

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**202080Orig1s000**

**PHARMACOLOGY REVIEW(S)**

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

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: 202080  
Supporting document/s: 1  
Applicant's letter date: December 17, 2010  
CDER stamp date: December 17, 2010  
Product: TRADENAME® (oxycodone HCl, USP) Tablets  
Indication: Management of moderate to severe pain where use  
of an opioid is appropriate  
Applicant: King Pharmaceuticals Research and Development,  
Inc.  
Review Division: Division of Anesthesia, Analgesia, and Addiction  
Products  
Reviewer: Jay H. Chang, Ph.D.  
Supervisor/Team Leader: Adam Wasserman, Ph.D.  
Division Director: Bob Rappaport, M.D.  
Project Manager: Lisa Basham, M.S.

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# 1 Executive Summary

## 1.1 Introduction

NDA 202080 was submitted by King Pharmaceuticals Research and Development, Inc. for approval to market TRADENAME® (oxycodone HCl, USP) Tablets, which are an immediate-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain where use of an opioid analgesic is appropriate. This NDA was submitted via the 505(b)(2) pathway with Roxicodone® (NDA 21-011) as the listed drug. According to the applicant, the clinical formulation of TRADENAME® (oxycodone HCl, USP) Tablets includes excipients that are intended to introduce limits or impediments to 2 common methods of opioid analgesic product abuse: (1) intravenous injection of oxycodone extracted from dissolved tablets, and (2) nasal snorting of crushed tablets. (b) (4)



## 1.2 Brief Discussion of Nonclinical Findings

### Excipients

Per agreement with the sponsor at a PreNDA meeting held on 9/27/2010 (Meeting minutes dated 11/5/2010), no new nonclinical toxicology studies with TRADENAME® (oxycodone HCl, USP) Tablets were required with this NDA submission. However, the applicant was required to provide a safety assessment to justify the level of crospovidone in TRADENAME® (oxycodone HCl, USP) Tablets based on a total daily intake of 16 tablets. Note that though the maximum recommended daily dose (MRDD) of TRADENAME® (oxycodone HCl, USP) Tablets is 12 tablets per day, we stated at the Pre-NDA meeting that the maximum theoretical daily dose for an opioid-tolerant patient must be considered when determining the acceptable levels of excipients. A safety assessment based on 16 TRADENAME® (oxycodone HCl, USP) Tablets was determined by the Division based in part on prescribing data from a Drug Utilization Summary presented by the Agency at the 2010 Joint Meeting of the Anesthetic and Life Support and Drug Safety and Risk Management Advisory Committees to discuss Acurox with Niacin (NDA 22-451).

Crospovidone is present in numerous approved and marketed oral drugs in the US and is listed with a maximum potency of 792.0 mg according to the FDA Inactive Ingredient Guide (IIG). However, the TDI of crospovidone from 16 TRADENAME® (oxycodone HCl, USP) Tablets is (b) (4) than the maximum listed level found in the IIG. The NDA submission included a literature-based safety assessment, which cited information from the public domain and included a safety evaluation from the FAO/WHO (Food and Agriculture Organization of the United Nations/World Health organization) Joint Expert Committee on Food Additives (JEFCA). Note that no new or additional toxicology studies were conducted by the applicant to qualify this excipient. In brief, the JEFCA risk assessment stated that no adverse

toxicological findings were noted in a 90-day repeat-dose oral toxicity study in rat and a 6-month repeat-dose oral toxicity study in dog. Moreover, the highest doses tested were associated with human equivalent doses that provide adequate margins of safety relative to the potential TDI of crosopovidone in TRADENAME® (oxycodone HCl, USP) Tablets. Additionally, crosopovidone tested negative for mutagenicity in a standard battery of genetic toxicity studies, did not have teratogenic effects, and was found to be poorly absorbed by the gastrointestinal tract in humans following oral ingestion. Importantly, this reviewer identified an approved generic drug (Amitril®; Amitriptyline HCl; ANDA 83-939) with a TDI of crosopovidone that exceeds the amount in 16 TRADENAME® (oxycodone HCl, USP) Tablets (b) (4) when taken as recommended. Taken together, the information above provides adequate safety qualification for the level of crosopovidone in TRADENAME® (oxycodone HCl, USP) Tablets based on a total daily intake of 16 tablets.

### Impurities

The applicant also provided justification for the drug product (b) (4) specification limit of (b) (4) recommended by the ICH Q3B(R2) guidance document *Impurities in New Drug Products*. For this, the applicant submitted a Letter of Authorization to NDA (b) (4) (oxycodone HCl) to reference safety findings for (b) (4). In brief, NDA (b) (4) included safety studies with (b) (4) including a 3-month oral toxicity study in rat and a battery of in vitro genetic toxicology studies that together adequately qualify (b) (4) at the proposed specification limit of (b) (4).

## **1.3 Recommendations**

### **1.3.1 Approvability**

This NDA may be approved from the pharmacology toxicology perspective.

### **1.3.2 Additional Non Clinical Recommendations**

There are no recommendations for additional nonclinical studies.

### **1.3.3 Labeling**

The table below contains the draft labeling submitted by the Applicant, the proposed changes, and the rationale for the proposed changes. For the final version of the label, please refer to the Action Letter.

(b) (4)

## 2 Drug Information

### 2.1 Drug

**CAS Registry Number (Optional)**

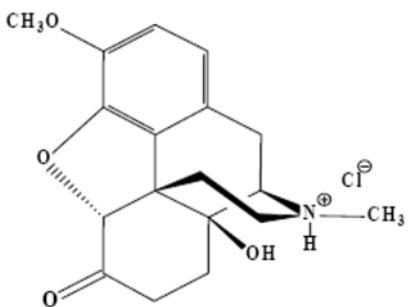
124-90-3

**Generic Name**

Oxycodone Hydrochloride USP tablets

**Code Name**

N/A

**Chemical Name**4, 5 $\alpha$ -epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride**Molecular Formula/Molecular Weight** $C_{18}H_{21}NO_4 \cdot HCl$  / MW 351.83 g/mol**Structure or Biochemical Description****Pharmacologic Class**

semi-synthetic opioid, narcotic, analgesic

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

IND/NDA/DMF	Drug/Compound	Sponsor	Office/Division	Comment/Status
IND 71,895	Acurox with Niacin (OxyADF)	(b) (4)	DAAAP	Active: 3/8/2005
NDA 21-011	Roxicodone (Oxycodone HCl)	Xanodyne Pharmaceuticals	DACCADP	Reference drug Approved: 2000
NDA (b) (4)	(b) (4) (Oxycodone (b) (4))	(b) (4)	DAAAP	Letter of authorization to cross-reference safety findings for (b) (4)
NDA 22-451	Acurox with Niacin (Oxycodone HCl plus Niacin)	Acura Pharmaceuticals, Inc.	DAAAP	Prior formulation of Acurox Submitted 12/30/2008 Complete Response 6/30/2009
DMF (b) (4)	Oxycodone HCl	(b) (4)	N/A	Reviewed: 6/2007

## 2.3 Drug Formulation

TRADENAME® (oxycodone HCl, USP) Tablets are available in strengths of 5 mg and 7.5 mg oxycodone HCl. In addition to oxycodone HCl, TRADENAME® (oxycodone HCl, USP) Tablets contain the following excipients: sodium lauryl sulfate, polyethylene oxide, colloidal silicon oxide, crospovidone, microcrystalline cellulose, and magnesium stearate as shown in the table below. According to the applicant, the clinical formulation of TRADENAME® (oxycodone HCl, USP) Tablets include excipients that are intended to introduce limits or impediments to 2 common methods of opioid analgesic product abuse: (1) intravenous injection of oxycodone extracted from dissolved tablets, and (2) nasal snorting of crushed tablets. (b) (4)



**Clinical Formulation of TRADENAME® (oxycodone HCl, USP) Tablets**

<i>Component</i>	<i>Function</i>	<i>mg/ 5 mg tablet</i>	<i>mg/ 7.5 mg tablet</i>	<i>TDI (mg/16 x 7.5 mg tablets)</i>	<i>IIG max potency (mg)</i>	<i>Rationale for acceptability of level in TRADENAME® (oxycodone HCl, USP) Tablets</i>
Oxycodone HCl USP	API	5.0	7.5			
Sodium lauryl sulfate NF	(b) (4)					
Polyethylene oxide NF						
Colloidal silicon dioxide NF						
Crospovidone NF						
Microcrystalline cellulose NF						
Magnesium stearate NF						
<b>Total</b>		<b>490.0</b>	<b>490.0</b>			

**2.4 Comments on Novel Excipients**

All of the excipients in the TRADENAME® (oxycodone HCl, USP) Tablets formulation are present in approved drug products at levels below the maximum potency listed in the FDA Inactive Ingredient Guide (IIG) when considering a single tablet. However, several excipients, which include sodium lauryl sulfate (SLS), crospovidone, and microcrystalline cellulose (MCC), are above the IIG listed levels when considering the maximum recommended daily dose (MRDD) of 12 TRADENAME® (oxycodone HCl, USP) Tablets per day.

The applicant was informed during a pre-NDA meeting held on 9/27/2010 (Meeting minutes dated 11/5/2010) and through subsequent correspondences that justification of excipient levels in TRADENAME® (oxycodone HCl, USP) Tablets would have to be based on a total daily intake of 16 tablets. Though the MRDD of TRADENAME® (oxycodone HCl, USP) Tablets is 12 tablets per day, we stated at the Pre-NDA meeting that the maximum theoretical daily dose for an opioid-tolerant patient must be considered when determining the acceptable levels of excipients. A safety assessment based on 16 TRADENAME® (oxycodone HCl, USP) Tablets was determined by the Division based in part on prescribing data from a Drug Utilization Summary presented by the Agency at the 2010 Joint Meeting of the Anesthetic and Life Support and Drug Safety and Risk Management Advisory Committees to discuss Acurox with Niacin (NDA 22-451). In addition, we informed the sponsor that upon further internal evaluation, no further justification would be required for the levels of SLS and microcrystalline cellulose in TRADENAME® (oxycodone HCl, USP) Tablets. However, the sponsor must provide a safety assessment for the level of crospovidone in TRADENAME® (oxycodone HCl, USP) Tablets based on a total daily intake of 16



tablets. Note that prior to the Pre-NDA meeting, this reviewer identified currently marketed drugs that contain levels of SLS and MCC that exceed the TDI of these excipients contained in 16 TRADENAME® (oxycodone HCl, USP) Tablets when taken at their respective MRDDs. For example, Visicol®, an approved tablet used as a bowel purgative prior to colonoscopy, contains (b) (4) of MCC per tablet. With an allowed dosing regimen of 40 tablets per day, the TDI of MCC from the recommended daily dose of the Visicol® tablets is (b) (4) which exceeds the amount of MCC in 16 TRADENAME® (oxycodone HCl, USP) Tablets (b) (4). In addition, an approved extended-release tablet formulation of metformin marketed as Fortamet® (NDA 21-674), which is an antihyperglycemic agent indicated for chronic use to treat Type 2 Diabetic mellitus, contains (b) (4) of SLS per tablet. When the MRDD of Fortamet® is consumed, the TDI of SLS is (b) (4), which exceeds the TDI of SLS in 16 TRADENAME® (oxycodone HCl, USP) Tablets (b) (4).

Per our agreement at the Pre-NDA meeting, the applicant submitted a safety assessment with the NDA to justify the level of crospovidone in TRADENAME® (oxycodone HCl, USP) Tablets based on 16 tablets per day. Note that no new or additional toxicology studies were conducted to qualify this excipient. Rather, the applicant submitted a written justification that cited literature from the public domain that included a safety evaluation from the FAO/WHO (Food and Agriculture Organization of the United Nations/World Health organization) Joint Expert Committee on Food Additives (JEFCA). JEFCA is a program under the WHO that significantly contributes to internationally-recognized, science-based risk assessments of food additives, contaminants, and residues of veterinary drugs in foods. A detailed discussion regarding the safety of crospovidone is below.

#### **Crospovidone, NF (CAS Registry #9003-39-8)**

(b) (4)

Crospovidone is present in numerous approved and marketed oral drugs in the US and is listed with (b) (4). The total daily intake (TDI) of crospovidone from 16 TRADENAME® (oxycodone HCl, USP) Tablets is (b) (4) than the maximum listed level found in the IIG. This reviewer identified the drug containing (b) (4) of crospovidone as a generic formulation of amitriptyline marketed as Amitril® (ANDA 83-939), an oral tertiary amine tricyclic antidepressant. Amitril® was originally approved in 1975 for the treatment of major depression (including patients with schizophrenia or psychosis with depressive symptoms) but was later discontinued and withdrawn in 1992, presumably because of the increased availability of higher dosage amitriptyline generic tablets. Note that amitriptyline is currently available in 10, 25, 50, 75, 100 and 150 mg tablet strengths. Amitril® was available only in a 10 mg tablet strength, which contained (b) (4).

(b) (4) of crosopvidone per tablet. According to the Clinical Pharmacology website, the maximum dosage limit of amytryptiline is 200 mg/day PO in outpatients and 300 mg/day for hospitalized patients. However, such doses are probably achieved currently with higher dosage tablets. The Clinical Pharmacology website also indicates that the recommended dose of amitryptiline for adolescent and elderly patients is three doses of 10 mg throughout the day, in addition to a dose of 20 mg at bedtime. This equates to a total daily dose of 50 mg, and would require the use of 10 mg tablets. Based on this recommended dosing, the TDI of crosopvidone would be (b) (4) the amount in 16 TRADENAME® (oxycodone HCl, USP) Tablets (b) (4)

A toxicological evaluation of crosopvidone (referred to as PVPP) was conducted by JECFA (WHO Food Additive Series 18) in 1983. In their report, the committee determined an acceptable daily intake (ADI) of PVPP for man through a review of available nonclinical toxicology studies, which included subchronic repeat-dose toxicity studies in rat and dog, a chronic repeat-dose oral toxicity study in dog, and a reproductive toxicity study on teratogenicity in rats. (Reviewer's Note: most of the toxicology studies described in the JECFA report were conducted by the (b) (4) a manufacturer of PVPP, which were submitted directly to the JECFA but not published.)

Rats fed diets containing up to 10% PVPP (approximately 9,000 mg/kg/day) for 90 days did not show any compound related effects on food consumption, body weight gain, behavior, or on gross pathology parameters and histological evaluation of tissue from principal organs (not list but organs weighed included brain, heart, pituitary, thyroid, liver, kidney, spleen, adrenals, and gonads) from high-dose and control animals. Though the JECFA review did not report a NOEL/NOAEL for this rat study, the high-dose (e.g., 9,000 mg/kg/day) showed no adverse toxicity and is associated with a human equivalent dose of (b) (4) (based on mg/kg body surface area and a human weight of 60 kg). This represents a safety margin of (b) (4) relative to the level of crosopvidone in 16 TRADENAME® (oxycodone HCl, USP) Tablets (b) (4)

The JECFA report summarized their review of a chronic repeat-dose toxicity study in dogs treated with PVPP at 0, 300, 1,200, 4,888 mg/kg/day via stomach tube for 26 weeks. The study evaluated clinical signs, hematology, clinical chemistry, urinalysis parameters, absolute and relative organ weights, and a complete histology of organs and tissues. In addition, electrocardiograms, ophthalmic and auditory tests, and specialized staining to investigate possible PVPP deposition in the liver, kidneys, and mesenteric lymph nodes were performed. No compound-related effects were observed on behavior, food intake, and body weight gain, or hematology, clinical chemistry, and urinalysis parameters. Moreover, no compound-related histopathology findings were observed and no accumulation of PVPP was noted in the examined tissues at any doses tested. Though the report did not state an identified NOEL/NOAEL, the high dose (e.g., 4,888 mg/kg/day) could be considered a NOAEL and is associated with a human equivalent dose of (b) (4) (based on mg/kg surface area and a human weighing 60 kg). This represents a safety margin of (b) (4) fold relative to the level of crosopvidone in 16 TRADENAME® (oxycodone HCl, USP) Tablets.

The JECFA evaluation also included a review of an embryo-fetal development study conducted in 26 pregnant rats dosed at 1000 or 3000 mg/kg/day via oral gavage from gestation days 6 to 15. Aside from a slight weight gain in dams from the high-dose group, no significant clinical symptoms were observed and no toxicologically significant findings were noted in dams or fetuses including skeletal and visceral abnormalities.

JEFCFA also noted that PK studies showed an almost complete lack of absorption of <sup>14</sup>C-labelled PVPP when administered orally to rats. Radioactivity was almost exclusively detected in the feces (80 – 99%) with negligible amounts found in urine, gastrointestinal tract, or lungs. Based on the available nonclinical data, the JECFA designated the ADI status of PVPP as “not specified,” meaning that a numerical figure for an ADI was not deemed necessary.

In summary, crosopovidone is considered by this reviewer to be reasonably safe at levels found in 16 TRADENAME® (oxycodone HCl, USP) Tablets. Higher levels have been allowed by the Agency based on the TDI of PVPP contained in an FDA approved drug (Amitril®). Notably, Amitril® was approved for chronic use. Moreover, the international risk assessment committee JEFCFA has determined that an acceptable daily intake designation was not necessary since oral intake of PVPP is not considered a toxicological risk to humans based on a weight of scientific evidence.

## 2.5 Comments on Impurities/Degradants of Concern

### Drug substance

According to the ICH Guidance for Industry document Q3A(R2) Impurities in the New Drug Substances, the qualification threshold for identified impurities is (b) (4) intake, whichever is lower, for a drug substance with a maximum daily dose (MDD) of (b) (4). The proposed specifications for the (b) (4) oxycodone HCl drug substance indicate testing for three impurities, which are presented in the table below. Specification limits of NMT (b) (4)

(b) (4) Based on 16 tablets per day (e.g., 120 mg of oxycodone), the potential maximum total daily intake (TDI) of either impurity is (b) (4) which is acceptable. The (b) (4) oxycodone HCl drug substance also contains the (b) (4)

Note that current Agency policy on acceptable levels for potentially genotoxic agents is NMT (b) (4). The specification limit for this impurity has been set to NMT (b) (4). Based on 16 tablets per day, the potential TDI of (b) (4) is (b) (4), which is acceptable. The specification limit for unknown total impurities of NMT (b) (4) is acceptable.



(b) (4)

The specifications for the (b) (4) oxycodone HCl drug substance indicate testing for three residual solvents, which are presented in the table below. The specification limits for all of the tested residual solvents in the drug substance are within ICH Q3C recommended thresholds.

(b) (4)

### Drug product

For a drug product with a maximum daily dose (MDD) >100 mg to 2 g, the ICH Guidance for Industry document Q3B(R2) Impurities in New Drug Products recommends the qualification threshold to be NMT 0.2% or 3 mg TDI, whichever is lower and the identification threshold to be NMT 0.2% or 2 mg TDI, whichever is lower. The proposed specification limits for TRADENAME® (oxycodone HCl, USP) Tablets are shown in the sponsor's table below. The applicant has proposed an acceptance limit for individual unspecified impurities of (b) (4), which is acceptable. However, the proposed acceptance limit for (b) (4) which exceeds the ICH Q3B(R2) threshold of NMT 0.2%. To justify the proposed specification for this impurity, the applicant submitted a Letter of Authorization to cross-reference safety findings for (b) (4) in NDA (b) (4) (oxycodone HCl), (b) (4). The NDA (b) (4) submission included safety studies conducted with (b) (4) that included a 3-month repeat-dose oral toxicity study in rat and a battery of in vitro genetic toxicology studies (e.g., bacterial reverse mutation assay, in vitro mammalian chromosomal aberration test), which would be appropriate for

qualification according to ICH Q3B(R2). Note that these studies were previously reviewed in the Pharmacology Toxicology review of NDA (b) (4) by Dr. Mamata De (dated 11/24/2008).

(b) (4)

In brief, (b) (4) was found to be negative in the mutagenicity (Ames) assay and in vitro mammalian chromosomal aberration assay under the experimental conditions tested. Moreover, the NOAEL of the 3-month oral toxicity study in rat was considered by Dr. De to be 8 mg/kg/day. The human equivalent dose (HED) associated with the NOAEL is 77 mg (based on mg/kg body surface area and a human weight of 60 kg), which represents a safety margin of >64-fold relative to the potential TDI of (b) (4) from 16 TRADENAME® (oxycodone HCl, USP) Tablets (b) (4). Taken together, these results adequately qualify (b) (4) at the proposed specification limit of (b) (4).

Dr. De's reviews of the three studies are reproduced verbatim below as they appeared in her original review for NDA (b) (4).

**Study title:** (b) (4) **Three-Month Oral Toxicity Study in Sprague-Dawley Rats**

*[Excerpted verbatim from the original (b) (4) review by Mamata De, Ph.D. dated November 24, 2008]*

**Key study findings**

- Sprague Dawley rats 20/sex/group were treated with (b) (4) (b) (4) for 13 weeks.
- Parameters evaluated include mortality, clinical observation, body weight, food consumption, clinical pathology, ophthalmology, organ weights, macroscopic evaluation, and microscopic evaluation of all of the tissues from the control and the high dose group animals.
- Clinical observations included hypersensitivity and aggressive behavior in approximately 10% animals from all test article related group. Because no such

findings were noted from the control animals and similar behavior were observed to occur in opioid treated animals, the effect is considered test article related.

- The histopathological lesions consisted of higher incidence of hyperplasia in lymph node in animals at high dose compared to those of the control animals; therefore NOAEL from this study was established to be 8 mg/kg (HED= 77 mg, based on a 60 kg man, or 293 mg/m<sup>2</sup>). Applicant's NOAEL for this study is 20 mg/kg/day.

**Study number:** 1053-031  
**Volume # and page #:** eCTD submission module 2 and 4; 1-1155  
**Conducting laboratory and location:** (b) (4)  
**Date of study initiation:** June 25, 2007  
**GLP compliance:** Yes  
**QA reports:** Yes  
**Drug, lot #, and % purity:** (b) (4) 88-05 & 92-12, 98%  
Vehicle: Methyl Cellulose, Spectrum Quality Products, VX 0055, Vitamin E, Eastman Chemical Company, 60018.

## Methods

Dose: 0, 2, 8, and 20 mg/kg

Species/strain: Sprague-Dawley rats [CrI: CD® (SD)]

Number/sex/group or time point (main study): 20 animals /sex/group

Route formulation and volume: Oral gavage. The test article was formulated in the vehicle containing 0.5 % methyl cellulose and 1% alpha tocopheryl glycol 1000 succinate (Vitamin E) in deionized water.

Satellite groups used for recovery: None

Age: Approximately 7-weeks

Weight: Males: 233-266 g; Females: 182-206 g

Unique study design or methodology (if any): The animals were administered with the test article once daily for 91-consecutive days (refer to Applicant's study design table).

## Study Design

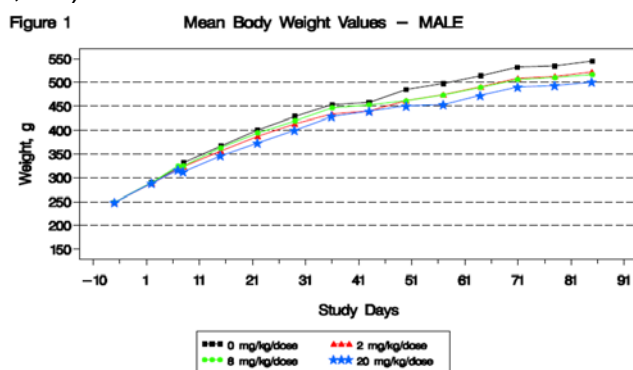
Group Assignments			
Group Number	Dose Level (mg/kg/dose)	Number of Animals	
		Male	Female
1	0	20	20
2	2	20	20
3	8	20	20
4	20	20	20

## Observations times and results

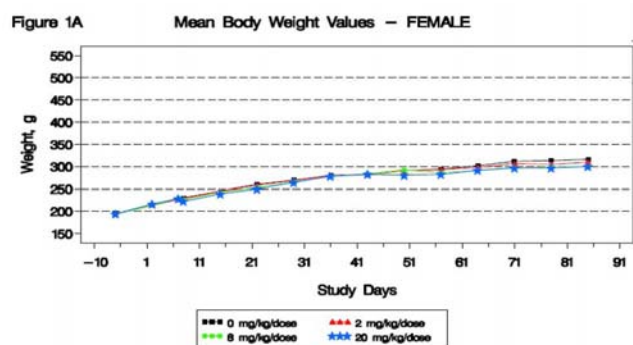
**Mortality:** Observation for mortality, morbidity, injury, and the availability of food and water were conducted twice daily for all animals. There was one unscheduled death in this study. One mid dose male died at Day 48, cause of death could not be determined but the death is not considered test article related due to the lack of dose response.

**Clinical signs:** Detailed clinical observations were carried out prior to randomization and weekly during the study. There were no test article related clinical signs. Aggressive behavior and hypersensitivity to touch was noted in 10% animals from all test article treated groups. Although not dose related, the findings are considered test article related because similar findings were related to the pharmacological activity of the opioids.

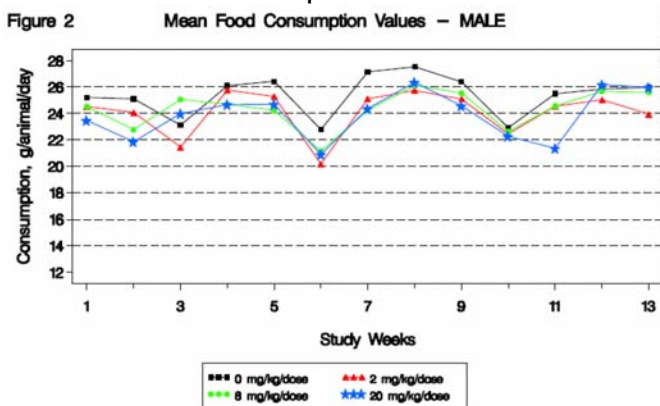
**Body weight:** Body weights were recorded prior to randomization, on Days 2, 7, and 8 and weekly thereafter. There was a dose related decrease in the body weight, the decrease in body weight at high dose was approximately 6-8% (refer to Applicant's figure 1, 1A)



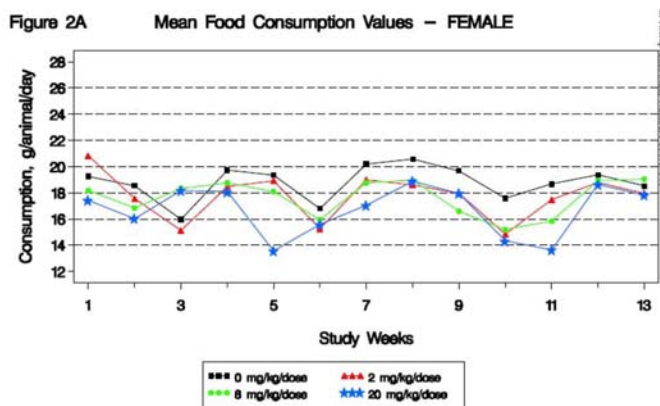
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**Food consumption:** The food consumption was measured weekly during the study. As depicted in the Applicant's figures 2, 2A, there were no apparent test article related changes in the food consumption.







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**Ophthalmoscopy:** The ophthalmic examinations were performed prior to the initiation of the treatment and prior to necropsy. There were no test article related changes in the ophthalmoscopic evaluation.

**Hematology and coagulation and clinical chemistry:** Blood samples for hematology, coagulation, and clinical chemistry evaluation were collected from animals at pretest, Week-6, and terminal necropsy. Following parameters were evaluated.

- leukocyte count (total and differential)
- erythrocyte count
- hemoglobin
- hematocrit
- mean corpuscular hemoglobin
- mean corpuscular volume
- mean corpuscular hemoglobin concentration
- absolute and percent reticulocytes
  
- platelet count
- prothrombin time
- activated partial thromboplastin time
  
- alkaline phosphatase
- total bilirubin (with direct bilirubin if total bilirubin exceeds 1 mg/dL)
- aspartate aminotransferase
- alanine aminotransferase
- gamma glutamyl transferase
- sorbitol dehydrogenase
- urea nitrogen
- creatinine
- total protein
- triglycerides
- albumin
- globulin and A/G (albumin/globulin) ratio (calculated)
- glucose
- total cholesterol
- electrolytes (sodium, potassium, chloride)
- calcium
- phosphorus

The analyses of hematological parameters showed sporadic, statistically significant changes in the erythrocytes parameters, however, the changes were within the historical control range and not dose related, therefore the findings were not considered test article related.

There analyses of clinical chemistry parameters showed mild decrease of triglycerides in mid (24%) and high (28%) dose animals compared to those of the controls. Therefore, these changes were considered test article related. The modulation of plasma triglycerides levels were historically associated with stress. The changes are, however, monitorable in clinical settings.

**Urinalysis:** Urine samples were collected from animals pretest, during Weeks 2 and 6, and prior to terminal necropsy. The metabolites of oxycodone were determined. In addition, following parameters were tested.

- volume
- specific gravity
- pH
- color and appearance
- protein
- glucose
- bilirubin
- ketones
- occult blood
- urobilinogen
- microscopy of spun deposit

There were sporadic changes in the urine volume, specific gravity, and pH. These changes are not considered test article related because the magnitudes of changes were low, not statistically significant, and not dose related. The quantitative order of urinary excretion levels of (b) (4)

**Gross pathology:** Necropsy observation was performed in all animals. No test article related findings were noted.

**Organ weights:** The organ weights were recorded for all animals at the schedule necropsy as listed in the applicant's table. There were no test article related organ weight changes in this study.

**Histopathology:** Adequate Battery: Yes. Peer review: No.  
All tissues examined and preserved are listed in the Applicant's table.

Best Available Copy

Organs or Tissues to be Weighed, Preserved, and Microscopically Examined

Tissue	Organ Weight Taken	Collected and Preserved	Microscopic Examination	
			1, 4	2, 3
Adrenal gland	X	X		
Aorta		X		
Bone with bone marrow, femur		X		
Bone with bone marrow, sternum		X		
Bone marrow smear <sup>a</sup>		X		
Brain (cerebrum, midbrain, cerebellum, medulla/pons)	X	X		
Epididymis	X	X		
Esophagus		X		
Eye (with optic nerve)		X		
Heart	X	X	X	
Joint, tibiofemoral		X		
Kidney	X	X	X	
Lacrimal gland, exorbital		X		
Large intestine, cecum		X		
Large intestine, colon		X		
Large intestine, rectum		X		
Larynx		X		
Liver	X	X	X	
Lung with bronchi	X	X		

<sup>a</sup> Latendresse JR, Warbritton AR, Jonassen H, Creasy DM. Fixation of testes and eyes using a modified Davidson's fluid: comparison with Bouin's fluid and conventional Davidson's fluid. Toxicol Pathol. 2002 Jul-Aug;30(4):524-33.

Tissue	Organ Weight Taken	Collected and Preserved	Microscopic Examination	
			1, 4	2, 3
Lymph node, mandibular		X		
Lymph node, mesenteric		X		
Mammary gland		X		
Nerve, sciatic		X		
Pancreas		X		
Peyer's patch		X		
Pituitary	X	X		
Prostate		X		
Salivary gland, mandibular <sup>b</sup>	X	X		
Salivary gland, parotid		X		
Salivary gland, sublingual		X		
Seminal vesicles		X		
Skeletal muscle, biceps femoris		X		
Skin		X		
Small intestine, duodenum		X	X	
Small intestine, ileum		X	X	
Small intestine, jejunum		X	X	
Spinal cord, cervical		X		
Spinal cord, lumbar		X		
Spinal cord, thoracic		X		
Spleen	X	X		
Stomach, glandular		X	X	
Stomach, nonglandular		X	X	
Target organs <sup>c</sup>		X		X
Testis	X	X		
Thymus	X	X		
Thyroid gland (with parathyroid) <sup>d</sup>	X	X		
Tongue		X		
Trachea		X		
Ureters		X		
Urinary bladder		X		
Gross lesions		X	X	X

The only plausible test article related microscopic findings in this study are mandibular lymph node hyperplasia (minimal) in one high dose male. No such changes were noted in control males. However, one female from the control group had similar finding with severity index designated as mild. Similar findings were also noted in one high dose group female (1/20) and in 1/1 low dose group female. Thus the incidence and severity of the hyperplasia findings in this study were 1/40 (mild), 1/1 (minimal), 0/40, and 2/40 (minimal) with 0, low, mid, and high dose group. Based on this finding, the NOAEL from this study was determined to be 8 mg/kg.

Note that no such findings were noted in the historical control database from the same laboratory from 2004 in females and from 2000 in males. In females, between the years 2000-2003 similar findings were noted in 8 (minimal) females.

### Histopathological findings:

Summary of Microscopic Observations - MALE										
Table 10		Terminal								
Tissue		0 mg/kg/dose		2 mg/kg/dose		8 mg/kg/dose		20 mg/kg/dose		
Observation	Severity	DOS	SNC	DOS	SNC	DOS	SNC	DOS	SNC	
lymph node, mandibular hyperplasia, lymphocyte/plasmacyte		(0)	(20)	(0)	(0)	(1)	(0)	(0)	(20)	
	- mild	0	0	0	0	0	0	0	1	
Summary of Microscopic Observations - FEMALE										
Table 10		Terminal								
Tissue		0 mg/kg/dose		2 mg/kg/dose		8 mg/kg/dose		20 mg/kg/dose		
Observation	Severity	DOS	SNC	DOS	SNC	DOS	SNC	DOS	SNC	
lymph node, mandibular hyperplasia, lymphocyte/plasmacyte		(0)	(20)	(0)	(1)	(0)	(0)	(0)	(20)	
		0	1	0	1	0	0	0	1	
	- minimal	0	0	0	1	0	0	0	1	
	- mild	0	1	0	0	0	0	0	0	

**Toxicokinetics:** Toxicokinetic analyses were not conducted from this study.

**Study title: Bacterial Reverse Mutation Assay:**

(b) (4)

*[Excerpted verbatim from the original*

(b) (4)

*review by Mamata De, Ph.D. dated November 24, 2008]***Key findings:**

- The test article was negative in the definitive mutagenicity assay (plate incorporation) under this experimental condition. The concentrations tested were 50, 150, 1500, and 5000 µg/plate. This is in concurrence with the Applicant's conclusion.

**Study number:**

AC01FX.503.BTL

**Volume # and page #:**

eCTD submission; Page#: 1-89

**Conducting laboratory and location:**

(b) (4)

**Date of study initiation:**

September 19, 2007

**GLP compliance:**

Yes

**QA reports:**

Yes

**Drug, Manufacturer, lot #, and % purity:**

(b) (4)

Lot # 92-

12; 98.0%

**Methods:** The assay was conducted in two phases using the plate incorporation method. The first phase was the toxicity-mutation assay used to establish the dose-range for the mutagenicity assay and get a preliminary mutagenicity evaluation. The second phase was the mutagenicity assay. Dosing was adjusted to compensate for test article activity.

Tester strain TA98 and TA1537 are reverted from histidine dependence to histidine independence by frame shift mutagens. Tester strain TA1535 is reverted by mutagens that cause base pair substitution. Tester strain TA100 is reverted by mutagens that cause both frame shift and base pair substitution mutations. Specificity in E.coli is sensitive to base-pair substitution mutations, rather than frame shift.

**Bacterial Strains:** Salmonella typhimurium tester strains TA98, TA100, TA1535, TA1537, and WP2 uvrA.

**Doses used in definitive study:** Concentrations of 50, 150, 1500, and 5000 µg/plate for (b) (4) were tested in both the presence and absence of metabolic activation.

**Basis of dose selection:** Doses used in initial cytotoxicity-mutation assay ranged from 2.5 to 5000 µg/plate for (b) (4), one plate per dose, both in presence and absence of the metabolic activation system. The test article was soluble in acetone at the highest concentrations tested. No precipitate was observed in the definitive test. No appreciable toxicity was observed. No positive mutagenic responses were observed in any tester strains either with or without S9 activation. The definitive study therefore used the maximum recommended concentrations of test article as the basis for dose selection.

Negative controls: Water

Positive controls: Refer to the following table.

Strain	S9 Activation	Positive Control	Concentration (µg/plate)
TA98	Rat	2-aminoanthracene	1.0
TA100, 1535, 1537		2-aminoanthracene	10
WP2 <i>uvrA</i>			25.0
TA98	None	2-nitrofluorene	1.0
TA100, TA1535		Sodium azide	1.0
TA1537		9-aminiacridine	75
WP2 <i>uvrA</i>		Methyl methane sulfonate	1000.0

**Comments:** Controls are acceptable according to current standards.

**Incubation and sampling times:** 48 to 72 hours at 37°C

## Results:

Study validity: The study appears to be valid for the following reasons: 1) the appropriate controls were used, 2) the appropriate strains were tested, 3) the positive control substances produced reliable positive results, 4) the highest concentration of the test article tested reached the maximum recommended concentration that is 5,000 µg/plate, and 5) there was no evidence for a dose dependent increase in revertants following drug treatment.

Study outcome: The test article did not produce any increases in the number of revertants in any tester stain under the conditions tested (refer to the Applicant's table 32); this is in concurrence with the Applicant's conclusion.

Bacterial Mutation Assay  
Summary of Results – Confirmatory Mutagenicity Assay  
Table 32

Test Article Id	: oxycodone-n-oxide									
Study Number	: AC01FX.503.BTL									
Experiment No	: B2									
Average Revertants Per Plate ± Standard Deviation										
Activation Condition	: None									
Dose (µg/plate)*	TA98		TA100		TA1535		TA1537		WP2 <i>uvrA</i>	
Vehicle	17 ±	4	146 ±	4	19 ±	3	8 ±	4	37 ±	21
50	17 ±	5	156 ±	10	21 ±	7	7 ±	2	26 ±	2
150	17 ±	6	154 ±	4	19 ±	11	8 ±	2	26 ±	6
500	15 ±	1	144 ±	11	20 ±	4	8 ±	5	28 ±	5
1500	17 ±	6	158 ±	20	19 ±	3	7 ±	2	35 ±	2
5000	14 ±	6	158 ±	15	21 ±	2	6 ±	0	34 ±	4
Positive	201 ±	27	507 ±	89	463 ±	128	1282 ±	562	150 ±	11

Activation Condition	: Rat Liver S9									
Dose (µg/plate)*	TA98		TA100		TA1535		TA1537		WP2 <i>uvrA</i>	
Vehicle	28 ±	3	161 ±	3	13 ±	5	6 ±	1	31 ±	7
50	23 ±	1	162 ±	6	17 ±	4	8 ±	2	32 ±	11
150	24 ±	6	165 ±	8	10 ±	5	5 ±	2	32 ±	4
500	24 ±	10	161 ±	18	12 ±	5	7 ±	1	27 ±	10
1500	22 ±	1	172 ±	17	8 ±	6	7 ±	3	32 ±	5
5000	18 ±	2	170 ±	40	10 ±	4	10 ±	4	27 ±	3
Positive	430 ±	58	486 ±	113	83 ±	21	41 ±	1	223 ±	67

Vehicle = Vehicle Control

Positive = Positive Control (50 µL plating aliquot)

Plating aliquot = 100 µL

\*The 50 mg/mL formulation did not meet the acceptance criterion.

**Study title: In Vitro Mammalian Chromosomal Aberration Test:**

(b) (4)

[Excerpted verbatim from the original

(b) (4)

review by Mamata De, Ph.D. dated November 24, 2008]

**Key findings**

- The chromosomal aberrations were tested in the Chinese hamster ovary cells in a valid assay; the concentrations tested in the definitive test for the metaphase analyses were 827.5, 1655, and 3310 µg/mL with and without metabolic activation for 4 and 20 hrs.
- There were no substantial toxicity in the pilot study with and without metabolic activation at 4 hrs; a cytotoxicity of >50% was noted with metabolic activation at 3310 µg/mL; therefore the dose selection was appropriately based on either the maximum feasible dose or cytotoxicity.
- There were no chromosomal aberrations without metabolic activation at 4 and 20 hrs of the incubation period.
- A dose related statistically significant increase in cells w/structural chromosomal aberration was noted in the treatment group w/metabolic activation at 4 hrs 0.5, 2.5, and 5% at low, mid, and high dose. The Applicant mentioned that the increase was within the historical control range (0-5%). Therefore, although statistically significant the increase is not considered biologically relevant.
- Therefore, (b) (4) is believed to be not clastogenic under this experimental condition.

**Study number:**

AC1FX.331.BTL

**Volume # and page #:**

eCTD submission; Page 1-58

**Conducting laboratory and location:**

(b) (4)

**Date of study initiation:**

September 27, 2007

**GLP compliance:**

Yes

**QA reports:**

Yes

**Drug, Manufacturer, lot #, and % purity:**

(b) (4)

Lot #

Std.92-12; 98%.

**Methods:**Cell line: Chinese hamster ovary (CHO-K1)

Doses used in definitive study: 413.75-3310 µg/mL (10 mM) w/wo S9 for 4 and 20 hrs incubation. Following table reproduced from the Applicant described the treatment regimen in the definitive study.

Treatment Condition	Treatment Time	Recovery Time	Dose levels (µg/mL)
Non-activated	4 hr	16 hr	413.75, 827.5, 1655, 3310
	20 hr	0 hr	413.75, 827.5, 1655, 3310
S9-activated	4 hr	16 hr	413.75, 827.5, 1655, 3310

Basis of dose selection: Less than 50% inhibition of cell growth inhibition (cytotoxicity) was observed in the preliminary toxicity study (dose range finding study) up to 3310 µg/mL (10 mM) with and without metabolic activation for 4 hrs of incubation period. The maximum concentration tested in the preliminary toxicity study soluble in water and cell culture medium. A mitotic index of 53% was noted without metabolic activation for 20 hrs of incubation at 3310 µg/mL, therefore the maximum dose selected in this study was also 3310 µg/mL.

Negative controls: Water

Positive controls: Mitomycin C for non activated system and cyclophosphamide for the S9 activated system.

Incubation and sampling times: In the definitive chromosomal aberration assay the cells were treated for 4 and 20 hrs in the non activated test system and 4 hrs in the S9 activated system. The cells were harvested 20 hrs after the initiation of the treatment.

## **Results:**

Study validity: The study is considered valid because the positive and the negative controls were used appropriately, the dose selection was based accurately on the formation of the visible precipitate in absence of substantial toxicity, the use of cell line was according to the OECD protocol, the CHO-K1 cell lines were also appropriately maintained in the test facility and tested negative for mycoplasma. The Applicant's methods of evaluation of the metaphase cells were appropriate i.e. sufficient # of metaphase cells were counted/treatment as ensured by the percentage of cells in mitosis/500 cells scored; metaphase cells w/20 ± 2 centromeres were examined, and a minimum of 200 metaphase spreads were analyzed per treatment group for chromatid (breaks and symmetric and asymmetric exchange) and chromosome-type aberrations (breaks and exchange figures such as dicentrics and rings).

Study outcome: The Applicant's summary of results is reproduced in the following table. Note that chromosomal aberrations were not noted wo/S9 activation for 4 and 20 hrs. The cytotoxicity observed in the two experiments mentioned above was 17 and 53% respectively. Based on these findings maximum dose for the metaphase analysis was chosen appropriately as 3310 µg/mL. There was an increase in the chromosomal aberrations w/S9 activation for the 4 hrs treatment period. There was a non dose related increase in the cells w/numerical aberrations (4.5-5%). This increase was less than that of the negative control 'water' (5%) but higher than the positive control cyclophosphamide (3%). There was a statistically significant dose related increase in the structural aberration at high dose (0.5, 2.5, and 5% at 827.5, 1655, and 3310 µg/mL respectively). The Applicant mentioned that these increases are within the historical control range of 0-5%, therefore the increased structural aberrations noted are artifacts. The reviewer observed that the increases of the structural damage at high dose are similar to the highest point observed in the historical control. Therefore the positive



results appeared to be test article related. The summary table below was reproduced from the Sponsor's submission.

TABLE 10  
SUMMARY

Treatment µg/mL	S9 Activation	Treatment Time	Mean Mitotic Index	Cells Scored		Aberrations Per Cell (Mean +/- SD)		Cells With Aberrations	
				Numerical	Structural			Numerical (%)	Structural (%)
Water	-S9	4	10.0	200	200	0.000	±0.000	3.0	0.0
(b) (4)									
MMC, 0.2	-S9	4	5.8	200	50	0.240	±0.476	2.5	22.0**
Water	+S9	4	10.6	200	200	0.000	±0.000	5.0	0.0
(b) (4)									
CP, 10	+S9	4	6.1	200	100	0.290	±0.624	3.0	21.0**
Water	-S9	20	9.4	200	200	0.000	±0.000	1.5	0.0
(b) (4)									
MMC, 0.1	-S9	20	6.3	200	50	0.280	±0.536	1.5	24.0**

**Treatment:** Cells from all treatment conditions were harvested 20 hours after the initiation of the treatments.

**Aberrations per Cell:** Severely damaged cells were counted as 10 aberrations.

**Percent Aberrant Cells:** \*,  $p \leq 0.05$ ; \*\*,  $p \leq 0.01$ ; using Fisher's Exact test.

## 2.6 Proposed Clinical Population and Dosing Regimen

TRADENAME® (oxycodone HCl, USP) Tablets are indicated for the management of moderate to severe pain where use of an opioid is appropriate. According to the proposed label, the dosage and administration of TRADENAME® (oxycodone HCl, USP) Tablets are based on the label for Roxicodone® Tablets. Patients who have not been receiving opioid analgesics should be started on TRADENAME® (oxycodone HCl, USP) Tablets in a dose range of 5 to 15 mg every 4 to 6 hours as needed for pain (up to 12 tablets).

## 2.7 Regulatory Background (related to nonclinical issues)

- Sept. 27, 2010: Type B (Pre-NDA) Meeting for TRADENAME® (oxycodone HCl, USP) Tablets with King Pharmaceuticals, Inc.
  - No new nonclinical studies with oxycodone HCl are required to support the submission and filing of this NDA.
  - Without niacin in the current TRADENAME® (oxycodone HCl, USP) Tablets formulation to discourage excessive administration, the maximum theoretical daily dose for an opioid-tolerant patient must be considered when determining the acceptable levels of excipients. The sponsor must justify the level of

crospovidone by providing a safety assessment based on a total daily intake of 16 TRADENAME® (oxycodone HCl, USP) Tablets per day.

### 3 Studies Submitted

#### 3.1 Studies Reviewed

No new pharmacology or toxicology studies were submitted with this NDA.

#### 3.2 Studies Not Reviewed

N/A

#### 3.3 Previous Reviews Referenced

- Refer to the Pharmacology Toxicology Review of NDA (b) (4) by Dr. Mamata De (dated 11/24/2008 in DARRTS). Note that the applicant submitted a Letter of Authorization to cross-reference safety findings for the impurity (b) (4) in NDA (b) (4) (Oxycodone HCl). The NDA (b) (4) submission included safety studies conducted with (b) (4) that included a 3-month repeat-dose oral toxicity study in rat and a battery of in vitro genetic toxicology studies (e.g., bacterial reverse mutation assay, in vitro mammalian chromosomal aberration test). Portions of Dr. De's review including these three studies are excerpted verbatim in this review.
- Refer to the Pharmacology Toxicology Review of the original Roxicodone NDA (Roxane Laboratories; NDA 21-011) by BeLinda Hayes, Ph.D. dated June 12, 2000. Portions of Dr. Hayes' review have been reproduced verbatim in this review for background purposes.

### 4 Pharmacology

#### 4.1 Primary Pharmacology

No primary pharmacology studies were submitted by the sponsor. The following summary of oxycodone pharmacology was excerpted verbatim from the original Roxicodone (Roxane Laboratories, NDA 21-011) review by BeLinda Hayes, Ph.D. dated June 12, 2000.

Oxycodone hydrochloride, a semisynthetic derivative of thebaine, is an opioid agonist that is pharmacologically similar to morphine. Preclinical studies have shown that oxycodone is a weak  $\mu$  agonist with potent analgesic activity in a variety of preclinical antinociceptive assays. Oxycodone also has the typical opioid-like CNS depressant activity.

The analgesic activity of oxycodone has been evaluated in rats<sup>1,2,3</sup> and mice<sup>4,5</sup>. The analgesic activity of oxycodone was compared to that of morphine and

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<sup>1</sup> Carter RB: Differentiating analgesic and non-analgesic drug activities on rat hot plate: effect of behavioral endpoint. Pain 1991; 47: 211-20

codeine in the rat 55° hot plate assay using hind paw lick and hind paw lick or jump as the endpoint<sup>1</sup>. Oxycodone's analgesic activity was qualitatively similar to morphine and codeine regardless of the endpoint measured. Oxycodone (p.o.) was more potent than codeine (p.o.) but less potent than morphine (i.p., s.c.).

The antinociceptive activity of oxycodone hydrochloride was compared to that of morphine hydrochloride in the rat tail flick and hot plate nociceptive tests following intraperitoneal, intrathecal and subcutaneous administrations<sup>2</sup>. Poyhia and Kalso (1992) reported that the strength of oxycodone's analgesic activity is route-dependent. Oxycodone was more potent than morphine in both thermal nociceptive tests following systemic administration; oxycodone was 2 and 4 times more potent than morphine following subcutaneous and intraperitoneal administration, respectively. However, weak antinociceptive effects were observed following intrathecally administered oxycodone; it was approximately 14 times less potent than morphine. Plummer et al. and Poyhia et al. have also reported similar findings in rats using the hot plate and tail flick assays<sup>6,7</sup>.

Poyhia and Kalso (1992) also compared the onset and duration of oxycodone's analgesic activity to that of morphine following intraperitoneal, intrathecal and subcutaneous administrations. In the rat tail flick and hot plate nociceptive assays, the antinociceptive effects of oxycodone (2.5-5.0 mg/kg) had a significantly ( $p \leq 0.05$ ) faster onset (mean = 15 min) in comparison to morphine (5-10 mg/kg) which had a mean onset of 30 minutes following both subcutaneous and intraperitoneal administrations. In contrast to the onset of antinociceptive effects observed with the lower doses, the highest dose of oxycodone (10 mg/kg) and morphine (20 mg/kg) had similar onset of analgesic activity following both routes of administration. The duration of action was similar for both drugs following subcutaneous administration; whereas, intraperitoneal oxycodone had a significantly ( $p \leq 0.05$ ) longer duration of action in comparison to intraperitoneal morphine. Intrathecal oxycodone had a shorter onset and duration of action in comparison to morphine. Plummer et al. (1990) postulated that the weak antinociceptive effects, fast onset and short duration of action, observed following intrathecal administration are due to its low polarity in comparison to the high polarity of morphine.

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<sup>2</sup> Poyhia R, Kalso EA: Antinociceptive effects and central nervous system depression caused by oxycodone and morphine in rats. *Pharmacol Toxicol* 1992; 70: 125-30

<sup>3</sup> Leow KP, Smith MT: The antinociceptive potencies of oxycodone, noroxycodone and morphine after intracerebroventricular administration to rats. *Life Sci* 1994; 54: 1229-36

<sup>4</sup> Weinstein SH, Gaylord JC: Determination of oxycodone in plasma and identification of a major metabolite. *J Pharm Sci* 1979; 68: 527-8

<sup>5</sup> Swedberg MD: The mouse grid-shock analgesia test: pharmacological characterization of latency to vocalization threshold as an index of antinociception. *J Pharmacol Exp Ther* 1994; 269: 1021-8

<sup>6</sup> Plummer JL, Cmielewski PL, Reynolds GD, Gourlay GK, Cherry DA: Influence of polarity on dose-response relationships of intrathecal opioids in rats. *Pain* 1990; 40: 339-47

<sup>7</sup> Poyhia R, Seppala T, Olkkola KT, Kalso E: The pharmacokinetics and metabolism of oxycodone after intramuscular and oral administration to healthy subjects. *Br J Clin Pharmacol* 1992; 33: 617-21

The antinociceptive activity of oxycodone was compared to morphine and its metabolite noroxycodone in Sprague Dawley rats following intracerebroventricular (ICV) administration<sup>3</sup>. Oxycodone and its metabolite noroxycodone were effective analgesics following ICV administration. Relative to morphine, oxycodone and noroxycodone were 2.3 and 5.9 times less potent than morphine, respectively. Oxycodone's analgesic activity had a more rapid onset than morphine or noroxycodone. Oxycodone's maximum antinociception occurred at 9.3 minutes ( $p \leq 0.05$ ) post-injection; whereas morphine's and noroxycodone's antinociceptive effects occurred at 31.8 and 34.6 minutes post-dosing, respectively. Consistent with morphine-induced analgesia, the analgesic effects of oxycodone and noroxycodone are mediated by opioid receptors. Naloxone pre-administration (55 nmol, ICV, 15 min pre) abolished the antinociceptive effects of oxycodone (227 nmol) and reduced the antinociceptive effects of both noroxycodone (332 nmol) and morphine (93 nmol).

The analgesic activity of oxycodone and its metabolite noroxycodone has also been evaluated in mice<sup>4</sup>. Using a modification of the mouse phenylquinone test, noroxycodone was less potent than oxycodone following oral or subcutaneous administration. It was 35 and 138 times less potent than oxycodone following oral and subcutaneous administration, respectively.

Using the mouse grid-shock analgesia test, Swedberg (1994) compared the analgesic activity of oxycodone to that of morphine and several other mu agonists (i.e. methadone, fentanyl, codeine, etorphine and meperidine). Consistent with results obtained in rats following subcutaneous administration, oxycodone was more potent than morphine. The ED<sub>50</sub>s (95% C.L.) for oxycodone and morphine were 1.87 (1.26-2.77) mg/kg and 2.36 (1.50-3.71) mg/kg, respectively. Analysis of the data showed that the results in mice correlated well ( $R=0.989$ ) with their clinical doses.

Oxycodone produces opioid-type CNS depression (i.e. loss of righting, placing and corneal reflexes and catalepsy) in rats. The CNS depressant effects of oxycodone were compared to those of morphine following subcutaneous, intraperitoneal and intrathecal administration<sup>2</sup>. Consistent with its analgesic properties, its CNS depressant effects are route-dependent. Oxycodone (2.5-10.0 mg/kg) was more potent than morphine in eliciting CNS depressant effects following both subcutaneous and intraperitoneal administrations. Subcutaneously and intraperitoneally administered oxycodone caused a dose-dependent loss in all reflexes measured and induced catalepsy; whereas subcutaneously administered morphine (10 and 20 mg/kg) only affected the righting and corneal reflexes and induced catalepsy. Only the righting reflex was lost and morphine-induced catalepsy were observed following the intraperitoneal administration of 20 mg/kg morphine. Neither oxycodone (12.5 and 100 µg) nor morphine (6.25 and 50 µg) elicited any CNS depressant activity following intrathecal administration.

The binding profile of oxycodone has been evaluated in rat brain<sup>8,9</sup>. Using <sup>3</sup>H-naloxone or <sup>3</sup>H-DAMGO as the ligand for the mu opioid receptor, both groups of investigators demonstrated that oxycodone binds to the mu opioid receptors with weak affinity. These results were surprising considering that oxycodone was a potent analgesic agent in rats and has an analgesic potency approximately 0.7-fold that of morphine in humans<sup>10</sup>. These findings suggest that oxycodone's analgesic efficacy may be due to the formation of an active metabolite or metabolites. Beaver (1978), Kalso (1990) and Inturrisi (1990) have suggested that part of the analgesic effects of oxycodone can be attributed to active metabolites<sup>11,12,13</sup>. In a clinical study comparing the pharmacokinetic profile of oxycodone after intramuscular and oral administrations, Poyhia (1992) reported that noroxycodone and oxymorphone are two major metabolites of oxycodone<sup>7</sup>.

## 4.2 Secondary Pharmacology

No secondary pharmacology studies were submitted by the sponsor.

## 4.3 Safety Pharmacology

No safety pharmacology studies were submitted by the sponsor.

# 5 Pharmacokinetics/ADME/Toxicokinetics

## 5.1 PK/ADME

No nonclinical pharmacokinetic studies were submitted by the sponsor.

## 5.2 Toxicokinetics

N/A

# 6 General Toxicology

## 6.1 Single-Dose Toxicity

No single-dose toxicity studies were required or submitted by the applicant for this NDA.

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<sup>8</sup> Pert CB, Snyder SH: Properties of opiate-receptor binding in rat brain. Proc Natl Acad Sci U S A 1973; 70: 2243-7

<sup>9</sup> Chen ZR, Irvine RJ, Somogyi AA, Bochner F: Mu receptor binding of some commonly used opioids and their metabolites. Life Sci 1991; 48: 2165-71

<sup>10</sup> Ross A, Hill A: Intrathecal morphine and herpes reactivation. Anaesth.Intensive Care 1993; 21: 126

<sup>11</sup> Beaver WT, Wallenstein SL, Rogers A, Houde RW: Analgesic studies of codeine and oxycodone in patients with cancer. I. Comparisons of oral with intramuscular codeine and of oral with intramuscular oxycodone. J Pharmacol Exp Ther 1978; 207: 92-100

<sup>12</sup> Inturrisi CE, Portenoy RK, Max MB, Colburn WA, Foley KM: Pharmacokinetic-pharmacodynamic relationships of methadone infusions in patients with cancer pain. Clin Pharmacol Ther 1990; 47: 565-77

<sup>13</sup> Kalso E, Vainio A, Mattila MJ, Rosenberg PH, Seppala T: Morphine and oxycodone in the management of cancer pain: plasma levels determined by chemical and radioreceptor assays. Pharmacol Toxicol 1990; 67: 322-8

## 6.2 Repeat-Dose Toxicity

No repeat-dose toxicity studies were required or submitted by the applicant for this NDA.

## 7 Genetic Toxicology

No genetic toxicology studies were required or submitted by the applicant for this NDA.

### 7.4 Other Genetic Toxicity Studies

N/A

## 8 Carcinogenicity

No carcinogenicity studies were required or submitted by the applicant for this NDA.

## 9 Reproductive and Developmental Toxicology

No reproductive and developmental toxicology studies were required or submitted by the applicant for this NDA.

## 10 Special Toxicology Studies

N/A

## 11 Integrated Summary and Safety Evaluation

NDA 202080 was submitted by King Pharmaceuticals Research and Development, Inc. for approval to market TRADENAME® (oxycodone HCl, USP) Tablets, which are an immediate-release oral formulation of oxycodone HCl indicated for the management of moderate to severe pain where use of an opioid analgesic is appropriate. This NDA was submitted via the 505(b)(2) pathway with Roxicodone® (NDA 21-011) as the listed drug for immediate-release oxycodone HCl. According to the applicant, the clinical formulation of TRADENAME® (oxycodone HCl, USP) Tablets includes excipients that are intended to introduce limits or impediments to 2 common methods of opioid analgesic product abuse: (1) intravenous injection of oxycodone extracted from dissolved tablets, and (2) nasal snorting of crushed tablets. (b) (4)

[REDACTED]

Per agreement with the sponsor through a PreNDA meeting held on 9/27/2010 (Meeting minutes dated 11/5/2010) and subsequent correspondences, no new nonclinical toxicology studies were required with this NDA submission. However, the applicant was required to provide a safety assessment to justify the level of crosprovidone in TRADENAME® (oxycodone HCl, USP) Tablets based on a total daily intake of 16 tablets. Note that a safety assessment based on 16 TRADENAME® (oxycodone HCl, USP) Tablets was determined by the Division based in part on prescribing data from a Drug Utilization Summary presented by the Agency at the 2010



Joint Meeting of the Anesthetic and Life Support and Drug Safety and Risk Management Advisory Committees to discuss Acurox with Niacin (NDA 22-451). Crespovidone is present in numerous approved and marketed oral drugs in the US and is listed with a maximum potency of 792.0 mg according to the FDA Inactive Ingredient Guide (IIG). The TDI of crespovidone from 16 TRADENAME® (oxycodone HCl, USP) Tablets is (b) (4) than the maximum listed level found in the IIG. Note that no new or additional toxicology studies were conducted by the applicant to qualify this excipient. Rather, the applicant submitted a written justification that cited literature from the public domain that included a safety evaluation from the FAO/WHO (Food and Agriculture Organization of the United Nations/World Health Organization) Joint Expert Committee on Food Additives (JEFCA). The JEFCA report summarized the committee's review of nonclinical studies that addressed the repeat-dose toxicity, reproductive toxicity, and genetic toxicity of this excipient. In brief, no adverse toxicological findings were noted in a 90-day repeat-dose oral toxicity study in rat and a 6-month repeat-dose oral toxicity study in dog. The highest doses tested were associated with human equivalent doses (HEDs) that provide adequate margins of safety relative to the potential TDI of crespovidone in TRADENAME® (oxycodone HCl, USP) Tablets. Moreover, crespovidone tested negative for mutagenicity in a standard battery of genetic toxicity studies, did not have teratogenic effects, and was found to be poorly absorbed by the gastrointestinal tract in humans following oral ingestion. Based on this information, JEFCA determined that an acceptable daily intake (ADI) designation was "not specified" since oral intake of crespovidone was not considered a toxicological risk to humans based on a weight of scientific evidence. Additionally, this reviewer identified an approved drug (Amitril®; ANDA 83-939) with a TDI of crespovidone that exceeds the amount in 16 TRADENAME® (oxycodone HCl, USP) Tablets (b) (4) when taken as recommended. Taken together, the information above provides adequate qualification for the level of crespovidone in TRADENAME® (oxycodone HCl, USP) Tablets based on a total daily intake of 16 tablets.

The applicant provided justification for the drug product impurity (b) (4) specification limit of (b) (4) which exceeds the threshold recommended by the ICH Q3B(R2) document Impurities in New Drug Products. For this, the applicant submitted a Letter of Authorization to NDA (b) (4) (oxycodone HCl) to reference safety findings for (b) (4). NDA (b) (4) included safety studies with (b) (4) including a 3-month oral toxicity study in rat and a battery of in vitro genetic toxicology studies. Note that these studies were previously reviewed in the Pharmacology Toxicology review of NDA (b) (4) by Dr. Mamata De (dated 11/24/2008). (b) (4) was negative in both the mutagenicity (Ames) assay and in vitro mammalian chromosomal aberration assay under the experimental conditions tested. Moreover, the HED associated with the NOAEL of the 3-month oral toxicity study in rat represents a safety margin of >64-fold relative to the potential TDI of (b) (4) from 16 TRADENAME® (oxycodone HCl, USP) Tablets. Taken together, these results adequately qualify (b) (4) at the proposed specification limit of (b) (4).

In summary, the applicant has adequately addressed all outstanding nonclinical safety concerns. No additional nonclinical concerns arose during the current review



cycle of the NDA. Therefore, from the pharmacology toxicology perspective this NDA may be approved.

## **12 Appendix/Attachments**

N/A

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JAY H CHANG  
05/20/2011

ADAM M WASSERMAN  
05/20/2011

I concur NDA 202080 may be approved from the nonclinical perspective.

**PHARMACOLOGY/TOXICOLOGY NDA FILEABILITY CHECKLIST**

**NDA Number:** 202080      **Applicant:** King Pharmaceuticals Research and Development, Inc.      **Stamp Date:** 12/17/2010

**Drug Name:** Acurox Tablets      **NDA Type:** 505(b)(2)      **DAAP/OND/CDER/FDA**

On **initial** overview of the NDA application for filing:

	Parameters	Yes	No	Comment
1	On its face, is the pharmacology section of the NDA/BLA organized (in accord with 21 CFR 314 and current guidelines for format and content) in a manner to allow substantive review to begin?			<i>Not applicable.</i> Module 4 (nonclinical section) is omitted from the NDA. The Sponsor cites PreNDA meeting minutes indicating that FDA concurs that nonclinical studies are not required for submission of NDA. Module 2 contains a Nonclinical Overview.
2	Is the pharmacology/toxicology section of the NDA/BLA indexed and paginated in a manner allowing substantive review to begin?			<i>Not applicable.</i> No Module 4. No nonclinical studies were required.
3	On its face, is the pharmacology/toxicology section of the NDA/BLA legible so that substantive review can begin?			<i>Not applicable.</i> No Module 4. No nonclinical studies were required.
4	Are all required (*) and requested IND studies (in accord with 505(b1) and (b2) including referenced literature) completed and submitted in this NDA/BLA (carcinogenicity*, mutagenicity*, teratogenicity*, effects on fertility*, juvenile studies, acute and repeat dose adult animal studies*, maximum tolerated dose determination, dermal irritancy, ocular irritancy, photo co-carcinogenicity, animal pharmacokinetic studies, safety pharmacology, etc)?			<i>Not applicable.</i> No nonclinical studies were required. However, Sponsor submitted information to qualify the level of excipients in the drug product. This information is located in Module 3 (Quality) and was linked (eCTD) to the Nonclinical overview located in Module 2.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies been conducted with the appropriate formulation?			<i>Not applicable.</i> No nonclinical studies were required.

6	Is (are) the excipient(s) appropriately qualified (including interaction between the excipients if applicable)?			The sponsor has submitted sufficient information for review to evaluate whether excipient levels are adequately qualified.
7	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 <u>submitted</u> a rationale to justify the alternative route?			<i>Not applicable.</i> No nonclinical studies were required.
8	Has the sponsor <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			<i>Not applicable.</i> No nonclinical studies were required.
9	Has the sponsor submitted all special studies/ data requested by the Division during pre-submission discussions with the sponsor?			<i>Not applicable.</i> No nonclinical studies were required.
10	Are the proposed labeling sections relative to pharmacology, reproductive toxicology, and carcinogenicity appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
11	Has the sponsor submitted any toxicity data to address impurities, new excipients, leachables, etc. issues.	X		Sponsor has submitted literature and other information to qualify level of excipients based on 16 tablets per day (as previously agreed with Division) and has cross referenced NDA (b) (4) for safety information to justify the specification limit of NMT (b) (4) for the impurity (b) (4) in the drug product.
12	Has the sponsor addressed any abuse potential issues in the submission?	X		

13	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			<i>Not applicable.</i>
14	From a pharmacology/toxicology perspective, is the NDA/BLA fileable? If ``no`` please state below why it is not.	x		

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes**

**Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.**

**Comments to Sponsor:**

None.

Reviewing Pharmacologist: Jay H. Chang, Ph.D. 2/1/2011  
Date

Team Leader: Adam Wasserman, Ph.D. 2/1/2011  
Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JAY H CHANG  
02/02/2011

ADAM M WASSERMAN  
02/03/2011