringer Ingelheim, Inc.; Roxane Laboratories

Study # 20 was a randomized, double-blind, placebo-controlled, single-dose clinical trial to demonstrate the degree to which 600 mg acetaminophen (APAP) and 30 mg codeine administered together would produce an effect superior to that of either drug in the same dosage administered alone, or to that of PBO. This clinical trial was 4 hours in duration. The patient population was maternity patients with moderate to severe pain following episiotomy.

With the complaint of moderately severe to very severe pain following episiotomy, patients received study medication/PBO. The elapsed time between delivery and the administration of medication was approximately two days. No patients had eclampsia and no patient had received any analgesic during the 12-hour period prior to the clinical trial.

Treatment

As each patient complained of severe pain, she received a single dose of medication consisting of *two capsules*, each of which contained one of the following: 1) 300 mg APAP with 15 mg codeine, 34 patients; 2) 15 mg codeine phosphate alone, 34 patients; 3) 300 mg APAP alone, 34 patients; or 4) PBO, 35 patients.

Efficacy Assessments

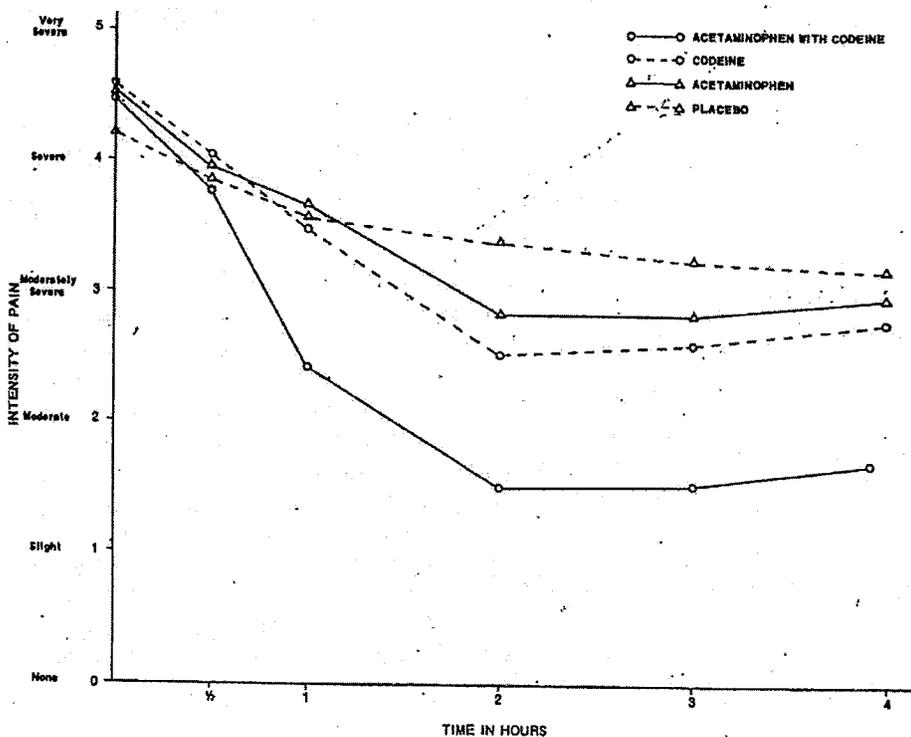
The evaluation of each patient's response to medication was made in a patient interview at ½, 1, 2, 3 and 4 hours after dosing. The patient reported her estimate of the severity of pain and the degree of relief from pain achieved relative to the preceding assessment. The assessments of pain were based on the following: intensity of pain: from 0 (none) to 5 (very severe); pain relief: 1 (worse) to 5 (completely gone); and the investigator's impression of the patient's overall response to medication. Any patient who required supplemental medication to control pain was considered a treatment failure and no further evaluation was conducted. Scores recorded prior to the time each patient was classified as a treatment failure were included in the statistical comparisons.

The results of this trial were statistically analyzed using the Mantel and Haenzel technique. Separate pair-wise comparisons of all treatments were made of scores for pain severity and scores for relief from pain. The Chi Square statistic with one degree of freedom is used to test for association between treatment and response, each pair of treatments being compared at each interview time with the previous pain level. There did not appear to be any adjustments made for the analysis of multiple endpoints.

Results

A total of 137 postpartum patients were enrolled with moderate to severe pain following episiotomy. The mean age was 23 years and the range was 15 to 38 years of age. At the completion of the this trial (4 hours in duration) a dose of 600 mg APAP administered with 30 mg codeine was reported by the authors to be statistically superior ($p < 0.01$) to 600 mg APAP alone, 30 mg codeine alone or PBO in reducing and relieving pain resulting from episiotomy. The initial mean severity of pain for each of the treatment groups was rated at least 4 (severe) at the beginning of this trial. Within 2 hours, the authors reported that the mean severity of pain in the patients administered APAP with codeine was reduced to a rating of 1.5 (slight to moderate pain). See Figure 1.

Figure 1. Comparison of the Change in Severity of Pain (Revised from literature reference.)



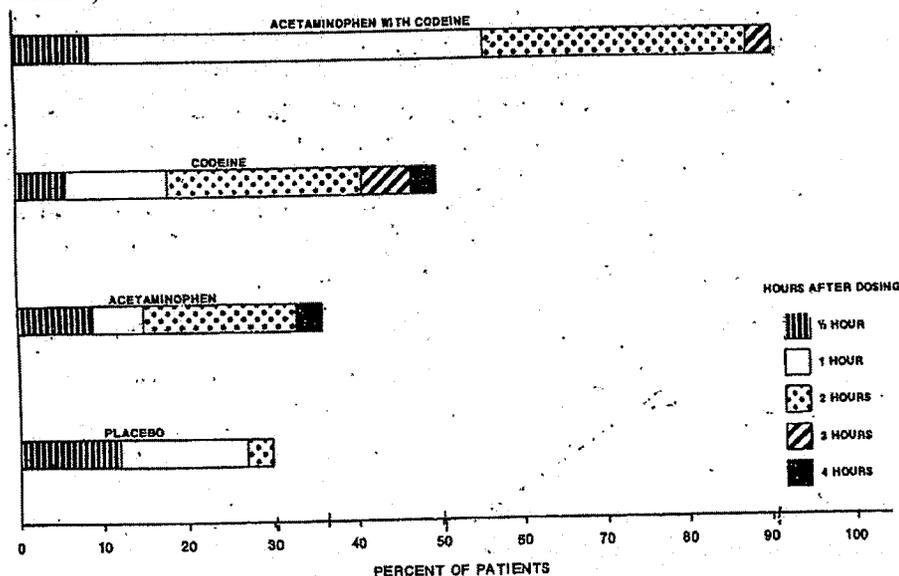
Additionally, 30 mg codeine alone at 4 hours was significantly ($p < 0.01$) superior to 600 mg APAP, and each of these drugs was significantly superior to PBO at 4 hours ($p < 0.01$).

The authors reported treatment failures (patients requiring rescue analgesia) across the four treatment groups: one patient administered the combination of APAP with codeine required supplemental medication to relieve pain, 5 patients administered APAP alone, 6 patients administered codeine alone, and 9 patients administered PBO required supplemental medication. The number of treatment failures among patients given APAP with codeine was significantly smaller than among patients given PBO alone. As reported earlier in the treatment section of this study, each active treatment group had 34 patients and the PBO group had 35 patients.

As explained by the authors, 91% of the 600 mg APAP with 30 mg codeine patients showed good to excellent response within 2 hours after dosing and their relief was reported to be sustained for the total trial duration of 4 hours. As further explained by the authors, at the first-hour patient reported response, 46% of the patients administered APAP with codeine reported that the severity of their pain had been reduced from a rating of *severe* or worse to *moderate* to less.

In the relief of pain, APAP with codeine was significantly superior to the other study treatments, e.g. codeine alone, APAP alone, and or PBO. The authors reported that 56% of patients administered APAP with codeine achieved effective relief of pain within the first-hour, 88% within two-hours, and 91% within 3-hours. See **Figure 2**.

Figure 2. Patients Reporting Effective (over 50%) Pain Relief (Revised from literature reference.)



Based on the secondary efficacy endpoint, the global evaluation appeared to support acetaminophen with codeine being superior to the other study treatments, e.g., codeine alone, APAP alone and or PBO. See Table 1.

Table 1. Global Evaluation (Revised from literature reference.)

| DRUG GROUP | Evaluation in No. of Patients | | | | | No. of Patients |
|----------------------------|-------------------------------|------|------|------|-----------|-----------------|
| | Excellent | Good | Fair | Poor | No Effect | |
| Acetaminophen with Codeine | 9 | 22 | 2 | 1 | 0 | 34 |
| Codeine | 0 | 13 | 11 | 5 | 5 | 34 |
| Acetaminophen | 1 | 7 | 18 | 5 | 3 | 34 |
| Placebo | 2 | 1 | 10 | 13 | 9 | 35 |

Overall, 30 mg codeine, administered as two 15 mg capsules of codeine, appears to be superior to PBO in this clinical trial of moderately to severe pain in post partum patients who have undergone episiotomy. There was no reported statistically significant difference between 600 mg APAP alone, and 30 mg codeine, alone. Each drug alone, e.g., APAP and codeine, is reported to produce results which were statistically superior ($p < 0.01$) to PBO.

Limitations of Study # 20

In summary, the limitations of this clinical trial appear to include 1) the study design is limited to a single-dose of 30 mg codeine (15 mg codeine in each capsule, administered as two capsules) over a 4-hour duration in post partum patients who underwent episiotomy; 2) that is no apparent correction for the multiplicity of endpoints employed in

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this clinical trial; 3) this single-dose clinical trial was not primarily conducted to assess codeine alone.

Codeine 60 mg
Single Dose/ Acute Pain, Post-Oral Surgery
Study # 69
Bentley KC et al. 1987

Study Design and Objectives

Study # 69 was a randomized, double-blind, placebo-controlled, single-dose clinical trial in healthy males and females undergoing oral surgery (e.g., removal of impacted tooth with or without mucoperiosteal flap and removal of bone). The objectives of this trial were to examine the analgesic efficacy of 1000 mg APAP and 60 mg codeine phosphate and then determine their respective contributions of the combination of these two medications in patients with acute pain secondary to oral surgery.

The patients in this study had undergone one of the following procedures: 1) surgical removal of an impacted tooth; 2) surgical removal of a tooth necessitating the reflection of a mucoperiosteal flap and the removal of bone; or 3) other oral surgical procedures requiring reflection of a mucoperiosteal flap and removal of overlying bone.

Patients were randomized to 1000 mg APAP with 60 mg codeine phosphate, 1000 mg APAP alone, 60 mg codeine phosphate alone, or PBO. The designation of treatment to a drug code number involved a random allocation procedure with blocking. For every six consecutive numbers, two were designated 1000 mg APAP with 60 mg codeine phosphate, two were designated 1000 mg APAP, one was designated 60 mg codeine phosphate, and one was PBO. This distribution of patients to treatment groups provided increased power for testing the two treatments expected to be most efficacious while minimizing the number of patients exposed to the less effective treatments. Patients were instructed to take the medication when they could not tolerate the post oral surgery pain.

The study medication was the first medication taken after surgery. No other sedative or narcotic agents were used before, during or after surgery. All the patients were outpatients who provided patient reported outcomes. Patients reported their pain intensity and the time of day. As reported, additional medication (Tylenol with Codeine No. 3) was provided as a "rescue" analgesic and for use as needed beyond the trial period. Patients who re-medicated before the fifth hour recorded the time of taking the medication.

Treatments

Study drugs included: 1000 mg APAP with 60 mg codeine phosphate, 1000 mg APAP alone, 60 mg codeine phosphate alone, or PBO.

Efficacy Endpoints

Both pain intensity and pain relief ratings were employed to assess efficacy. Pain intensity and pain relief were recorded at 1, 2, 3, 4 and 5 hours after study drug administration. Pain intensity was rated on a nine-point scale at baseline (severe 9, 8, 7/

moderate 6, 5, 4/ mild 3, 2, 1) and on a 10-point scale that included “no pain” (0) for the ensuing hourly ratings. Pain relief employed a five-point scale ranging from “excellent” (4) through “no relief” (0). As noted above, patients who re-medicated before the fifth hour recorded the time of taking re-medication. The pain relief and pain intensity ratings at the time of re-medication were carried over for the remaining time points in the statistical analysis.

The hourly ratings were used to derive the following measures of analgesia: hourly pain intensity difference (PID) scores, sum of PID (SPID) scores, largest PID (PEAKPID) score, hourly pain relief score, total pain relief (TOTPAR) score, largest pain relief (PEAKREL) score, and time to re-medication in hours. The PID score was computed by subtracting the hourly pain intensity rating from the initial (baseline) pain intensity. The time between ingestion of the study drug and the additional analgesic was calculated and used as a measure of the duration of analgesia. The hourly scores were summed to compute the SPIDs and TOTPARs. The study was analyzed by the classic 2 x 2 factorial design appropriate for testing the contribution of two constituent compounds in a combination drug.

Results

The study was a two-by-two factorial clinical trial in which 120 patients suffering from acute pain as a result of oral surgery rated their pain intensity and pain relief for up to 5 hours after a single dose of one study drug.

A total of 128 patients were enrolled in this clinical trial and 120 patients were included in the efficacy analysis. The remaining 8 patients were excluded for the following reasons: three patients did not take the study medication, one patient each took only a portion of the study medication, did not take the medication until the day after surgery, re-medicated within 30 minutes of taking the study medication, vomited within 30 minutes of taking the study medication, and did not return the study forms.

Treatment groups were: APAP 1000 mg, 42 patients; APAP 1000 mg + codeine 60 mg, 42 patients; codeine 60 mg, 22 patients; and PBO, 19 patients. The patient characteristics by treatment group including age, sex, surgical procedure and initial pain level were similar across the four treatment groups. Baseline pain by treatment group was reported as: 1000 mg APAP/60 mg codeine 5.88 (1.76); 1000 mg APAP 5.44 (1.66); 60 mg codeine 5.48 (1.63); and PBO 5.24 (1.86).

A summary of efficacy parameters is shown in Table 1. The sum of the analgesia of the 1000 mg APAP alone and the 60 mg codeine alone appear to almost equal that of the combination product, 1000 mg APAP/ 60 mg codeine, e.g., the sum of the mean SPID scores for the constituents was 10.50, which is close to the mean SPID for the combination (9.71). See Table 1.

The authors report that both the acetaminophen effect and the codeine effect were statistically significant for all measures of efficacy”, as shown in Table 2. The authors also report that the analgesia of the combination (1000 mg APAP/60 mg codeine) appears to show additive effects of the two constituents.

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Table 1. Summary of Efficacy Measures (Revised from literature reference.)

| Summary of Efficacy Measures - Literature Reference # 68 | | | | |
|----------------------------------------------------------|-----------------|---------------------------|--------------|-----------------------------|
| Treatment | No. of Patients | Mean (standard deviation) | | |
| | | SPID | TOTPAR | Median time to remedication |
| 1000 mg APAP/ 60 mg Codeine | 41 | 9.71 (10.49) | 11.45 (5.01) | 4.17 |
| 1000 mg APAP | 41 | 8.17 | 8.88 (3.25) | 3.25 |
| 60 mg Codeine | 21 | 4.33 (11.60) | 7.48 (3.58) | 2 |
| PBO | 17 | -2 | 4.94 (8.13) | 1.47 |

Abbreviations: PBO = placebo; APAP = acetaminophen; mg = milligrams; SPID = sum pain intensity difference score; TOTPAR = total pain relief score

Table 2. Significance levels (one tailed) [Revised from literature reference.]

| | Acetaminophen 1000 mg | Codeine 60 mg |
|------------------------------------------------------------|--------------------------|------------------|
| Contribution to the analgesic effect of the combination | | |
| SPID | 0.0014 | 0.0246 |
| PEAKPID | 0.0002 | 0.032 |
| TOTPAR | 0.0001 | 0.0012 |
| PEAKREL | 0.0001 | 0.012 |
| Duration of analgesia combination versus | 0.0047 | 0.0021 |

The time-effect curves for mean PIDs and mean pain relief scores are shown in Figure 1 and Figure 2. The duration of analgesia was tested by comparing the remedication rates in the active treatment groups. The authors report a significant difference between the remedication rates of the combination group and each of the individual drugs alone (e.g., 1000 mg APAP and 60 mg codeine). Figure 3 shows the curves which demonstrate the proportion of patients remedivating overtime for all treatments.

Figure 1. Mean PID scores versus time in hours (Revised from literature reference.)

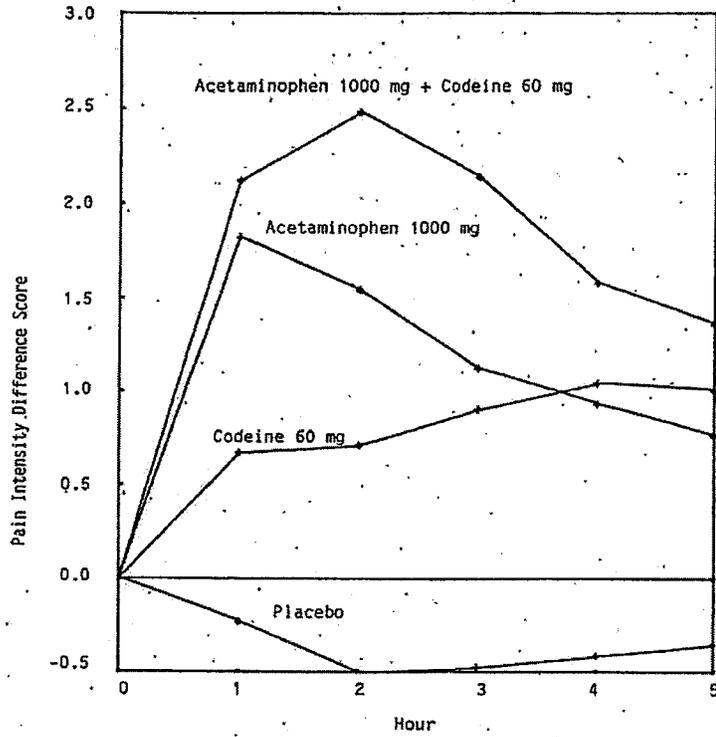


Figure 2. Mean pain relief scores versus time in hours. (Revised from literature reference.)

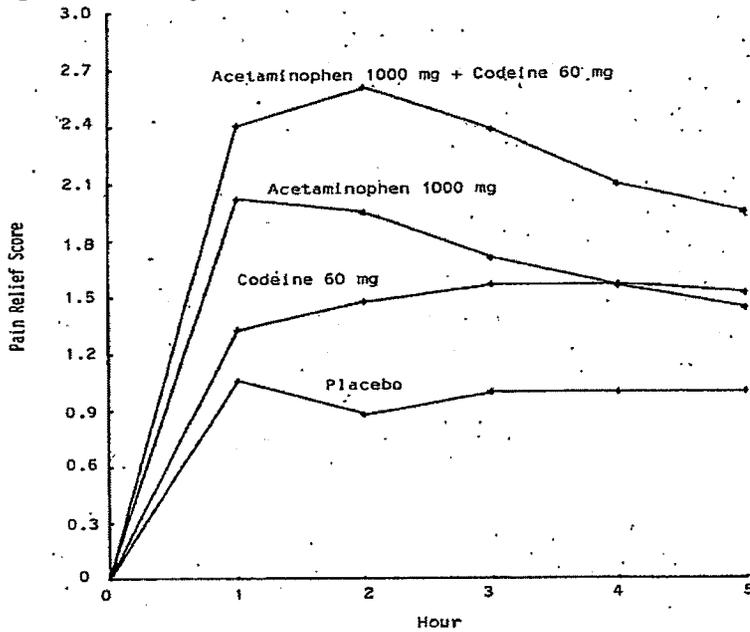
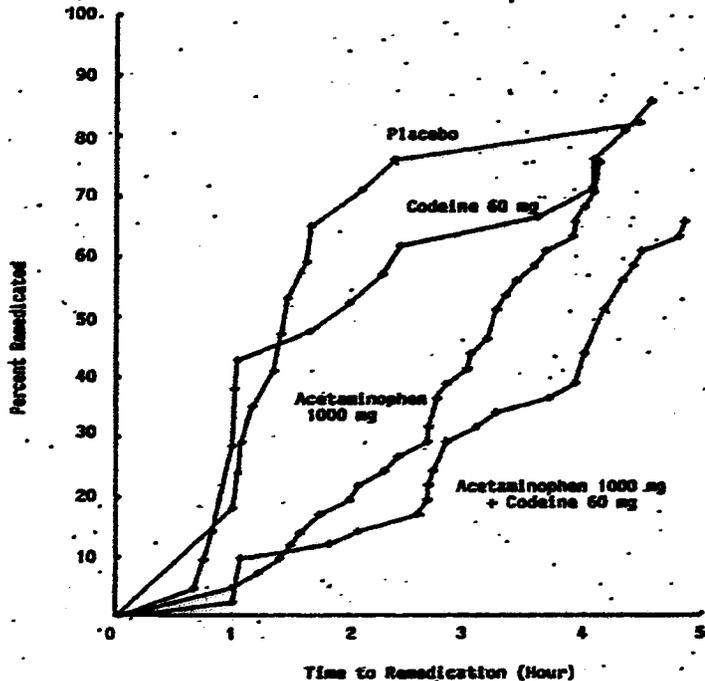


Figure 3. Percent of patients remediate versus time in hours (Revised from literature reference.)



In summary, a single dose of 60 mg codeine phosphate appears to provide better analgesia than PBO in the population of post operative oral surgery patients. The statistical analysis appears to demonstrate that both 1000 mg APAP and 60 mg codeine show a statistically significant ($p < 0.05$) contribution to the analgesic effectiveness of the combination, 1000 mg APAP/60 mg codeine, on all measures of efficacy.

Limitations of Study #69

The limitations of this study include: 1) no reported correction for multiplicity of efficacy endpoints.

Codeine 60 mg

Multiple Dose/ Mild to Moderate Acute Pain, Post Oral Surgery

Study # 56

Chilton NW et al. 1978

Study Design and Objectives

Study # 56 was a randomized, double-blind, placebo-controlled, multiple-dose study to evaluate the comparative analgesic effectiveness of 60 mg codeine, 60 mg Ro 4-1778/1, 65 mg dextro propoxyphene (DXP) and PBO after oral extractions or other minor oral surgical procedures. Ro 401778/1 is 1-(p-chlorophenethyl)-6,7-dimethoxy-2-methyl-1, 2, 3, 4-tetrahydroisoquinoline. The authors report that various derivatives of 1-phenethyl-2-methyl-1, 2, 3, 4-tetrahydroisoquinoline contain a halogenated phenethyl group which

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appears to show pain-relieving properties. The authors report that Ro 4-1778/1 was found to have analgesic properties similar to codeine phosphate when administered to mice. Sadove, Ali and Schiffrin¹ reported that Ro 4-1778/1 and codeine appear to be approximately equianalgesic if administered orally to patients with post operative oral surgery pain.

It is reported in this reference that oral 60 mg Ro 4-1778/1, 60 mg codeine, and 65 mg DXP produced analgesia with post operative oral surgery pain more frequently than did 32 mg DXP, and that 60 mg Ro 4-1778/1 and 60 mg codeine were more effective than 30 mg codeine in post operative oral surgery patients. Therefore, the comparative analgesic effects of multiple-dose 60 mg codeine and 60 mg Ro 4-1778/1 (four-doses in 24 hours), post oral extraction or other minor oral surgical procedures, was investigated in this clinical trial

Reference

1. Sadove, D.S., ali S.M. and Schiffrin, M. J.: Illinois State Med. J., 117, 425, 1960.

Treatment

Patients were randomized to: 60 mg Ro 4-1778/1; 60 mg codeine sulfate; 65 mg DXP, or PBO. Patients with mild to moderate post oral surgery acute pain were instructed to return for follow re-examination in 48 hours. Patients were instructed to take one capsule every 4 hours, if necessary, for pain.

Efficacy Assessments

At the time of re-examination, the authors report the effectiveness of the four treatment group medications. Two measures were reported by the authors: patient reported pain relief afforded by the first-dose and by multiple-doses.

Results

A total of 600 hundred patients (349 females and 251 males) ages 14 to 84 years of age were enrolled in this clinical trial from a university oral surgery dental clinic. A total of 16 patients (3%) were lost from follow-up and 584 patients were available for re-examination in 48 hours. Of the available 584 patients, 83 patients (14%) failed to experience sufficient postoperative pain or discomfort to take any medication. Data from a total of 501 patient responses were obtained from the follow-up assessments.

The 60 mg codeine sulfate proved more effective than either 65 mg DXP or PBO, and 60 mg Ro 4-1778/1 did not differ from 60 mg codeine sulfate in its effectiveness as a postoperative dental pain analgesic agent. The percent of patients who obtained analgesia after all study medication doses was reported as 65 mg DXP (89%), 60 mg Ro 4-1778/1 (96%), 60 mg codeine sulfate (98%), and PBO (88%).

Table 1a shows the reported analgesia produced by the first dose of study medications. These data appear to indicate that the incidence of pain relief from the first dose of Drugs A (65 mg DXP) and D (PBO) was almost identical, that the frequency of analgesia provided by the first dose of Drug C (60 mg codeine sulfate) was highest, and that the

efficacy of Drug B (60 mg Ro 4-1778/1) appeared to be close to that of Drug C (60 mg codeine sulfate).

Table 1b shows the reported analgesia by all doses of study medications. Nine, 13, 16 and 20 patients were reported to require only one dose of Drugs A (65 mg DXP), B (60 mg Ro 4-1778/1), C (60 mg codeine sulfate), and D (PBO), respectively. All other patients appear to have taken more than one dose. In **Table 1b**, the reported incidence of analgesia from all doses taken appears to demonstrate that Drug A and D were similar in analgesic effect, the frequency of pain relief from Drug C was the highest, and Drug B was the second highest for analgesia effect. As reported by the authors, only one patient each who did not experience analgesia from the first dose of Drugs A, B and C, respectively, derived relief from multiple doses. The authors also report that none of the patients who failed to have pain relief from the first dose of drug D achieved analgesia after multiple doses.

Table 1a. Analgesia Produced by the First Dose of Four Medications in 501 Patients with Pain Due to Oral Surgical Procedures (revised from literature reference Study #56)

| Medication | Analgesia | | No Analgesia | | Totals | |
|------------|-----------------|------|-----------------|------|-----------------|-------|
| | Number Patients | % | Number Patients | % | Number Patients | % |
| A | 112 | 88.2 | 15 | 11.8 | 127 | 100.0 |
| B | 111 | 94.9 | 6 | 5.1 | 117 | 100.0 |
| C | 124 | 97.6 | 3 | 2.4 | 127 | 100.0 |
| D | 114 | 87.7 | 16 | 12.3 | 140 | 100.0 |

Abbreviations: Drug A= 65 mg DXP; Drug B= 60 mg Ro 4-1778/1; Drug C= 60 mg codeine sulfate; Drug D= PBO.

Table 1b. Analgesia Produced by all Doses of Four Medications in 501 Patients with Pain Due to Oral Surgical Procedures (revised from literature reference Study #56)

| Medication | Analgesia | | No Analgesia | | Totals | |
|------------|-----------------|------|-----------------|------|-----------------|-------|
| | Number Patients | % | Number Patients | % | Number Patients | % |
| A | 113 | 89.0 | 14 | 11.0 | 127 | 100.0 |
| B | 112 | 95.7 | 5 | 4.3 | 117 | 100.0 |
| C | 125 | 98.4 | 2 | 1.6 | 127 | 100.0 |
| D | 114 | 87.7 | 16 | 12.3 | 130 | 100.0 |

Abbreviations: Drug A= 65 mg DXP; Drug B= 60 mg Ro 4-1778/1; Drug C= 60 mg codeine sulfate; Drug D= PBO.

The authors report that the differences between the following drugs were statistically significant at the 1% level: *after the first dose*, Drugs A (DXP 65 mg) and C (codeine 60 mg), and Drugs D (PBO) and C (codeine 60 mg); and *after all doses*, Drugs A (DXP 65 mg) and C (codeine 60 mg), and Drugs D (PBO) and Drug C (codeine 60 mg). In both these comparisons, according to the authors, Drug C (codeine 60 mg) was significantly better than either Drug A (DXP 65 mg) or Drug D (PBO). When Drug C (codeine 60 mg) and Drug B (Ro 4-1778/1 60 mg) were compared, statistically significant differences were not reported by the authors.

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In summary of Study #56, codeine sulfate 60 mg was reported to be statistically significantly more effective than either DXP 65 mg or PBO in providing pain relief in patients with mild to moderate pain relief following oral surgery. There was no reported statistically significant difference between effectiveness of 60 mg codeine sulfate and 60 mg Ro 4-1778/1 in pain relief.

Limitations of Study #56

The limitations in Study #56 include: 1) the high incidence of analgesia from PBO medication reported as 88% in this trial. It is a well known in dental pain trials, that many patients do not require treatment for pain; however, for those patients who do require treatment for pain, the post oral surgery model remains a good study population; (2) the lack of correction for the multiplicity of efficacy endpoints.

SUPPORTIVE EFFICACY STUDIES

Codeine 30 mg (Single-Dose) and Codeine 60 mg (Multiple-Dose)

Single-Dose and Multiple-Dose/ Chronic Pain Conditions (e.g., skeletal, neural, visceral, headache)

Study # 78:

Martinetti L et al. 1970

Study Design and Objectives

Study # 78 was a randomized, double-blind, placebo-controlled, crossover clinical trial to evaluate the relative analgesic efficacy and occurrence of side effects of a new molecular entity oral compound, Z424, 1- α -(N-0-chlorobenzyl) pyrrol-2-di-sec-butylanine ethanol (Z424) after oral administration, in patients with chronic pain described as moderate or severe. Z424 (diviminol) is a new oral analgesic compound with analgesic activity of central origin not structurally related to the narcotics or non-narcotic analgesic agents. Diviminol has been studied in patients with chronic bronchitis for pathologic cough, as an analgesic for chronic in pain in elderly patients and in cancer patients with chronic pain.

The clinical effects of 30 mg Z424, 30 mg codeine phosphate, and PBO were compared after single-dose and after repeat oral doses in two double-blind, crossover studies referred to as Study # 1 and # 2, respectively. The study population was hospitalized patients with a variety of chronic pain conditions (e.g., skeletal, articular, neural, visceral, neoplastic, obstructive arterial disorders, and headache) that were likely to persist for a total of at least 3 days (not necessarily 3 consecutive days) and were associated with pain of sufficient severity to require narcotics. In Studies #1 and #2, patients were randomized to 30 mg Z424, 30 mg codeine phosphate, and PBO capsules. See the results section for the total number of enrolled patients.

Study #1. Treatment

In Study #1, each patient received one-dose of two capsules of all three preparations at 8:00 AM on 3 mornings, not necessarily on three consecutive days. No patient received any analgesic for at least 3 hours prior to administration of the study drug preparations.

Only patients who received all three medications (e.g., a single round) were included in the study.

Just prior to the administration of the study drug and at hourly intervals, thereafter, for 5 hours, the patients were questioned about pain intensity: no pain (0); slight pain (1); moderate pain (2); severe pain (3). Study treatments were given only when the patient complained of moderate to severe pain. At the conclusion of each round, patients were asked their preference for the treatment which provided the most pain relief. Initial pain intensity scores were nearly always 3; if the score remained unchanged up to 3 hours after medication, known analgesics were given and the same score was assigned for subsequent hourly ratings. See Figure 1 in the results section of this study.

In Study #2, all patients received each of the three medications for one day in a dosage of two capsules, three times daily at 9 AM, 2 PM and 8 PM on three days, not necessarily consecutive. As in Study #1, the pain intensity score before treatment was nearly always 3. No analgesics, other than the study preparation, were allowed during the study. As shown in Figure 1 (Study #1) and Figure 2 (Study #2), the assessments for pain intensity were measured hourly for a total of 5 hours.

Efficacy Assessments

In Study #1, the hourly pain intensity difference from baseline (PID) was calculated; and the sum of the hourly (5 hours) pain intensity differences (SPID) was calculated for each patient. Post medication scores were also reported according to the amount of pain relief: complete – all post medication pain intensity scores 0, with a single 1 permitted; partial – all scores between the above and a maximum of all scores 1, with a single 3 permitted; unsatisfactory – all others. The sum of complete and partial defined as equivalent to the “50% or more relief”.

In Study #2, the data were evaluated in terms of the pain intensity scores for each post-medication rating and the total pain intensity scores, the sum of the intensity scores of the four daily post-medication ratings.

Results. Study #1

Study #1 included 44 patients (64% females) with a mean age of 62 years (range 36 to 84 years). A total of 44 patients completed 54 rounds of medication administration.

By subtracting the baseline pain intensity score from the hourly post-medication pain intensity scores for each patient, hourly pain intensity difference (PID) was obtained. The sum of the hourly (5 hours) pain intensity differences (SPID) was calculated for each patient. Both the mean PID and the mean SPID of the three treatments indicated a difference in their analgesic efficacy compared to each other.

See Figure 1. The SPID (5 hours) for each treatment was reported as follows: 60 mg Z424, 7.98 ± 0.67 ; 60 mg codeine, 11.24 ± 0.53 , and PBO, 3.59 ± 0.53 . As reported by the authors, the analysis of variance of the latter (e.g., analgesic efficacy) showed that

both codeine and Z424 had an analgesic effect significantly greater than PBO and that codeine and Z424 differed significantly from each other.

Figure 1. Pain Intensity Scores before Drug and at Four Ratings during One Day of Treatment with Repeated Doses (mean). (Revised from literature reference.)

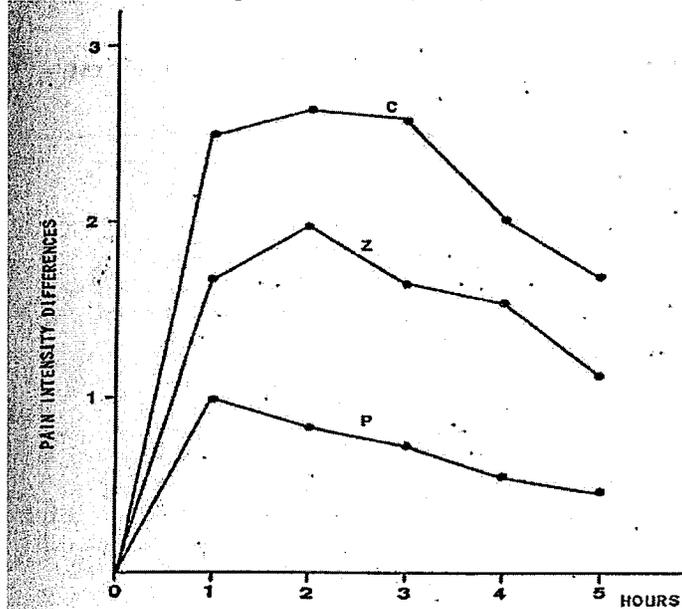


Fig. 1. Time course of pain intensity differences after single doses in 54 rounds (means). P=Placebo; Z=Z.424, 60 mg; C=codeine, 60 mg.

Results, Study #2

In Study #2, there were 60 patients (82% females) with a mean age of 56 years (range 19 to 79 years). A total of 60 patients completed 67 rounds of medication administration.

These data were evaluated in terms of the pain intensity scores for each post-medication rating and total pain intensity scores, and the sum of the pain intensity scores of the four daily post-medication ratings. The initial pain intensity scores were equal for the three groups. The individual pain intensity scores were not reported by the authors in this reference but baseline through 5-hour pain intensity scores are shown in **Figure 2** and in **Table 1**.

The mean post-medication intensity scores and the mean total (four observations) pain intensity scores appeared to demonstrate a difference in the analgesic effects of the three medications. See **Figure 2** and **Table 1**. Of the 15 patients who expressed a preference for one of the three treatments, 5 patients chose Z424 and 10 patients chose codeine. As explained by the authors, the analysis of the variance of the total pain intensity scores appeared to show that the difference between 60 mg Z424 and 60 mg codeine was not significant but that both 60 mg Z424 and 60 mg codeine appeared to differ significantly from PBO.

Figure 2. Pain Intensity Scores before Drug and at Four Ratings during One Day of Treatment with Repeated Doses (means). (Revised from literature reference)

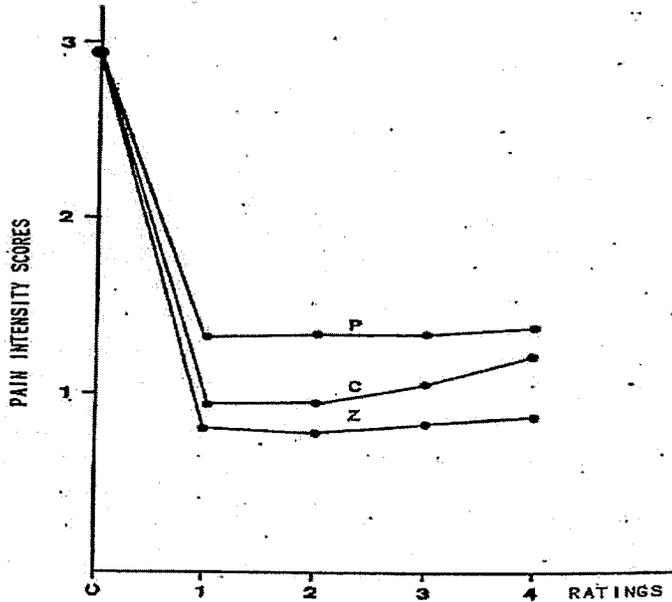


Fig. 2. Pain intensity scores before drug and at the four ratings during one day of treatment with repeated doses (means). P=Placebo t.i.d.; Z=Z.424, 60 mg t.i.d.; C=codeine, 60 mg t.i.d.

Table 1. Study #2 (Repeated Doses): total Daily Pain Intensity Scores in 67 Rounds, and Analysis of Variance (revised from literature reference)

| Source of variation | d.f. | Sum of squares | Mean squares | f | Total daily intensity score (4 postmedication ratings; mean ± S.E.) | |
|-------------------------|------|----------------|--------------|---------|---------------------------------------------------------------------|-------------|
| | | | | | Treatment | |
| | | | | | Z.424, 60 mg t.i.d. | 3.30 ± 0.43 |
| | | | | | Codeine, 60 mg t.i.d. | 4.11 ± 0.43 |
| | | | | | Placebo t.i.d. | 5.39 ± 0.44 |
| Between treatments | 2 | 151.07 | 75.54 | 6.63** | | |
| Z vs C | 1 | 21.76 | 21.76 | 1.91 | | |
| Z+C vs P | 1 | 129.31 | 129.31 | 11.35** | | |
| C vs P | 1 | 56.49 | 56.49 | 4.95* | | |
| C+P vs Z | 1 | 94.59 | 94.59 | 8.30** | | |
| Between blocks (rounds) | 66 | 1036.16 | 15.70 | 1.38 | | |
| Error | 132 | 1504.26 | 11.40 | — | | |
| Total | 200 | 2691.49 | | | | |

* P < 0.05.

** P < 0.01.

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Boehringer Ingelheim, Inc.; Roxane Laboratories

A total of 35 patients were reported to have preferred 60 mg Z424, 20 patients were reported to have preferred 60 mg codeine, and only four patients were reported to have preferred PBO.

In summary, codeine 60 mg was reported to be superior to PBO for the relief of chronic pain characterized as moderate to severe pain in this patient population with diverse conditions. In addition, the results of these two double-blind, randomized, placebo-controlled, crossover studies appear to demonstrate that 30 mg (SD) and 60 mg (MD) Z424, respectively, have analgesic activity distinguishable from PBO when administered orally in single or in repeat-doses (t.i.d.) to patients with chronic pain characterized as moderate to severe pain. The analgesic efficacy of 60 mg Z424 appeared to be of the order of that of 60 mg codeine.

Limitations of Study # 78

The limitations across these two clinical trials include: 1) Study #1 and Study #2 assessed patient populations with diverse conditions, e.g., skeletal, articular, neural, visceral, neoplastic, obstructive arterial disorders, and headache, with chronic pain. These two studies include patients with chronic diseases associated with chronic pain. Therefore, the application of these results to an acute pain population must be done cautiously; 2) these efficacy data were not statistically analyzed according to each group of patients with a specific disorder because of the small number of cases in each reported condition; 3) Study #1 and Study #2 appear to lack correction for multiplicity of efficacy endpoints.

Codeine 60 mg

Multiple Dose/ Acute Pain, Patients with Episiotomy

Study # 24

Levin HM et al. 1978

Study Design and Objectives

Study # 24 was a randomized, double-blind, placebo-controlled, multiple-dose study in which 8 mg and 16 mg butorphanol tartrate, 60 mg codeine phosphate, and PBO were compared for evaluation of analgesic activity in hospitalized women suffering from moderate to very severe post-partum episiotomy pain. Butorphanol tartrate (levocyclobutylmethyl-6, 10 β -dihydroxy-1, 2, 3, 9, 10, 10 α -hexahydro-(4H)-10, 4a-iminoethanophenanthrene tartrate) is reported to be a new molecular entity synthetic analgesic.

Treatment

Study drugs included: 8 mg and 16 mg butorphanol tartrate, 60 mg codeine phosphate, and PBO. Patients were randomized to receive identical capsules of study drug every 6 hours for a total of 4 doses in this 24-hour clinical trial.

Efficacy Assessments

Baseline evaluation of pain severity was assessed as follows: absent = 0, mild = 1, moderate = 2, severe = 3 and very severe = 4. Only patients satisfying the entry criteria

and experiencing episiotomy pain of at least moderate to severe intensity were entered into this study. The doses (2 capsules) of study medication were given at 0, 6, 12 and 18 hours. Pain severity was reported at ½, 1, 2, 3, 4, 5, 6, 8, 12, 18, 20 and 24 hours following the initial dose. The 6, 12, and 18 hour ratings represented 6 hour post-dose readings as well as baseline for the next dose. An investigator's global assessment on the overall patient's improvement was made at the end of the study.

Results

A total of 127 hospitalized women between 20 and 35 years of age who were suffering from moderate to very severe episiotomy pain participated in this clinical trial. There were 31 patients in the 8 mg butorphanol treatment group; and 32 patients in the 16 mg butorphanol, 60 mg codeine, and the PBO treatment groups.

The initial pain severity scores for all treatment groups were not significantly different from each other. Analysis of the pain severity data appeared to demonstrate that all of the active treatments were significantly better than PBO at 1, 2 and 3 hours. Only 8 mg and 16 mg butorphanol (means) appeared to be consistently better than PBO at all of the subsequent observation periods to 3 hours. Codeine 60 mg did not appear to be significantly different from PBO at 5 and 6 hours following the first dose nor at 6 hours following the second and third doses. Codeine did appear to achieve statistical significance at 6 hours following the fourth doses.

The pain intensity data sums appears to demonstrate that 16 mg butorphanol was significantly better than 60 mg codeine and PBO according to the 6 and 18 hour sums and that 8 mg butorphanol was not significantly different from either 16 mg butorphanol or 60 mg codeine. All active treatments appeared to be better than PBO as determined by the 2, 4, 6, 12 and 24 hour post-partum episiotomy pain intensity sums. The comparative pain scores appeared to support a longer duration of action for butorphanol over codeine as indicated by activity at the longer time intervals (4 to 6 hours). Both 8 mg and 16 mg butorphanol doses appeared to be significantly more effective than 60 mg codeine at 4, 5, and 6 hours following the first dose and 6 hours following the third dose. Butorphanol 16 mg was significantly better than 8 mg butorphanol which was, in turn, better than 60 mg codeine at the 6 hour observation following the first dose.

The summed data appeared to support a longer duration of action for butorphanol. All active treatments appeared to be significantly better than PBO as determined by the 2, 4, 6, 12, 18, and 24 hour sums. For the global assessments, all treatments were better than PBO ($p < 0.05$).

Regarding the onset of effect, 60 mg codeine and 8 mg butorphanol appeared to demonstrate significant analgesic activity at 1 hour post treatment, while 16 mg butorphanol appeared to be significantly effective at 30 minutes. The peak effect for all active treatments was reported at 2 hours.

In summary, 60 mg codeine appears to be superior to PBO as an analgesic in this study of patients experiencing episiotomy pain of at least moderate to severe intensity. Codeine 60

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mg had an onset of action as determined by PI measurements at 1 hour post treatment, the peak effect for codeine 60 mg occurred at 2 hours and the duration of action of codeine 60 mg was 4 hours in this study. Codeine 60 mg appears to be equivalent in activity to butorphanol 8 mg.

Limitations of Study # 24

The limitations in this study include: 1) the limited 24-hour study duration; 2) the efficacy data lacks correction for the multiplicity of efficacy endpoints; 3) onset of analgesia was not determined using the currently accepted standard (double stop watch) but only estimated using periodic principal investigator evaluations; and 4) concern about a carryover effect in this study.

Codeine 65 mg

Multiple Dose/ Acute Pain, Post Orthopedic Surgery

Study # 40

Bergen WS et al. 1978

Study Design and Objectives

Study # 40 was a randomized, double-blind, crossover, placebo-controlled clinical trial to determine the comparative value of pain relief drugs in patients who had undergone orthopedic surgery. The study treatments included: 100 mg dextro propoxyphene hydrochloride (DXP); 65 mg codeine phosphate; 100 mg meperidine hydrochloride; and PBO. Patients in this clinical trial were started on medication 48 hours post-operatively and continued for three days at four-hourly intervals (Study Day 3, 4, and 5), if possible. No other analgesics were administered.

Treatments

Capsules (100 mg DXP; 65 mg codeine phosphate; 100 mg meperidine hydrochloride; and PBO) were given every four hours on a 2-6-10 o'clock schedule. The order of administration was systematically randomized and all patients received all four medications with the exception of 20 patients who did not receive the PBO.

Efficacy Assessments

Patients were questioned three or four times per day about premedication pain, post-medication pain and duration of relief obtained. The patient reported outcome for pain was scored as: 1 = no pain; 2 = mild pain; 3 = moderate pain; and 4 = severe pain. The intensity of pain was also patient reported. No attempt was made to determine hourly pain scores. Relief from pain was defined as the difference between the pre-drug score and the lowest score reported in the four hours after taking a capsule. The mean pain relief patient reported scores were determined for each study treatment on each post operative day. The percentage of administration of each drug giving relief was reported. The degree of relief afforded by only the first dose administered each patient was also reported. Data concerning constant reactors, inconstant reactors, and constant non-reactors to PBO were separated and analyzed. Only those patients who had received two or more doses of PBO while they had pain were included in these groups.

Results

A total of 94 post orthopedic surgery patients likely to remain in the hospital for at least 5 post-operative days were enrolled into this three-day clinical trial. There were 38 (40%) men and 56 (60%) women enrolled with a mean age of 45 years. Sixty-three (67%) of the patients completed the three-day study. A total of 32% of patients had severe pain (grade 4) sometime during the trial and only 8% reported no pain at any time during the trial.

Pain relief with the active treatments was reported to be significantly greater than PBO on Day 1 (Day 3 post-operative) and on Day 3 (Day 5 post-operative). Merperidine 100 mg and DXP 100 mg were reported to significantly lower the mean pain score on post operative Day 4 but there was no reported difference between the effects of any of the study drugs on the last day of the study (Day 5 post-operative). The authors reported that none of the three active drugs (DXP 100 mg, merperidine 100 mg, and 65 mg codeine) differed significantly from each other. The authors also reported a progressive daily decline in relief by all the study drugs except PBO.

The total mean pain relief scores for each medication were reported as: PBO, 0.41; codeine phosphate (65 mg), 0.67; DXP (100 mg), 0.72; and merperidine (100 mg), 0.77. All the active treatments were significantly different from PBO ($p < 0.01$) on the last day of the study (Day 5 post-operative).

The study medications which gave some relief of pain were reported as: pain was relieved to some extent about 42% of the time by PBO and about 58% of the time by the active treatments, specifically, 57% of the time by codeine phosphate 65 mg, 61% of the time by DXP, and 65% of the time by merperidine compared with the PBO response ($p < 0.001$). There were no differences in the duration of pain relief afforded by any of the drug capsules including PBO, the mean duration in hours reported as 3.26 hours for PBO, 3.28 hours for codeine phosphate, 3.17 hours for DXP, and 3.20 hours for merperidine.

In summary, orally administered DXP, merperidine and codeine phosphate were significantly more effective than PBO. In the doses used, the study medications were indistinguishable from each other. In approximately 40% of the time, the PBO was followed by a reduction in the severity of pain. The failure to detect drug effects on study Day 3 (post operative Day 5) may have resulted from the condition of less severe pain overtime post operatively, so that the PBO effect became more important in providing relief. Patients appeared to discriminate between the effect of PBO and the analgesics best on the first day of this clinical trial when the pain was most severe.

Limitations of Study #40

The limitations of this study include: 1) no reported correction for multiplicity of efficacy endpoints; and 2) the carryover effect as patients received all treatments over the 24-hour trial duration; hence, the effect of one drug could carryover to another active treatment assessment period.

DOSING RECOMMENDATIONS

The reviewed literature regarding the efficacy of oral codeine sulfate supports the proposed dosage strength tablets of 15 mg, 30 mg and 60 mg in single-dose or multiple-doses in adult patients with mild to moderately severe acute pain. Since opioid analgesics are titrated to effect, all proposed strengths are appropriate.

SAFETY

The safety for the proposed codeine sulfate oral tablets will rely upon the safety reported in the current approved labeling for Tylenol® with Codeine No. 3. In summary, the most commonly reported adverse events reported in the current labeling for Tylenol® with Codeine No. 3 include light-headedness, dizziness, sedation, shortness of breath, drowsiness, nausea, vomiting, and sweating. The single- or multiple-dose exposures reveal these commonly reported adverse events. These adverse events may differ from one patient to another patient based on an individuals' genetic capability to metabolize codeine. The warnings reported with codeine phosphate include respiratory depression, gastrointestinal obstruction, hypotension, as well as the abuse and diversion potential, dependence and tolerance, and sedation risks. See below Section on Schedule II Controlled Substance and Section on Overdose.

Class labeling has been added to all codeine containing products which addresses the ultra-rapid metabolizers of codeine. Some patients may be ultra-rapid metabolizers of codeine phosphate due to a specific CYP2D6 genotype. These patients convert codeine into its active metabolite, morphine, more rapidly and completely than patients who are normal metabolizers of codeine, resulting in higher than expected serum morphine levels. Toxic serum levels of morphine have been reported in infants of nursing mothers who were reported to be ultra-rapid metabolizers. In these cases, the mother is at risk to experience overdose symptoms such as respiratory depression, extreme sleepiness, or delirium. Infant death has been reported secondary to breast feeding from a mother who is a ultra-rapid metabolizer of codeine.

Inter-individual and diverse ethnic groups demonstrate differences in the ability to metabolize codeine to morphine via O-demethylation. The cytochrome (CYP) 450 2D6 enzyme is responsible for the conversion of codeine to morphine. Some individuals may be ultra-rapid metabolizers of codeine sulfate due to the specific CYP2D6 enzyme. It is recognized that human genetic polymorphisms result in different CYP2D6 phenotypes which are directly responsible for the O-demethylation of codeine to morphine. The patients who are rapid metabolizers of codeine convert into its active metabolite, morphine, more rapidly and completely than individuals who are normal metabolizers of codeine. This results in higher than expected serum morphine levels. Ultra-rapid metabolizers of codeine may experience overdose symptoms such as respiratory depression, extreme sleepiness, or delirium. Toxic and even lethal serum levels of morphine have been reported in infants of nursing mothers who may be ultra-rapid metabolizers of codeine sulfate. The use of codeine during labor may cause respiratory depression in the neonate.

NDA 22-402 Codeine Sulfate Tablets: 15, 30, and 60 mg
Boehringer Ingelheim, Inc.; Roxane Laboratories

As stated in the current labeling for Soma Compound with Codeine, “the prevalence of the CYP2D6 phenotype has been estimated at 16 to 28% in North Africans, Ethiopians and Arabs; 1 to 10% in Caucasians; 3% in African Americans; and 0.5 to 1% in Chinese, Japanese, and Hispanics. When physicians prescribe codeine-containing products, they should choose the lowest effective dose for the shortest period of time”.

Schedule II Controlled Substance

Codeine phosphate is a Schedule II controlled substance under the Division of Drug Enforcement Administration (DEA), Office of Diversion Control. Accordingly, if approved, oral codeine sulfate would be a Schedule II controlled substance. The use of opioids, including codeine phosphate, can result in psychological and or physical dependence as well as tolerance. As reported in the current Soma Compound with Codeine labeling, “withdrawal symptoms associated with abrupt opioid discontinuation include restlessness, irritability, anxiety, lacrimation, rhinorrhea, sweating, chills, mydriasis, insomnia, diarrhea, tachypnea, tachycardia, and or hypertension. The use of opioids, including codeine phosphate, can result in tolerance, specifically, the need for increasing doses to maintain a desired effect in the absence of other factors (e.g., disease progression)”.

Overdose

Acute overdose of opioids, including codeine phosphate, can be characterized by respiratory depression, central nervous system (CNS) depression (somnia progressing to coma), hypotension, miosis, skeletal muscle flaccidity, and cold and clammy skin.

There are no other safety signals noted in the review of the literature for this NDA.

OTHER REGULATORY ISSUES

There are no outstanding regulatory issues beyond those discussed in the CMC section of this review.

LABELING

No proprietary names have been proposed for this product formulation.
Proposed labeling revisions: will follow.

CONSULTS

A consult was submitted to the Office of Surveillance and Epidemiology (OSE) for response back to DAARP by November 14, 2008. The consult request included the division’s need to know the doses prescribed and the duration of use for morphine oral liquid and solid orange dosage forms for combination products and single entity products containing codeine in order to justify Roxane Labs’ proposed dosing.
OSE Response: pending.

POSTMARKETING COMMITMENTS AND REQUIREMENTS

Pediatrics

NDA 22-402 Codeine Sulfate Tablets: 15, 30, and 60 mg
Boehringer Ingelheim, Inc.; Roxane Laboratories

See conclusions and recommendations for the pediatric population deferred studies and the pediatric waiver as reported in this review.

SUMMARY

The results from review of published clinical trials submitted under 505(b)(2), NDA 22-402 support the efficacy of oral codeine sulfate tablets (15, 30, and 60 mg) in mild to moderately severe acute pain in adults, and, therefore, support the regulatory decision of approval. Though safety was not formally reviewed in the literature, the published papers reported adverse events which concur with the reported safety in the approved labeling for the combination product, Tylenol® with Codeine No. 3.

Note

1. *There are outstanding CMC issues to be done.*
2. *The labeling negotiations will follow.*
3. *The PDUFA date is May 2, 2009.*

RECOMMENDATIONS

1. Risk/Benefit Assessment:

The overall benefit associated with immediate-release oral codeine sulfate tablets outweighs the overall risk associated with this opioid analgesic.

2. Recommendation for Postmarketing Risk Management Activities:

The product labeling and routine pharmacovigilance plan are adequate, at this time, in terms of post marketing risk management.

APPENDIX

LITERATURE STUDY REFERENCES

Study # 20

Levin HM, Bare WW, Berry FN, Miller JM. Acetaminophen with codeine for the relief of severe pain in postpartum patients. *Current Therapeutic Research*, Vol. 16, No. 9, September 1974: 921-927.

Study # 24

Levin HM. Double-blind oral analgesic study of butorphanol in episiotomy pain: a comparison with codeine and placebo. *J Int Med Res*. 1978; 6:24-33.

Study # 40

Van Bergen WS, North WC, Karp M. Effect of dextro propoxyphene, meperidine and codeine on postoperative pain. *JAMA*, 1960; 172:1372-5.

Study # 56

Chilton NW, Lewandowski A, Cameron JR. Double-blind evaluation of a new analgesic agent in post-extraction pain. *Am J Med Sci*. 1961; 242:702-6.

Study # 69

Bently KC, Head TW. The additive analgesic efficacy of acetaminophen, 1000 mg, codeine, 60 mg, in dental pain. *Clin Pharmacol Ther*. 1987;42:634-40.

**NDA 22-402 Codeine Sulfate Tablets: 15, 30, and 60 mg
Boehringer Ingelheim, Inc.; Roxane Laboratories**

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Martinetti L, Lodola E, Monafò V, Ferrari V. Clinical evaluation of an oral analgesic, Z.424, in patients with chronic pain. J.Clin Pharmacol J New Drugs, 1970; 10:390-9.

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/s/

Carolyn L. Yancey
12/22/2008 04:19:26 PM
MEDICAL OFFICER

Clinical Review NDA 22402 Oral Codeine Sulfate Tablets

Ellen Fields
12/22/2008 05:37:28 PM
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Concur with regulatory action. See CDTL Memo for details.