

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-402

PHARMACOLOGY REVIEW(S)



FDA Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Rheumatology Products
10903 New Hampshire Avenue, Silver Spring, MD 20993

**SUPERVISOR'S SECONDARY REVIEW
PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION**

NDA number: 22-402
Drug Substance: Codeine sulfate tablets
PDUFA Goal Date: 2-Aug-2009
Sponsor: Roxane

Reviewer name: R. Daniel Mellon, Ph.D., Pharmacology Toxicology Supervisor
Division name: Division of Anesthesia, Analgesia, and Rheumatology Products
HFD #: 170

Recommendation: Approval

I have read Dr. Marcus Delatte's review of the nonclinical pharmacology and toxicology sections of NDA 22-402 and agree with his conclusion that the NDA may be approved. I also concur with his recommendations for the nonclinical portions of the labeling and the recommended post-marketing requirements (PMRs).

The NDA applicant, Roxane, will complete the definitive safety qualification studies of the drug substance impurity, codeine methyl ether, as post marketing requirements.

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this page is the manifestation of the electronic signature.**

/s/

R. Daniel Mellon
7/15/2009 05:58:36 PM
PHARMACOLOGIST



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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22-402

SERIAL NUMBER: 000

DATE RECEIVED BY CENTER: 07/03/08

PRODUCT: Codeine Sulfate Tablet

INTENDED CLINICAL POPULATION: Treatment of mild to moderate pain

SPONSOR: Roxane Laboratories, Inc.

DOCUMENTS REVIEWED: Vol. 1 of 53

REVIEW DIVISION: Division of Anesthesia, Analgesia and
Rheumatology Drug Products (HFD-170)

PHARM/TOX REVIEWER: Marcus S. Delatte, Ph.D.

PHARM/TOX SUPERVISOR: R. Daniel Mellon, Ph.D.

DIVISION DIRECTOR: Bob A. Rappaport, M.D.

PROJECT MANAGER: Matthew W. Sullivan

Date of review submission to Division File System (DFS): 06/01/09

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

This NDA application may be approved from a nonclinical pharmacology and toxicology perspective.

B. Recommendation for nonclinical studies

The proposed specification for the drug substance impurity codeine methyl ether (CME) of NMT _____ exceeds the ICH Q3A(R2) qualification threshold. CME has been reported to be a known impurity of codeine; however, the sponsor has not provided adequate safety qualification for this impurity. Therefore, either the DMF holder or the Sponsor must submit adequate safety qualification data for this impurity. Adequate safety qualification must include:

b(4)

- Minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
- Repeat dose toxicology of 90-days duration to support the proposed _____ indication.

b(4)

Drug product stability specifications for degradation products have been determined by the Sponsor (see Table 6). Codeinone and _____ were identified as degradation products of codeine sulfate. Of these products, only codeinone exceeded ICH Q3B(R2) standards. The genetic toxicity of this compound has been tested by the drug substance manufacturer, as noted above. As the current specification of this compound is only marginally outside of the ICH Q3B(R2) specification, given the extensive long clinical experience with codeine that appears to have contained this impurity, the general toxicity of codeinone has been adequately characterized via the existing human data. General toxicology studies with the isolated impurity are not necessary to justify the specification of NMT _____ for the following reasons:

b(4)

b(4)

1. codeinone has probably been present in drug products marketed by Roxane prior to this NDA application,
2. there is evidence that this compound is a minor metabolite in some animal species (see Nagamatsu, et al., 1985),
3. and the specification of NMT _____ compared to _____ results in an added exposure of _____ for the maximum daily dose of _____ and

b(4)

4 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Roxanne Laboratories, Inc. has submitted a New Drug Application (NDA) for codeine sulfate (15, 30, and 60 mg) for the treatment of mild to moderate pain. Codeine has been marketed in drug combination products (see Table 2) for many years and has been studied extensively in various species. No new nonclinical studies were submitted with this NDA application. The Sponsor is relying upon the Agency's previous finding of safety and efficacy of Tylenol with Codeine No. 3 tablets (acetaminophen and codeine phosphate) and published data in the scientific literature to support this 505(b)(2) application.

B. Pharmacologic activity

The Sponsor did not conduct formal pharmacological studies in support of the submitted NDA application. The application is partly supported by published nonclinical studies demonstrating the therapeutic potential of codeine. Codeine has analgesic and antitussive properties that have been demonstrated in experimental animal species (Adcock JJ, et al., 1988; Chau TT and Harris LS, 1980; Erichsen, et al., 2005; Meert TF and Vermeirsch HA, 2005). Studies have examined the receptor pharmacology of codeine, in regard to these properties, as well as its binding affinity to mu- and delta-opioid receptors (Kotzer CJ, et al., 2000; for review see, Trescot AM, et al., 2008).

The pharmacology of codeine has been thoroughly studied using various animal models to demonstrate its efficacy as an analgesic and antitussive agent. Previous studies have demonstrated that codeine produces anti-nociceptive effects in mice, rats, and guinea pigs using a variety of tests (Adcock JJ, et al., 1988; Chau TT and Harris LS, 1980; Meert TF and Vermeirsch HA, 2005). For example, the anti-nociceptive effects of codeine in rats have been demonstrated in studies using the formalin, tail withdrawal, Von Frey, as well as other experimental tests (Erichsen, et al., 2005; Meert TF and Vermeirsch HA, 2005). Studies have demonstrated that codeine produces antitussive effects in cats, guinea pigs and mice using variety of approaches to stimulate cough reflex (Chau TT and Harris LS, 1980; Kotzer CJ, et al., 2000; Saha K, et al., 1997). The antitussive effects of codeine have been demonstrated to be dose-related and reversed by opioid-receptor antagonists such as naloxone (Karlsson JA, et al., 1990; Kotzer CJ, et al., 2000).

C. Nonclinical safety issues relevant to clinical use

There are no new nonclinical safety issues relevant to this drug product. Nonclinical studies have previously demonstrated that codeine in experimental animals alters cardiovascular, respiratory, and gastrointestinal function, which is consistent with clinical findings (Adcock JJ, et al., 1988; Chau TT and Harris LS, 1980; Liguori A, et al., 1996; Meert TF and Vermeirsch HA, 2005). In general, the

magnitude of these effects produced by codeine is lower than those produced by the prototypical opioid analgesic morphine. For example, gastrointestinal studies have demonstrated that the peristalsis ratio in rats was reduced to approximately 40% and 20%, respectively, by codeine and morphine at 40 mg/kg (Meert TF and Vermeirsch HA, 2005). These safety issues are typical of opioid agonists and are monitorable in clinical settings.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number:	22-402
Review number:	1
Sequence number/date/type of submission:	000 / July 3, 2008 / Original NDA
Information to sponsor:	Yes (x) No ()
Sponsor and/or agent:	Roxanne Laboratories, Inc. Columbus, OH 43228
Manufacturer for drug substance:	Boehringer Ingelheim Roxane, Inc. Columbus, OH 43228
Reviewer name:	Marcus S. Delatte, Ph.D.
Division name:	Division of Anesthesia, Analgesia and Rheumatology Products
HFD #:	170
Review completion date:	June 1, 2009
Drug:	
Trade name:	N/A
Generic name:	Codeine Sulfate Tablets
Code name:	N/A
Chemical name:	Morphinan-6-ol, 7, 8-didehydro-4, 5- epoxy-3-methoxy-17-methyl-, (5 α ,6 α)-,sulfate (2:1) (salt), trihydrate
CAS registry number:	1420-53-7
Molecular formula/molecular weight:	(C ₁₈ H ₂₁ NO ₃) ₂ ·H ₂ SO ₄ ·3H ₂ O
Structure:	

Figure 1. Structure for codeine sulfate.

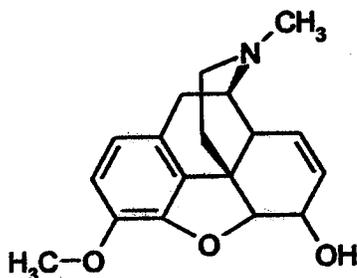


Table 2. Relevant IND/ANDA.

Application Type	Drug name	Status	Division	Indication	Stamp Date	Sponsor
IND						
75,764	Codeine sulfate tablet	Presubmission	DAARP	Relief of mild to moderately severe pain	7/17/06	Roxane, Laboratories
ANDA						
85-055	Tylenol w/codeine No. 3	Approved	OGD	Relief of mild to moderately severe pain	1/1/82	Ortho-McNeil Pharmaceutical, Inc.

Table 3. Relevant DMF.

DMF No.	Subject of DMF	Holder	Comment
			CMC review #14 deemed DMF inadequate as it lacked information on impurities (1/21/2009) PT review deemed inadequate in the evaluation of the

b(4)

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b(4)

Drug class: Opioid analgesic

Intended clinical population: Treatment of mild to moderately severe pain

Clinical formulation: Tablet

Table 4. List of the ingredients included in codeine sulfate tablets (15, 30 and 60 mg) proposed for marketing (see application volume 1, pg. 107).

Codeine Sulfate Tablets, USP, 15 mg, 30 mg and 60 mg

Ingredients	Purpose	Quality Standard	Amount (mg per tablet)		
			15 mg tablets	30 mg tablets	60 mg tablets
Codeine Sulfate, USP	Active Ingredient	USP; HRI Spec. No. 6081700R-01-02	15.0 mg	30.0 mg	60.0 mg
Microcrystalline Cellulose, NF		NF			
Pregelatinized Starch, NF		NF			
Colloidal Silicon Dioxide, NF		NF			
Stearic Acid, NF		NF			
Theoretical Tablet Weight					

b(4)

The proposed formulation for codeine sulfate includes excipients at levels that are equal to or less than amounts provided in FDA-approved products. As noted in the table below, the total daily dose of the excipients in up to 360 mg/day via 6 tablets of 60 mg is still within the maximum potency per dosage form listed in the Inactive Ingredient's Guide.

Excipient	Amount in 60 mg tablet (mg)	Amount in 360 mg (6 x 60 mg tablets)	IIG maximum potency for single dosage form
Microcrystalline cellulose			
Pregelatinized Starch			
Colloidal Silicon Dioxide			
Stearic Acid			

b(4)

Impurities: The Sponsor has proposed the following drug substance impurity specifications:

Table 5. Drug substance specifications (DSS) provided by the Sponsor are listed below for impurities from codeine sulfate tablets USP. The acceptability of DSS was discussed and verified with the CMC reviewer.

Impurity	Proposed Specification	ICH Q3A Qualification	Acceptability
	0.15%	0.15%	Yes
	0.15%	0.15%	Yes
	0.15%	0.15%	Yes
Codeinone	0.15%	0.15%	Yes ¹
Codeine Methyl Ether ²		0.15%	No

b(4)

¹See Chemist Review for further information.

²Codeine Methyl Ether has been previously reported to be a by-product impurity for codeine (Ayyangar et al., 1990). No published toxicology findings were identified in the limited literature available on this impurity. This impurity is presumably found in approved combination products, however, there is no available documentation of its qualification in toxicological studies. See CMC review for further details.

Although requested at the preNDA meeting, the Sponsor provided no data to justify the safety of the levels of codeine methyl ether in the drug substance, which clearly exceeds the qualification threshold of NMT 0.15% or 1 mg, whichever is lower. A review of the literature by this reviewer suggests that codeine methyl ether has been a known drug product impurity. This reviewer was able to find only one publication that describes the pharmacology and toxicology of codeine methyl ether via the current online resources. According to Eddy (1935), codeine methyl ether was originally prepared in 1916 and tested for activity and toxicity. Eddy reported that codeine methyl ether is more toxic than either codeine or morphine as measured by the average fatal dose and the minimal convulsant dose in mice. CME is more potent than codeine but less potent than morphine at depressing the righting reflex in rats, has similar potency as codeine at suppressing intestinal evacuation in rabbits. Therefore, CME does appear to have pharmacological activity consistent with codeine and morphine, although is also likely to contribute some degree of toxicity. This literature reference does not provide adequate data to establish a NOAEL for chronic toxicity, nor does it provide any assessment of the genotoxic potential of CME. Therefore, the safety of the proposed specification can only be supported by previous clinical experience. According to the drug substance manufacturer, codeine methyl ether has likely been present since they started marketing codeine phosphate products in — It has been specifically quantified in codeine phosphate drug substance since 1994; however, actual levels were not provided. In the absence of adequate clinical data, the sponsor should either reduce the specification to NMT 0.15% or 1 mg, whichever is lower, or submit the following studies:

b(4)

- Minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.

- Repeat dose toxicology of 90-days duration to support the proposed indication.

b(4)

Given the presumed clinical experience with codeine and the existing marketing experience with this unapproved marketed product, the above qualification studies for codeine methyl ether may be conducted post-approval.

The Sponsor has proposed the following drug product stability specifications:

Table 6. Drug product specifications (DPS) provided by the Sponsor (for stability testing) are listed below for degradation products from codeine sulfate tablets USP. The acceptability of DPS was discussed and verified with the CMC reviewer.

Degradation Product	Proposed Specification	ICH Q3B Qualification	Acceptability
Codeinone		0.20%	No
		0.20%	Yes

b(4)

Codeinone has been demonstrated to be an impurity and degradation product of codeine. Codeinone has been previously demonstrated in experimental animals to be toxic (Nagamatsu, et al., 1985).

Codeinone tested negative in the Ames bacterial reverse mutation assay and although the results of the in vitro chromosomal aberration assay were negative, the assay was not deemed to be conclusive due to excessive chromosomal condensation at higher concentrations. A repeat of this study will be requested of the (see Pharmacology/Toxicology reviews of and the related amendment to the Master File). The Reviewer does not concur with s previous justification for not repeating the assay, based on the lack of experimental evidence demonstrating that codeinone produces chromosomal condensation in multiple cell lines at cytotoxic concentrations. This is supported by evidence that codeinone reportedly produces various effects such as DNA fragmentation, which has not been observed across cell lines at cytotoxic concentrations (Hitosugi N, et al., 2003; Kawase M, et al., 2002; Takeuchi R, et al., 2005). For example, codeinone has been reported to induce DNA fragmentation in the human promyelocytic leukemia (HL-60) cell line, and not the human oral squamous cell carcinoma (HSC-2) cell line (Takeuchi R, et al., 2005). Findings that the effects of codeinone are not necessarily observed across cell lines support the Agency's suggestion that use another cell line if the chromosomal aberration test is repeated. Therefore, in order to complete the genetic toxicology safety qualification for codeinone should either repeat the in vitro study using a cell line that does not result in confounding "excessive chromosomal condensation" or conduct an in vivo genetic toxicology study. As this recently identified compound has likely been in currently approved codeine-containing drug products, the requested genetic toxicology study may be provided post approval.

NOTE REGARDING TERTIARY REVIEW AND FINAL CONCLUSION:

Following further discussion of this case with Dr. David Jacobson-Kram, Associate Director of Pharmacology Toxicology (OND CDER), the excessive chromosomal condensation has been deemed evidence of toxicity and therefore, the highest concentrations tested in the already completed assay are deemed to be the maximum feasible concentrations. As such, Dr. Jacobson-Kram deems these studies valid (see Attachment 1). Therefore, the Agency considers codeinone to have been adequately tested and deemed negative in a minimal genetic toxicology screen. In terms of genotoxic potential, this impurity can be considered as a non-genotoxic impurity and regulated as per ICH Q3A.

Route of administration: Oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: Except as specifically identified below, all data and information discussed below are necessary for the approval of NDA 22-402 and are owned by Roxane Laboratories or are data for which Roxane Laboratories has obtained a written right of reference. Any information or data necessary for approval of NDA 22-402 that Roxane Laboratories does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Roxane Laboratories does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-402.

The referenced drug is Tylenol with Codeine No. 3®, ANDA 85-055 (Ortho McNeil Pharm).

Studies reviewed within this submission: None.

Studies not reviewed within this submission: None.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

2.6.2.2 Primary pharmacodynamics

Primary pharmacodynamics: Opium poppy plant seeds contain various alkaloids such as codeine, which are employed clinically as analgesics (for review see, Trescot AM, et al., 2008). Codeine is classified as a phenanthrene, a chemical class that is separate from the benzisoquinoline alkaloids derived from the poppy plant seed (Trescot AM, et al., 2008).

Mechanism of action: Codeine is a mu-opioid agonist that has been demonstrated in experimental animals to produce a variety of physiological and behavioral effects (Karlsson JA, et al., 1990; Liguori A, et al., 1996; Meert TF and Vermeirsch HA, 2005). For example, codeine administered to rats produced analgesia, increased constipation, and decreased gastrointestinal motility and respiration across a range of doses (Meert TF and Vermeirsch HA, 2005).

Drug activity related to proposed indication: Codeine has been demonstrated to produce analgesia in experimental animal species that include monkeys, rats, mice, and guinea pigs (Adcock JJ, et al., 1988; Chau TT and Harris LS, 1980; Meert TF and Vermeirsch HA, 2005; Peckham and Traynor, 2006). Across these studies, codeine reduced measures of pain in a variety of assays. For example, Meert and Vermeirsch (2005) demonstrated that codeine in rats produced analgesia across a range of doses in the tail withdrawal, von Frey, and formalin assays (Meert TF and Vermeirsch HA, 2005).

2.6.2.3 Secondary pharmacodynamics

Secondary pharmacodynamics: The secondary pharmacodynamic effects of codeine in experimental animal species include decreased locomotor behavior, respiration and GI motility; as well as increased abuse liability (Carney JM, et al., 1976; Liguori A, et al., 1996; Meert TF and Vermeirsch HA, 2005; Teiger DG, 1974).

2.6.2.4 Safety pharmacology

No safety pharmacology studies or information from the literature were submitted by the Sponsor in support of the NDA application. Codeine has been used extensively in clinical and nonclinical settings and its long history of use precludes the need for safety pharmacology studies to be conducted in support of the current application.

Neurological effects: No nonclinical studies were submitted by the Sponsor.

Cardiovascular effects: No nonclinical studies were submitted by the Sponsor. The study below was identified by the reviewer during a literature search and summarized.

In anesthetized cats, the effects of intravenously administered l- and d- isomers of codeine on blood pressure and heart rate were evaluated (Chau TT and Harris LS, 1980). The highest dose of l-codeine and d-codeine, respectively, 1 and 4 mg/kg decreased respiration in 2 of 3 cats tested in each group. Compared to predrug levels, respiration levels were decreased by 20% at 1 mg/kg l-codeine, a dose that did not alter heart rate. Respiration was decreased by 65% at 4 mg/kg d-codeine, a dose that also decreased heart rate by 22%.

Pulmonary effects: No nonclinical studies were submitted by the Sponsor. The studies below were identified by the reviewer during a literature search and summarized.

The respiratory effects of codeine (0.3, 1.0, 3.0, and 30 mg/kg; IM) were evaluated in restrained rhesus monkeys (Liguori A, et al., 1996). Codeine reduced CO₂-stimulated minute volume ventilation in a dose-related manner. These effects in monkeys were dose-related and modulated by the percent of CO₂ presented. For example, the high dose of codeine (30 mg/kg) administered in monkeys presented 5% CO₂ decreased minute volume to 36% of control, demonstrating a more marked alteration of this measure compared to the opioids effect in animals presented unmixed air. Evidence from this study demonstrated that codeine in monkeys produced less pronounced respiratory depression compared to other opioids such as methadone, which is used clinically. In Dunkin-Hartley guinea pigs, the effects of codeine (10, 30, and 60 mg/kg; IV) was studied using a plethysmograph chamber (Adcock JJ, et al., 1988). At 10 mg/kg, codeine significantly decreased minute volume of ventilation. Codeine reportedly produced this effect with little or no alteration in tidal volume. In contrast, the 30 and 60 mg/kg codeine markedly increased minute volume of ventilation. The marked increase in minute volume at higher doses of codeine was in contrast to the decrease in this measure by morphine. These findings demonstrated that codeine (IV) in guinea pigs produced bi-directional effects on respiration depending on the dose administered.

Blood gas analysis of arterial PaCO₂ levels in rats was used to evaluate the effects of codeine (2.5, 10, 40, 80, and 160 mg/kg; SC) on respiratory function (Adcock JJ, et al., 1988; Meert TF and Vermeirsch HA, 2005). Codeine significantly increased PaCO₂ levels at the highest dose (160 mg/kg) tested. The magnitude of this effect was less than that produced by other opioids such as fentanyl and morphine, which also produced their peak effects faster than codeine. Findings from this study demonstrated that codeine was less potent than these opioids at increasing PaCO₂ levels (i.e., depressing respiration). Together, these findings demonstrate that codeine in rats decreases respiration; however, the magnitude of this effect is less pronounced than other prescribed opioids such as fentanyl and morphine.

In restrained male Wistar rats, the effects of codeine (1.9, 9.5, and 50 mg/kg; SC) on respiration were evaluated. At 50 mg/kg codeine, the highest dose tested, respiratory minute volume was decreased by 50%. The magnitude of this effect produced by codeine was similar to that of meperidine (18 mg/kg), but less than the magnitude of effect produced by morphine (6.7 mg/kg), which decreased respiratory minute volume by more than 60%. At the mentioned doses, the peak effect of codeine and the other opioids was measured. These findings demonstrated that codeine produced its peak respiratory depressive effects at a time point similar to that of other opioids studied; however, this effect occurred at a magnitude lower than that produced by the higher efficacy agonist morphine.

Renal effects: No nonclinical studies were submitted by the Sponsor. No published studies characterizing the renal effects of codeine were identified by the reviewer when a literature search was conducted.

Gastrointestinal effects: No nonclinical studies were submitted by the Sponsor. The study below was identified by the reviewer during a literature search and summarized.

In male Sprague Dawley rats, the effects of codeine (0.63, 2.5, 10, 25, and 40 mg/kg; SC) on intestinal propulsion of 2 mL of charcoal solution (10% charcoal in 5% Arabic gum) and on ricinus oil-induced diarrhea were evaluated. Codeine (10 and 40 mg/kg; SC) produced a dose-related decrease in intestinal propulsion, as measured by the average peristalsis ratio. At similar doses, codeine produced a dose-related decrease in ricinus oil-induced diarrhea. These effects were less pronounced than those produced by morphine, at the doses tested, and were consistent with clinical findings on the gastrointestinal effects of opioids.

Abuse liability: No nonclinical studies were submitted by the Sponsor. The information discussed below was obtained from the literature by the Reviewer.

Behavioral and physical endpoints have been evaluated to demonstrate the abuse liability of codeine. The abuse liability of codeine has been demonstrated in various experimental species that include monkeys and rats. Various behavior procedures such as drug self administration and drug discrimination have been employed to evaluate the abuse liability of codeine. Drug self administration procedures have demonstrated that codeine may serve as a reinforcer when presented by intravenous and intragastric administration (Herling S, 1981; Hoffmeister F, et al., 1980; Young AM, et al., 1979). Drug discrimination procedures have demonstrated that codeine produces subjective effects that overlap with those of other opioids with known abuse potential (Bertalmio AJ and Woods JH, 1987; Meert TF and Vermeirsch HA, 2005). In regard to physical endpoints, studies in codeine-treated animals have reported the observation of physical and behavioral signs when drug administration is suspended or an opioid antagonist was administered (Koga Y and Inukai T, 1981; Suzuki T, et al., 1991; Thornhill JA, et al., 1978). Although these findings are consistent with those of other opioids that are demonstrated to have abuse potential, the effects of codeine are generally less pronounced than agonists such as morphine during withdrawal.

Other: No nonclinical studies were submitted by the Sponsor.

2.6.2.5 Pharmacodynamic drug interactions

No nonclinical studies were submitted by the Sponsor.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Not applicable.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

The Sponsor did not conduct any Pharmacokinetic/Toxicokinetic studies.

2.6.4.2 Methods of Analysis

Not applicable because no data were submitted.

2.6.4.3 Absorption

Formal nonclinical studies were not submitted. See below the summary of a published study from the scientific literature.

Toxicokinetic studies were conducted in F344 rats (male/female) administered codeine (0, 400, 800, 1600 ppm) orally in NIH-07 feed available *ad libitum* over a two year period (Yuan J, et al., 1994). In blood samples taken, codeine plasma levels decreased from day 7 to 16 months and then increased at 24 months when measured. The plasma levels of codeine increased in a dose-related manner at the time points studied. Similarly, the bioavailability of codeine increased in a dose-related manner. Yuan et al. (1994) reported that based on the results from day 7 the bioavailability of codeine from the diet was estimated to be 10, 24, and 25% for the 400, 800, and 1,600 ppm dose groups, respectively.

Table 7. AUC values from toxicokinetic study in rats exposed to codeine mixed in daily NIH-07 feed available *ad libitum* over 2 years (see, Yuan J, et al., 1994).

*Estimated AUC values for morphine in rat chow feed codeine studies**

Sex	Days in Feed	Day 7		Day 21		Day 90	
		Morphine ^b	Total Morphine ^c	Morphine	Total Morphine	Morphine	Total Morphine
Male	400	437 ± 17	3,732 ± 296	472 ± 15	3,422 ± 122	398 ± 18	3,286 ± 366
	800	1,018 ± 32	13,728 ± 1,437	676 ± 22	3,944 ± 189	764 ± 30	7,838 ± 491
	1600	2,649 ± 155	24,970 ± 1,357	1,429 ± 135	14,882 ± 1,883	1,440 ± 25	13,182 ± 1,195
Female	400	382 ± 8	3,638 ± 143	394 ± 16	2,980 ± 87	275 ± 25	5,894 ± 514
	800	867 ± 76	18,236 ± 1,914	840 ± 36	3,778 ± 238	689 ± 27	12,882 ± 678
	1600	1,447 ± 97	22,586 ± 1,325	1,388 ± 185	13,946 ± 1,362	1,879 ± 89	24,254 ± 1,447

* AUC values are expressed as mean ± SD for the 12-hr dark cycle period.

^b Unconjugated morphine.

^c Unconjugated and conjugated morphine.

2.6.4.4 Distribution

No formal nonclinical studies were submitted for review.

2.6.4.5 Metabolism

No formal nonclinical studies were submitted for review. The metabolic profile of codeine has been evaluated in species that include humans, dogs, rabbits, guinea pigs and rats (Cone EJ, et al., 1979; Findlay, et al., 1977; WOODS LA, et al., 1956). Cone et al. has published urinalysis findings demonstrating that the metabolite norcodeine is

detected in all of these species; however, the metabolite hydrocodone is only detected in man, dog and guinea pig following codeine administration (Cone EJ, et al., 1979).

In humans, codeine is metabolized primarily by the liver (24-89%), with some metabolism also occurring in the brain and intestines. Approximately 50-70% of orally administered codeine is converted to codeine-6-glucuronide by UGT2B7. Codeine-6-glucuronide has similar affinity for the mu opioid receptor as morphine; however, it does not enter the brain to the same extent. Approximately 10-15% of codeine is N-demethylated to norcodeine by CYP 3A4. Norcodeine also has activity at the mu opioid receptor comparable to codeine itself. Approximately 0-15% of codeine is O-demethylated to morphine by CYP2D6.

2.6.4.6 Excretion

No formal nonclinical studies were submitted for review. The excretion of codeine has been studied in humans and various animal species (Oguri K, et al., 1990; WOODS LA, et al., 1956). Codeine is predominately excreted via renal elimination.

2.6.4.7 Pharmacokinetic drug interactions

No formal nonclinical studies were submitted for review.

2.6.4.8 Other Pharmacokinetic Studies

No formal nonclinical studies were submitted for review.

2.6.4.9 Discussion and Conclusions

The pharmacokinetic data for codeine is largely based upon the existing human experience with this drug.

2.6.4.10 Tables and figures to include comparative TK summary

Not applicable because no data were submitted.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Not applicable because no data were submitted.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

The Sponsor submitted published peer-reviewed research articles and reports in support of the NDA. See below for brief summaries, by the Reviewer, of findings from these published studies.

General toxicology: Based on findings in the submitted articles and reports, codeine administered to rats and mice did produce mortality at various doses. In surviving animals, dose-related decreases in body weight and food consumption were typically observed; and in some cases the effects on food consumption were reversed by the conclusion of the dosing schedule. Although nonneoplastic lesions were observed in rats exposed to codeine in their daily feed for 14-days; toxicologically significant gross and histopathological findings were not reported in the submitted research articles and reports.

Genetic toxicology: In vivo and in vitro assays have been employed to evaluate the potential mutagenic potential of codeine. Codeine reportedly increased the level of sister chromatid exchanges in Chinese Hamster Ovary (CHO) cells, a finding produced at doses that delayed cell cycling {National Toxicology Program, 1996 3003 /id}. However, this finding was difficult to interpret given that the delaying of the cell cycle prolonged the DNA exposure to chemicals that may have increased sister chromatid exchanges in CHO cells. Despite this confounded finding, these and other data submitted in support of the NDA clearly suggest that codeine is not a mutagen at the doses tested in the in vivo and in vitro assays employed.

Carcinogenicity:

Two year studies in rats and mice administered codeine were conducted by the National Toxicology Program to evaluate its potential carcinogenicity. In these studies, there were no apparent drug-related differences in the survival rate of the animals tested. Histological findings were observed in rats and mice; however, many of these findings were sporadic and were not dose-related. The NTP studies concluded that there was no evidence that codeine was carcinogenic in either the rat or mouse models under the conditions tested.

Reproductive toxicology: The potential reproductive toxicity of codeine administered in hamsters, rats, and mice was evaluated in the published studies submitted. In these studies, the effects of codeine on embryo-fetal development, as well as pre- and postnatal development were reported. Findings from the embryo-fetal development studies on codeine administered to hamsters and mice demonstrated an increase in resorptions and malformations in treated animals. Pre- and postnatal development studies on codeine administered to rats demonstrated an increase in mortality in treated animals. Together, these findings provided evidence that codeine may produce reproductive toxicities in experimental animal species.

Special toxicology:

2.6.6.2 Single-dose toxicity

The Sponsor did not conduct toxicology studies evaluating codeine.

2.6.6.3 Repeat-dose toxicity

The Sponsor did not conduct toxicology studies evaluating codeine. Codeine has been extensively studied in humans and experimental animals, and has a long history of use. As part of NDA 22-402, the Sponsor did submit published peer-reviewed research articles, as well as reports (National Toxicology Program) on toxicology studies that evaluated codeine. Please see below for brief reviews of these studies.

A 13-week repeat-dose toxicity study was conducted to evaluate the potential toxicities of codeine (0, 390, 781, 1562, 3125, and 6250 ppm) in male/female F344/N rats and B6C3F₁ mice (Dunnick JK and Elwell MR, 1989). In these studies, both species (10 animals/sex/dose level) were administered codeine mixed in NIH-07 feed daily for 13 weeks. Mortalities were reported in 2 male mice, which were exposed to 3125 ppm. During the initial 3 weeks of drug exposure in rats and mice, the 1562, 3125, and 6500 ppm treatments of codeine decreased feed consumption. In subsequent weeks, feed consumption returned to control levels until the conclusion of the study. In regard to body weight, the effects of codeine varied across species and genders. Findings in rats demonstrated that codeine decreased body weight in males at every exposure amount, and in females at 1562, 3125, 6250 ppm. In mice, codeine decreased body weight only at 6250 ppm in males. Treatment with codeine did not produce histopathological lesions or clinical signs at the amounts studied.

The effects of codeine in the daily diet of F344/N rats was evaluated in a 14-day toxicity study {National Toxicology Program, 1996 3003 /id}. The daily diets of rats (5/sex/group) contained 0, 1562, 3125, 6250, 12500 or 25000 ppm of codeine. Mortalities were reported in the 6,250 ppm (1 female), 12500 ppm (1 male and 3 females), and 25000 ppm (all animals) groups. The final body weight was decreased in a dose-related manner in treated animals. At treatment day 1, there was a substantial decrease in food consumption in codeine-treated animals compared to controls. There were no apparent relationships at day 1 between the amount of codeine exposure and alterations in food consumption. At day 14, food consumption was increased in codeine-treated animals when compared to day 1; and was slightly lower than control. In regard to organ weight, the absolute and relative weights for the thymus in both genders and the testis in males from the 12500 ppm group were significantly lower when compared to control. Reportedly, there were no toxicologically significant gross lesions observed in codeine-treated rats at necropsy. However, nonneoplastic lesions were observed in both genders, generally at \leq 12500 ppm. These lesions included lymphoid depletion of the thymus, and hyperplasia and hyperkeratosis in the forestomach mucosa. Testicular degeneration was reported in males.

In B6C3F₁ mice, the effects of codeine mixed in the daily diet of animals were evaluated in a 14-day toxicity study {National Toxicology Program, 1996 3003 /id}. The daily

diets of mice (5/sex/group) contained 0, 781, 1562, 3125, 6250, or 12500 ppm of codeine. No mortalities were reported. Mean body weight was significantly increased in females from the 3125 ppm group and decreased in both genders from the 12500 ppm group when compared to control. In males, absolute and relative weights were significantly decreased for the right kidney in the 12500 ppm group; as well as for the liver in the 3125, 6250, and 12500 ppm groups when compared to control. These weights were also significantly decreased for the liver in females from the 12500 ppm group. No gross or histopathology findings were reported in codeine-treated groups.

The effects of codeine in the daily diet of F344/N rats were evaluated in a 13-week toxicity study {National Toxicology Program, 1996 3003 /id}. The daily diets of rats (10/sex/group) contained 0, 390, 781, 1562, 3125 or 6250 ppm of codeine. A single mortality was reported in codeine-exposed rats (male from 390 ppm group; week 2) during treatment. In week 1 there was a decrease in food intake with increasing concentrations of codeine; however, by the conclusion of the study food intake was comparable to control levels. Significant decreases in the final mean body weights and mean body weight gains were reported in males from each treatment group and females in the 1562, 3125 and 6250 ppm groups when compared to control. Mild dose-dependent lymphopenia was reported in females fed ≥ 1562 ppm codeine and in males fed 6250 ppm codeine. Minimal to mild macrocytosis was reported males from groups treated and females in groups treated with ≥ 781 ppm codeine. There were no toxicologically significant effects observed in vaginal cytology parameters or sperm morphology. In regard to absolute and relative organ weights in males from treated groups, weights for the liver were significantly decreased, whereas those for the adrenal gland were significantly increased when compared to controls. In females, these weights for the adrenal gland were increased in the 3125 and 6250 ppm groups. In males from the 3125 and 6250 ppm groups, the relative weight for the thymus was significantly lower than control. There were no gross or histopathological lesions reported.

In B6C3F₁ mice, the effects of codeine mixed in the daily diet of animals were evaluated in a 13-week toxicity study {National Toxicology Program, 1996 3003 /id}. The daily diets of mice (10/sex/group) contained 0, 390, 781, 1562, 3125 or 6250 ppm of codeine. Two mortalities reportedly occurred during week 7 in male animals exposed to 3125 ppm. In the surviving animals, the feed consumption and mean body weights of treated animals were comparable to those of controls. No biologically significant alterations in hematology, urinalysis, clinical chemistry, and vaginal cytology or sperm morphology parameters were reported in treated animals. Significant decreases in the absolute and relative kidney weights in males from the 3125 and 6250 ppm groups were observed. No gross or histopathology lesions were observed in codeine-treated animals.

2.6.6.4 Genetic toxicology

Nonclinical studies evaluating the potential genetic toxicity of codeine and one of its impurities/degradation products codeinone have been, respectively, published in peer-reviewed research articles and included in DMF# . Findings from the published

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studies have been summarized below, and those from the DMF have been reviewed and submitted to DAARTS.

Published results. In vitro tests that included the *Salmonella* mammalian-liver homogenate test and *E. coli* mammalian-liver homogenate test, as well as in vivo assays that included the intrasanguineous host-mediated test, sex-linked recessive lethal test in *Drosophila melanogaster*, and the micronucleus test were used to evaluate the potential mutagenic effects of codeine phosphate (King MT, et al., 1979). Codeine did not produce mutagenicity in the *Salmonella typhimurium* (18 µg/plate) and *Escherichia coli* (30 mM) tests. Similarly, codeine did not produce mutagenicity in the intrasanguineous host-mediated test (0.18 mmoles/kg), sex-linked recessive lethal test in *Drosophila melanogaster* (5 mM) and micronucleus (0.25 mmoles/kg – ip; 0.5 mmoles/kg – po) tests.

The National Toxicology Program (NTP) evaluated codeine phosphate (100 to 10000 µg/plate) for its potential to induce genetic mutations in strains of *Salmonella typhimurium* (TA97, TA98, TA100, or TA1535; with or without liver S9 enzymes), as well as mutations in sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells {National Toxicology Program, 1996 3003 /id}. No mutagenesis was produced in the *Salmonella* strains exposed to the codeine concentrations tested. In cultured Chinese hamster ovary cells (with and without S9 enzymes), codeine increased the frequency of sister chromatid exchanges in a concentration-related manner. However, the increase occurred at concentrations that produced marked cell cycle delay, which is indicative of a high level of cytotoxicity. These findings are difficult to interpret given the delays in cell cycling, which may prolong DNA exposure to various factors (e.g., 5-bromodeoxyuridine) known to increase levels of sister chromatid exchanges. There were no reports of increases in the frequency of chromosomal aberrations in the cultured Chinese hamster ovary cells exposed to codeine.

Potential mutagenic effects of codeine phosphate were evaluated using in vivo (micronucleus and sperm abnormality assays) and in vitro (Ames *Salmonella* assay) tests (Bruce WR and Heddle JA, 1979). In the in vivo tests, hybrid mice (genotype C57BL/6 X C3H/He; F1 generation) at 11-14 weeks of age served as subjects (8/dose group). Males served as subjects in the sperm assay, whereas their female littermates served as subjects in the micronucleus assay. The highest dose was selected based on the LD₅₀ values determined in separate studies. Three lower doses were selected, which were 1/2, 1/4 and 1/8 of the highest dose tested in animals. Note that the authors presented data in tabular and graphical form; however, the actual doses were not mentioned. Codeine or vehicle was administered intraperitoneally for 5 consecutive days. In the micronucleus assay, the mice were sacrificed on the 5th day of treatment, approximately 4 hr after the final treatment. Bone marrow cells were prepared from the femur, and a total of 1000 reticulocytes were scored per group evaluated. In the sperm abnormality assay, the mice were sacrificed 35 days following the final treatment. Sperm cell suspensions were prepared from the cauda epididymus, and 1000 sperms were scored per treatment group. Positive findings were reported when the treated group values exceeded those of the control by 1%, which was reportedly twice the control value for both assays. In the

Ames assay several concentrations of codeine (0.05, 0.5, 5, 50, and 500 µg/plate; with and without S9 metabolic activation) were evaluated for potential mutagenicity in several *Salmonella typhimurium* strains that included TA1537, TA1535, TA100, and TA98. These strains, without S9, were irradiated at 10, 100, 1000, 10000, and 100000 rads. The criterion for a positive response was considered a 50% increase above the spontaneous frequency obtained at the same time. In these studies, codeine phosphate was not mutagenic in the micronucleus and sperm abnormality assays, as well as the Ames Salmonella assay.

2.6.6.5 Carcinogenicity

The Sponsor did not submit any new carcinogenicity studies in support of the submitted NDA application. Peer-reviewed publications on studies evaluating the carcinogenic potential of codeine were provided by the Sponsor and are briefly summarized below.

The NTP evaluated the effects of codeine fed in a daily diet to F344/N rats in a 24 month study {National Toxicology Program, 1996 3003 /id}. The daily diets of rats (60/sex/group) consisted of 0, 400, 800, or 1600 ppm of codeine. There were no apparent drug-related differences in the survival rates of the animals tested. Food consumption in codeine-treated rats was not significantly altered; however, mean body weight was decreased in the 1600 ppm group when measured during weeks 53-105. In regard to absolute and relative organ weights in males at the 15 month interim necropsy, there was a significant increase in the weight of the adrenal gland in the 800 and 1600 ppm groups and a decrease in the weight of the liver in all treated groups. Histological findings reported in males from these groups demonstrated that there was a larger amount of adrenal cortex relative to adrenal medulla; vascular dilation in the medulla and inner cortex was slightly increased; and the zona reticularis was slightly thickened and the cells of the inner portion of the zona fascicularis were decreased when compared to control at 15 months. At the 24 month necropsy, data in the 1600 ppm group demonstrated that there was a significant increase in the incidence of clitoral gland ectasia in females and preputial gland hyperplasia in males when compared to control. There were no reports of significant (i.e., dose-related) toxicological findings in codeine-treated animals.

In the same study, the NTP evaluated the effects of codeine fed in a daily diet to B6C3F₁ mice in a 24 month study {National Toxicology Program, 1996 3003 /id}. The daily diets of mice (60/sex/group) consisted of 0, 750, 1500, or 3000 ppm of codeine. There were no apparent drug-related differences in the survival rates of the animals tested. Food consumption in codeine-treated mice was not significantly altered; however, mean body weight was slightly decreased in the 3000 ppm group, during weeks 14-52 and 53-104, when compared to control. The weights of collected organs were reportedly comparable across groups and there were no significant toxicological effects in gross pathology studies in codeine-treated mice. Histological findings were limited to thyroid gland follicular cell hyperplasia, which significantly increased at 15 months in males from the 3000 ppm group and at 24 months in both genders from all codeine treatment groups. By 24 months, this hyperplasia was described as focal in distribution; minimal to

mild in severity; and involved up to 3 adjacent follicles, in which the number of epithelial cells was increased. In females, the incidence of this hyperplasia increased in a dose-related manner.

2.6.6.6 Reproductive and developmental toxicology

The Sponsor did not submit any new reproductive and developmental toxicology data in support of the NDA application. Peer-reviewed publications on studies evaluating these potential toxicities of codeine were provided by the Sponsor and are briefly summarized below.

Fertility. There were no fertility studies identified in the literature by either the Sponsor or the Reviewer.

Embryo-fetal development. Published embryofetal development studies for codeine have been reported using the hamster, rat, mouse, and rabbit models.

In a single-treatment study, the toxicity of codeine (0, 73, 96, 240 or 360 mg/kg; subcutaneous route) was evaluated in timed pregnant Lakeview outbred golden hamsters at gestation day 8 (Geber WF and Schramm LC, 1975). At 240 and 360 mg/kg, codeine produced dose-related increases in the percentage of maternal deaths when compared to control (10 and 20%, respectively). In codeine dose groups, there was a slight decrease in the mean number of fetuses/litter when compared to control. Codeine increased the number of malformed fetuses, an effect that wasn't dose-related. Across codeine dose groups, all of the malformed fetuses exhibited cranioschisis. A dose of 73 mg/kg represents a human equivalent dose of 592 mg/60 kg person based on body surface area. As the dose tested was far greater than the typical dose for an opioid naïve individual, the clinical significance of this finding is not clear. Further the study is difficult to interpret as the maternal toxicity at non-lethal doses was not described. It should be noted that GLP studies conducted by the National Toxicology Program tested lower doses of codeine and were able to identify a NOAEL for fetal effects (see below). Although the results of this study were not described in the referenced product labeling, probably due to the challenges associated with interpretation of these results due to significant maternal toxicity, these results were deemed adequate to be included in the proposed product labeling based on their relevance to toxicological findings reported at lower doses in other studies (National Toxicology Program, 1987b; Zellers JE and Gautieri RF, 1977).

The potential reproductive toxicity of oral codeine was evaluated in rabbits (5, 12.5 and 30 mg/kg) and rats (10, 35 and 120 mg/kg) during organogenesis (Lehmann H, 1976). Codeine in the rabbit did not produce any apparent teratogenic and embryotoxic effects at the doses tested. In the rat, no apparent teratogenic effects were produced up to 120 mg/kg; however, embryotoxic effects were observed at this dose. This toxicity was observed as an increase in resorptions in one of several groups of rats treated at this dose, which was reportedly in the toxic range for dams. This increase was observed in dams sacrificed at the 11th day of pregnancy, unlike those sacrificed at the 21st day. The results

of this study appear to be described in the referenced Tylenol with codeine product labeling.

The effects of 100 mg/kg codeine (SC) administered in CF-1 albino mice either on a single day during gestation from Day 7-12 or on Days 8 and 9 were studied to evaluate its potential embryo-fetal toxicities (Zellers JE and Gautieri RF, 1977). Codeine increased the starting and terminal weights of dams when administered at Gestation Day (GD) 10. In dams treated on days other than GD 11 or 12, the mean weight (g) of harvested fetuses was significantly decreased when compared to control. All treatment groups, except those administered codeine on GD 8 and 9 had increased skeletal abnormalities almost 15 fold higher than control. In the litters present, codeine reportedly increased delayed ossification of the supraoccipital bone, xiphoid, and paws in various treatment groups. Delayed ossification of the supraoccipital bone and paws reported in at least one litter present in the control and codeine treated groups. In regard to the supraoccipital bone, there was a significant increase in the number of litters from dams administered codeine on GD 9 or 10, and GD 8 and 9 when compared to control. Delayed ossification of the xiphoid was reported in fetuses harvested from dams treated with codeine on either GD 9, 10, 12, or GD 8 and 9. There were a significant number of litters present with delayed ossification of the paws in fetuses from dams for every treatment group, except those treated with codeine on GD 12 when compared to control. Sternebrae defects reportedly occurred in significantly more litters of fetuses from dams administered codeine, except GD 8 and GD 12, when compared to control. It appears as though the mouse data in the previously approved referenced drug product labeling is from this publication.

The National Toxicology Program conducted two definitive reproductive toxicology studies, which were also later summarized in a single journal article (see, Williams J, et al., 1991). Codeine (0, 10, 50, or 150 mg/kg; bid; oral) was administered in Lakeview outbred golden (LVG) hamsters on gestational days 5-13 to evaluate its potential teratogenic effects (National Toxicology Program, 1987b). In the pregnant LVG hamsters (12-18/group), maternal toxicity was clearly evident at the high dose, presenting as significantly reduced body weight gain compared to controls. In the litters studied, mean fetal body weights were significantly reduced in the 50 and 150 mg/kg treatment groups. The highest dose of codeine (150 mg/kg) increased the incidence of resorption per litter. Dead fetuses (n=3) were reportedly observed only in dams treated with 150 mg/kg. The number of live fetuses were comparable across groups, and litters from dams treated at each dose had comparable amounts of fetuses from both genders. Body weights of fetuses from dams treated with 50 and 150 mg/kg were substantially decreased compared to control. At the highest dose tested (150 mg/kg; bid), there was a non-statistically significant increase in fetuses demonstrating the external malformation meningoencephalocele and there was an increase in the number of variations such as supernumerary rib (in the Lumbar I full; n=7) and incomplete ossification (cartilage present; n=9) were observed. The authors report a NOAEL for developmental toxicity in hamsters as 20 mg/kg/day (100 mg/m², based on body surface area). This dose is approximately 0.5 times the maximum recommended human dose of 360 mg/day for adults based on body surface area.

The study in Swiss CD-1 mice administered codeine (0, 75, 150 or 300 mg/kg; bid; oral) during gestational days 6-15 evaluated its potential teratogenic effects (National Toxicology Program, 1987a). The 150 and 300 mg/kg dose significantly reduced maternal weight gain. The high dose also resulted in mortality in 19% of the dams, and increased the percentage of resorptions per litter by > 2-fold the level observed in controls. At the 150 and 300 mg/kg doses of codeine, fetal body weight was significantly decreased. Codeine exposure during gestation reportedly did not increase the incidence of major fetal malformations up to the 300 mg/kg dose. The authors report a NOAEL for developmental toxicity in mice as 150 mg/kg/day (450 mg/m², based on body surface area). This dose is approximately 2 times the maximum recommended human dose of 360 mg/day for adults based on body surface area.

Pre- and postnatal development studies. In repeat dose-studies the toxicity of codeine phosphate was evaluated in female Sprague Dawley rats subcutaneously administered 30 mg/kg starting 3 days after sperm were observed in their vaginal smears and continuing 25 days after neonates were delivered (Ching M and Tang L, 1986). Dams were treated during gestation and lactation periods. In codeine-treated dams, the mortality rate of neonates (3/41) was 7.3% at birth compared to 0% in controls; and their body weights (male and female) were slightly decreased compared to control. No neonate deaths were reported 1 week after delivery. In neonates, hypothalamic growth hormone releasing activity at 25 days of age in both genders and vaginal opening at 39 days of age in females were comparable to control.

2.6.6.7 Local tolerance

No local tolerance studies were conducted nor required.

2.6.6.8 Special toxicology studies

No special toxicology studies regarding local tolerance were conducted nor required.

2.6.6.9 Discussion and Conclusions

Codeine was approved by the FDA as early as 1952 in drug combinations products. This NDA; however, would be the first single entity codeine product approved by the Agency. Given the long history of use and the current marketed, but unapproved status of this drug product, nonclinical toxicology studies for codeine were not required for this NDA application, as per OND policy. Codeine has been demonstrated to produce analgesic and adverse effects in humans that correspond to effects observed in animal species. In animal species, codeine has not been demonstrated to be mutagenic, but does produce reproductive toxicities. For example, reproductive organ toxicity (i.e., testicular degeneration) has been reportedly produced in male rats administered ≥ 12500 ppm (i.e., ≥ 650 mg/kg) of daily codeine (at least 20 times the maximum recommended daily dose for adults on a mg/m² basis) for 14 days. Mortality was observed at these doses, unlike lower doses (i.e., ≥ 450 mg/kg) which did not produce testicular degeneration or, as an added measure, did not induce sperm morphology alterations in male rats and mice across

longer exposure periods. In pregnant animals, embryotoxicity and teratogenic effects of codeine have been demonstrated in hamsters, rats and mice. Such findings support the Pregnancy Category C label given to codeine.

2.6.6.10 Tables and Figures

None supplied by Sponsor.

2.6.7 TOXICOLOGY TABULATED SUMMARY

None supplied by Sponsor.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Based on current practice in the OND, no new nonclinical toxicology studies are required to support the approval of this NDA application.

Unresolved toxicology issues (if any):

The DMF holder should either reduce the specifications for codeine methyl ether in the drug substance to $\leq 0.15\%$ NMT or provide adequate safety qualification as per ICH Q3A. Adequate qualification should include:

- Minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
- Ninety day repeat-dose toxicology study to support the proposed indication.

As this recently identified impurity has likely been in the previously approved products, this safety qualification can be completed post-approval, as per Division policy.

Recommendation: From the nonclinical pharmacology and toxicology perspective, the NDA may be approved pending agreement on the labeling and with phase 4 requirements to either reduce the specification of the mentioned impurity to the appropriate levels established by the Agency or to provide adequate safety qualification.

Suggested labeling: See Table 1.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

ATTACHMENT 1:

Mellon, Dan

From: Jacobson-Kram, David
Sent: Thursday, May 21, 2009 11:53 AM
To: Mellon, Dan
Cc: Brown, Paul C
Subject: RE: Request tertiary input re: Codeinone

It appears that excessive chromosome condensation is precluding evaluation of metaphases at the ICH specified level of toxicity. However, some toxicity is present at lower concentrations and the material does not appear to be clastogenic. My recommendation is to accept the study as is and consider the highest scorable dose at the maximal feasible concentration.

David Jacobson-Kram, Ph.D., D.A.B.T.
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/s/

Marcus S Delatte
6/2/2009 06:21:03 PM
PHARMACOLOGIST

R. Daniel Mellon
6/2/2009 06:31:05 PM
PHARMACOLOGIST

I concur with Dr. Delatte's recommendation that NDA 22-402
may be approved from the nonclinical perspective. I
agree with the recommended post-marketing studies for codeine
methyl ether and with the recommended labeling changes.

PHARMACOLOGY/TOXICOLOGY NDA FILEABILITY CHECKLIST

Division of Anesthesia, Analgesia, and Rheumatology Products

NDA Number: 22-402

Applicant: Roxane

Stamp Date: 02-July-08

Drug Name: Codeine sulfate

IS THE PHARM/TOX SECTION OF THE APPLICATION FILEABLE? Yes [x] No []

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameters	Yes	No	Comment
1	On its face, is the Pharmacology/Toxicology section of the NDA organized in a manner to allow substantive review to begin?	X		
2	Is the Pharmacology/Toxicology section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X		
3	On its face, is the Pharmacology/Toxicology section of the NDA legible so that substantive review can begin?	X		
4	Are final reports of ALL required* and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility*, juvenile studies, ocular toxicity studies*, acute adult studies*, chronic adult studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)? Have electronic files of the carcinogenicity studies been submitted for statistical review?	-	-	Not applicable. The Sponsor did not conduct any nonclinical studies. The submitted 505(b)(2) New Drug Application (NDA) included referenced nonclinical studies.
			X	
5	If the formulation to be marketed is different from that used in the toxicology studies, has the sponsor made an appropriate effort to either repeat the studies with the to be marketed product or to explain why such repetition should not be required?	-	-	Not applicable.
6	Are the proposed labeling sections relative to pharmacology appropriate (including human dose multiples expressed in mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?	X		
7	For a 505(b)(2) submission, has the sponsor identified a referenced product?	X		As per 356h the referenced product is listed as Tylenol with Codeine No. 3.
8	For a 505(b)(2) submission, has the sponsor submitted patent certification information to support the information referenced in the proposed drug product labeling?	X		No, the original proposed annotated labeling reference _____, and Morphine sulfate oral solution and tablet in addition to Tylenol with Codeine. The Sponsor owns the Morphine sulfate oral solution and tablet NDAs and has removed the reference to _____ - citing the literature instead.
9	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions?	X		
10	Based upon a cursory review, do the excipients appear to have been adequately qualified?	X		
11	Has the applicant submitted any studies or data to address any impurity or extractable issues (if any)?	X		
12	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route?	X		

b(4)

b(4)

13	Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	-	-	Not applicable. A 505(b)(2) New Drug Application (NDA) submitted.
14	Has the sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?	-	-	Not applicable. A 505(b)(2) New Drug Application (NDA) submitted.
15	From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not.	X		FILING ISSUES: None
16	If the NDA is fileable, are there any filing review issues that need to be conveyed to Sponsor? If so, specify:		X	Filing review issues for the 74-day letter: None.

Note:

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this page is the manifestation of the electronic signature.**

/s/

Marcus S Delatte
8/19/2008 04:46:44 PM
PHARMACOLOGIST

R. Daniel Mellon
8/19/2008 06:07:12 PM
PHARMACOLOGIST
I concur.