

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202080Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Addendum to the Primary Clinical Pharmacology Review Dated May 16, 2011

NDA: 202080	Submission Date: 12/17/2010
Relevant IND(s):	NA
Submission Type; Code:	505 (b) (2)
Reference Drug:	Roxicodone® Tablets
Brand Name:	Oxecta®
Generic Name:	Oxycodone
Formulation; Strength(s):	Immediaite-release tablets, 5 and 7.5 mg
Clinical Pharmacology Reviewer:	Suresh B Naraharisetti, Ph.D.
Team Leader:	Yun, Xu, Ph.D.
OCP Division:	Division of Clinical Pharmacology II
OND Division:	Division of Anesthesia and Analgesia Products
Sponsor:	King Pharmaceuticals
Proposed Indication:	For the management of moderate to severe pain where the use of an opioid analgesic is appropriate.
Proposed Dosage Regimen:	<ul style="list-style-type: none">• Opioid naïve patients – start at 5 to 15 mg every 4 to 6 hours as needed for pain.• Titrate the dose based upon the individual patient's response to their initial dose of the drug.

This addendum to Primary Clinical Pharmacology review is to address the recommendations made by Division of Scientific Investigation (DSI) on the audited pivotal BE study, AP-ADD-100. At the time of signing-off the primary Clinical Pharmacology review for NDA 202080, DSI inspection-report for study AP-ADD-100 was pending. Subsequently, DSI finalized their reports for bioanalytical and clinical-site inspectional findings separately on June 03, 2011 and June 10, 2011, respectively (see review by Drs. Dasgupta, Arindam and Abhijit Raha, Ph.D. dated and 06/03/2011 and 06/10/2011 for details).

The DSI found that both bioanalytical and clinical data for the study AP-ADD-100 is acceptable accepted for Agency's review.

However, in the clinical-site inspection report, DSI has reported that there is a delay in blood sample collection at 6 time points for six different subjects (Table1) and recommended the Clinical Pharmacology reviewer to evaluate whether this deviation would impact the pharmacokinetic (PK) parameters.

Table 1: Subjects in which the blood sample collection was delayed in the study AP-ADD-100 (Copied from Drs. Dasgupta, Arindam and Abhijit Raha, Ph.D review dated 06/10/2011)

Time Point Deviations

Subject	Time point	Deviation
209	2.5hr	13 min late
220	6hr	16 min late
224	6hr	16 min late
233	3.5hr	11 min late
237	24hr	14 min late
240	8hr	15 min late

Recommendation:

AP-ADD-100 is a 3-period, 3-treatment, 3-way cross-over BE comparison study of Oxecta, Acurox® and Roxicodone® Tablets. In this study, a total number of 36 subjects completed three treatments. From each subject, a total of 19 blood samples were collected for PK analysis. As per DSI report, the blood sample collection was delayed >10 minutes (varies from 11 to 16 min) at 6 blood sampling time points, which were belonging to six different subjects. These delayed time points are at a relatively later time period of sample collection. The delayed sampling time points account for a very small fraction of the total blood samples. Therefore, these small time-deviations in the sampling will not affect the final outcome of the study AP-AD-100 and the hence the NDA 202080 is acceptable from the clinical pharmacology perspective.

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/s/

SURESH B NARAHARISETTI

06/13/2011

YUN XU

06/13/2011

CLINICAL PHARMACOLOGY REVIEW

NDA: 202080	Submission Date: 12/17/2010
Relevant IND(s):	NA
Submission Type; Code:	505 (b) (2)
Reference Drug:	Roxicodone® Tablets
Brand Name:	Oxecta (proposed)
Generic Name:	Oxycodone
Formulation; Strength(s):	Immediate-release tablets, 5 and 7.5 mg
Clinical Pharmacology Reviewer:	Suresh B Naraharisetti, Ph.D.
Team Leader:	Yun, Xu, Ph.D.
OCP Division:	Division of Clinical Pharmacology II
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Proposed Indication:	For the management of moderate to severe pain where the use of an opioid analgesic is appropriate.
Proposed Dosage Regimen:	<ul style="list-style-type: none">• Opioid naïve patients – start at 5 to 15 mg every 4 to 6 hours as needed for pain.• Titrate the dose based upon the individual patient's response to their initial dose of the drug.

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1.0 Executive Summary

1.1 Recommendation

From the Clinical Pharmacology perspective, NDA 202080 is acceptable provided that (a) DSI inspection finds the data from pivotal BE study AP-ADD-100 is acceptable and (b) agreement can be reached between the Sponsor and the Agency regarding the language in the package insert.

1.2 Phase 4 Commitments

None

1.3. Summary of Clinical Pharmacology Findings

King Pharmaceuticals submitted a 505 (b) (2) application for abuse deterrent, immediate-release (IR) formulation of Oxycodone HCl Tablets. This application references the NDA 021011 for Roxicodone® (Oxycodone HCl IR Tablets), and establishes safety and efficacy based on bioequivalence with Roxicodone® Tablets. There are no clinical safety and efficacy studies conducted for this product. The proposed indication is for the relief of moderate to severe pain where the use of an (b) (4) (b) (4) opioid analgesic (b) (4) is appropriate. The proposed dosage regimen is to start at 5 to 15 mg Oxycodone HCl Tablets every 4 to 6 hours as needed for pain. The dose strengths are 5 and 7.5 mg, which are compositionally proportional.

As per Sponsor, Oxycodone HCl Tablets is an abuse deterrent formulation, which in addition to oxycodone contains excipients such as polyethylene oxide, crospovidone and sodium lauryl sulphate (SLS) (b) (4)

Currently, several oxycodone IR products have been approved either as a single ingredient or in combination with aspirin, acetaminophen or ibuprofen. Some of these products are Roxicodone® (5, 15 and 30 mg), Percocet (Oxycodone/Acetaminophen), Combunox (Oxycodone/Ibuprofen), etc.

Complete Response Action on Acurox® (N22451) Submission:

In December 2008, this Sponsor submitted NDA for Acurox® Tablets (N22451) consisting of 5 or 7.5 mg of oxycodone hydrochloride with 30 mg of niacin as an abuse deterrent opioid drug product. The sponsor claimed that niacin was included in the formulation with the intent of causing aversive effects such as flushing if the labeled dose is exceeded via the oral route of administration. In the product development program for this NDA, sponsor conducted clinical, clinical pharmacology and abuse liability studies. The clinical study, AP-ADF-105 was an efficacy and safety study of Acurox® Tablets versus placebo in patients with postoperative pain following bunionectomy. The clinical pharmacology program included bioequivalence (AP-ADF-104), single and multiple dosing PK (AP-ADF-109), food effect and dose proportionality (AP-ADF-108) studies. Additionally studies exploring the abuse liability with regard to niacin dose selection and

nasal abuse were conducted. From the clinical pharmacology perspective, this NDA (N22451) was acceptable (b)(4)

This product, however, at the end of the review cycle was issued a Complete Response action due to 1) relatively higher incidence of flushing in patients taking Acurox® Tablets (ranging from 11% to 41% compared to 1.5% with placebo) and 2) little or no evidence that the inclusion of niacin in Acurox® Tablets will deter the abuse of oxycodone.

Current Submission:

The current Oxycodone HCl Tablets (NDA 202080) is a reformulated tablet formulation without niacin. (b)(4)

As per the sponsor, this reformulated Oxycodone HCl Tablets without niacin is also an abuse deterrent opioid drug product with inactive ingredients that prevent the abuse. There are no clinical safety and efficacy studies conducted for this product.

The clinical development program includes two clinical pharmacology studies and an abuse liability study as listed below:

- **Study AP-ADD-100:** A pivotal bioequivalence (BE) PK study with the reference listed drug, Roxicodone® in healthy volunteers. This was a three way cross over, three treatment study that compares the BE of Oxycodone HCl Tablets (2x7.5 mg) versus Roxicodone® Tablets (15 mg) and of Oxycodone HCl Tablets (2x7.5 mg) versus Acurox® Tablets (oxycodone/niacin, 2x7.5 mg/30 mg) (N22451)
- **Study K234-10-1001:** A dose-proportionality and food-effect PK study in healthy volunteers. This study was a 5-period, 5-way crossover study that evaluated the 1) dose-proportionality between 5, 10 and 15 mg Oxycodone HCl Tablets, 2) food effect on Oxycodone HCl Tablets 3) food effect comparison between Oxycodone HCl Tablets and Roxicodone® Tablets under fed conditions
- **Study K234-10-1002:** A relative abuse liability study in non-dependent recreational opioid users to assess the limits and impediments to abuse of Oxycodone HCl Tablets versus Roxicodone® Tablets when crushed and administered intranasally. The pharmacokinetics was not evaluated in this study.

Studies AP-ADD-100 and K234-10-1001 are reviewed by this reviewer and the study K234-10-1002 was reviewed by the control substance staff (CSS).

Bioequivalence under fasting conditions: The findings of the pivotal BE study show that Oxycodone HCl Tablets (2 x 7.5 mg) is bioequivalent to the Roxicodone® Tablets (15 mg) under fasting conditions. The BE was also established between Oxycodone HCl Tablets (2 x 7.5 mg) and Acurox® Tablets (oxycodone/niacin, 2 x 7.5 mg/30 mg). The point estimates and the 90% confidence intervals of geometric means ratio for Cmax, AUClast and AUCinf were within the accepted 80% to 125% limits for both Oxycodone HCl Tablets versus Roxicodone® Tablets and Oxycodone HCl Tablets versus Acurox® Tablets. The BE study was conducted using the final to-be-marketed formulation.

Food Effect: Administration of Oxycodone HCl Tablets with high-fat food increases the total systemic exposure (AUC) by 21% and decreases the Cmax by 14% and delays the

Tmax from 1.25 hours when fasting to 3.0 hours with food. The observed food effect for the Oxycodone HCl Tablets formulation was similar to that observed for previously submitted Acurox® Tablet formulation. For Acurox® Tablets, food increases AUC by 19% and delays Tmax from 1.3 hours when fasting to 2.9 hours with food. A similar food effect was also reported for oxycodone solution with a 27% increase in AUC, 7% decrease in Cmax and a delay in Tmax (1.25 h to 2.54 h). For Roxicodone® Tablets, no dose adjustments with food were warranted (Roxicodone® package insert).

Under fed conditions (in this study), in comparison to Roxicodone® Tablets, Oxycodone HCl Tablets showed similar AUC and 17% decrease in Cmax and a delayed Tmax (3 hours versus 1.3 hours).

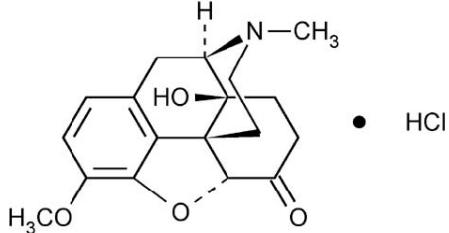
Taken together, the observed food effect for Oxycodone HCl Tablets does not warrant any dosing adjustments.

Overall, adequate information has been provided characterizing the clinical pharmacology aspects of Oxycodone HCl Tablets. At the time of finalizing this review, DSI inspection of study (AP-ADD-100) is pending and an addendum to this review will be written if DSI audit finds significant issues affecting the acceptability of the data.

2.0 Question Based Review

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance?

Table 2.2.1: Physical-Chemical Properties of Oxycodone Hydrochloride	
Drug Name	Oxycodone Hydrochloride
Chemical Name	4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride
Structure	 • HCl
Molecular Formula	C ₁₈ H ₂₁ NO ₄ ·HCl
Molecular Weight	351.82
Melting Point	218°C -223°C (range not to exceed 2°C)
Appearance	White to off-white, fine crystalline powder
Solubility	Up to 0.18 g/mL in water (pH 6.5-6.6); ~0.10 g/mL in water(pH>6.6)

2.1.2 What is the composition of the to-be-marketed formulation of Oxycodone HCl Tablets?

The proposed commercial dosage forms include 5 mg and 7.5 mg strengths of oxycodone HCl. Both the 5 mg and 7.5 mg strength tablets are white, debossed with unique identifiers with theoretical tablet weight of (b) (4) for both. Table 2.1.2 provides the quantitative composition for both tablet strengths and the function of each component. The theoretical quantity of oxycodone hydrochloride is listed; the actual amount used will vary depending upon the potency of the drug substance.

The two strengths of tablets meet the definition of *proportionally similar* as described in the March 2003 FDA “Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations.”

At the time of finalizing this review, the ONDQA biopharm review has not been documented in DARRTS yet. Based on the communication with the ONDQA reviewer, for Oxycodone HCl 5 mg tablet strength, biowaiver for *in vivo* BE studies can be granted on the basis of the dissolution data.

Table 2.1.2: Oxycodone HCl Tablet Composition

Component	Quality Standard	Function	IIG Levels	Strength			
				5 mg		7.5 mg	
				Quantity per Unit mg/tab	%	Quantity per Unit mg/tab	%
Oxycodone Hydrochloride USP	USP	Active pharmaceutical ingredient	Not applicable	5*	(b) (4)	7.5*	(b) (4)
Polyethylene Oxide NF (b) (4)	NF						(b) (4)
Sodium Lauryl Sulfate NF (b) (4)	NF						
Microcrystalline Cellulose NF (b) (4)	NF						
Crospovidone NF (b) (4)	NF						
Colloidal Silicon Dioxide NF (b) (4)	NF						
Magnesium Stearate NF (b) (4)	NF						
				Total:490	100	490	100

* Actual quantity will be corrected for potency.

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Oxycodone is a pure agonist opioid whose principle therapeutic action is analgesic. Oxycodone HCl Tablets is indicated for the management of moderate to severe pain where the use of an opioid analgesic is appropriate

2.1.4 What are the proposed dosage and route of administration?

Oxycodone HCl Tablets are intended for oral administration. The proposed dosage for Oxycodone HCl Tablets is to start at 5 to 15 mg every 4 to 6 hours as needed for pain. The proposed dosing regimen is similar to the RLD, Roxicodone® IR Tablets.

2.1.5 What are the core studies submitted in this NDA?

The clinical and clinical pharmacology program for this oxycodone HCl Tablets consisted of 3 prospective studies:

- **Study AP-ADD-100:** A pivotal bioequivalence (BE) PK study with the reference listed drug, Roxicodone® in healthy volunteers. This was a three way cross over, three treatment study that compares the BE of Oxycodone HCl Tablets versus Roxicodone® Tablets (15 mg) and of Oxycodone HCl Tablets (2x7.5 mg) versus Acurox® Tablets (oxycodone/niacin, 2x7.5 mg/30 mg) (N22451)
- **Study K234-10-1001:** A dose-proportionality and food-effect PK study in healthy volunteers. This study was a 5-period, 5-way crossover study that evaluated the 1) dose-proportionality between 5, 10 and 15 mg Tablets, 2) food effect on Oxycodone HCl Tablets 3) food effect comparison between Oxycodone HCl Tablets and Roxicodone® Tablets under fed conditions
- **Study K234-10-1002:** A relative abuse liability study in non-dependent recreational opioid users to assess the limits and impediments to abuse of Oxycodone HCl Tablets versus Roxicodone® Tablets when crushed and administered intranasally. The pharmacokinetics was not evaluated in this study.

Studies AP-ADD-100 and K234-10-1001 are were reviewed by this reviewer and the study K234-10-1002 was reviewed by the control substance staff (CSS).

2.2 General Clinical Pharmacology

2.2.1. What are the general PK characteristics of the drug?

When administered orally, oxycodone is well absorbed. The oral bioavailability of IR oxycodone ranges from 60% to 87% with different formulations. Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, and their glucuronide conjugates. The major circulating metabolite is noroxycodone. The formation of noroxycodone (N-demethylation) is mainly mediated by CYP3A4 and the formation of oxymorphone (O-demethylation) is mediated by CYP2D6. Oxymorphone is a known analgesic that is marketed in the US. However, although possessing analgesic activity, oxymorphone is present in plasma only in low concentrations (about 15% of administered dose), after oral administration of oxycodone. Oxycodone and its metabolites are excreted primarily via the kidney as both conjugated and unconjugated metabolites. Apparent elimination half-life of oxycodone is 3.5 to 4 hours.

Following intravenous administration, the volume of distribution (Vss) for oxycodone was 2.6 L/kg. Plasma protein binding of oxycodone at 37°C and a pH of 7.4 was about 45%. Oxycodone has been found in breast milk. Precautions should be taken for special populations.

2.2.2 Were the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Oxycodone analgesic activity is primarily due to the parent compound oxycodone, only the parent compound was measured to assess the PK parameters.

2.2.3. What are the characteristics of drug absorption? Are Oxycodone HCl Tablets parameters dose proportional?

From the IR Roxicodone® package insert, it is known that oxycodone oral bioavailability ranges from 60% to 87% with different formulations. This high oral bioavailability (compared to other oral opioids) is due to lower pre-systemic and/or first-pass metabolism of oxycodone (Roxicodone® package insert).

Dose Proportionality:

For Oxycodone HCl Tablets dose proportionality was assessed in the study K234-10-1001 over the dose range of 5 mg to 15 mg under fasting conditions.

Treatments:

- Treatment A: Oxycodone HCl Tablet 5 mg (1 x 5 mg) under fasted conditions
- Treatment B: Oxycodone HCl Tablets 10 mg (2 x 5 mg) under fasted conditions
- Treatment C: Oxycodone HCl Tablets 15 mg (2 x 7.5 mg) under fasted conditions

The mean concentration-time profiles for 5, 10 and 15 mg of Oxycodone HCl Tablets are shown in the Figures 2.2.3a. The mean PK parameters by treatment are shown in the Table 2.2.3. The results of the dose proportionality assessment using linear regression are presented in the Figure 2.2.3b. The results using the linear regression show that mean AUC and Cmax are dose proportional between 5, 10 and 15 mg for Oxycodone HCl Tablets.

Further, dose proportionality for Oxycodone HCl Tablets was estimated using the power model, $Y = \alpha \cdot \text{Dose}^{\beta}$ where Y, α and β correspond to the PK parameter (AUC or Cmax), proportionality constant and an exponent, respectively. If the 90% CI for the exponent β contains 1, the relationship between dose and the PK parameters is considered to be dose proportional. The slope (90%CI) for ln Dose Vs. ln (AUC) or ln(Cmax) are as follows for

- Cmax: 1.08 (0.96 – 1.19)
- AUCinf : 1.09 (0.98 – 1.19)

Figure 2.2.3a.: Mean (\pm SD) of oxycodone plasma concentration-time profiles after single dose administration of 5, 10 and 15 mg of Oxycodone HCl Tablets under fasted conditions.

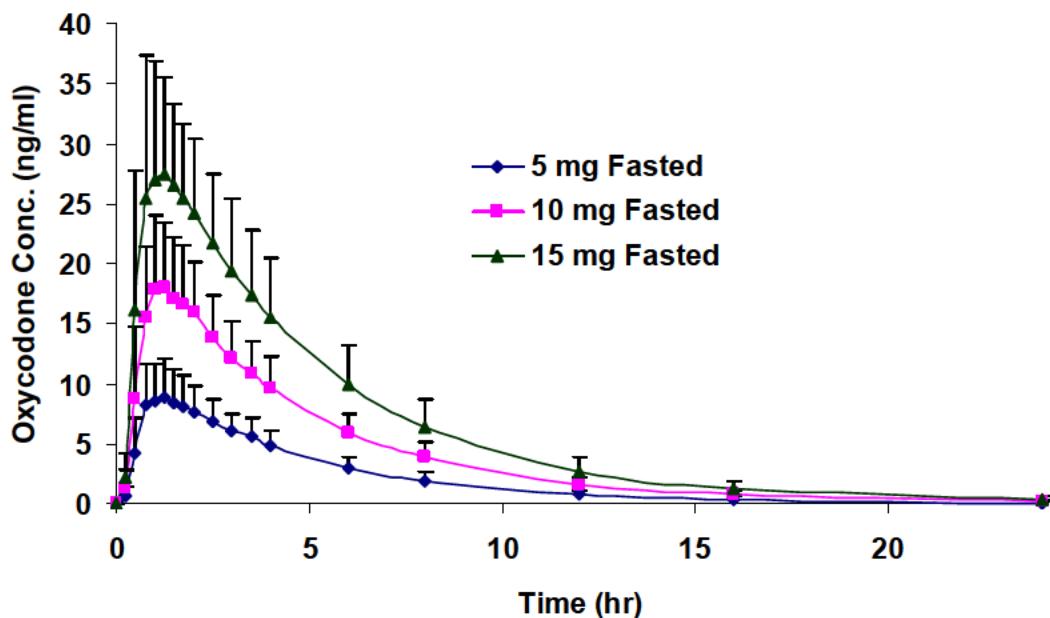
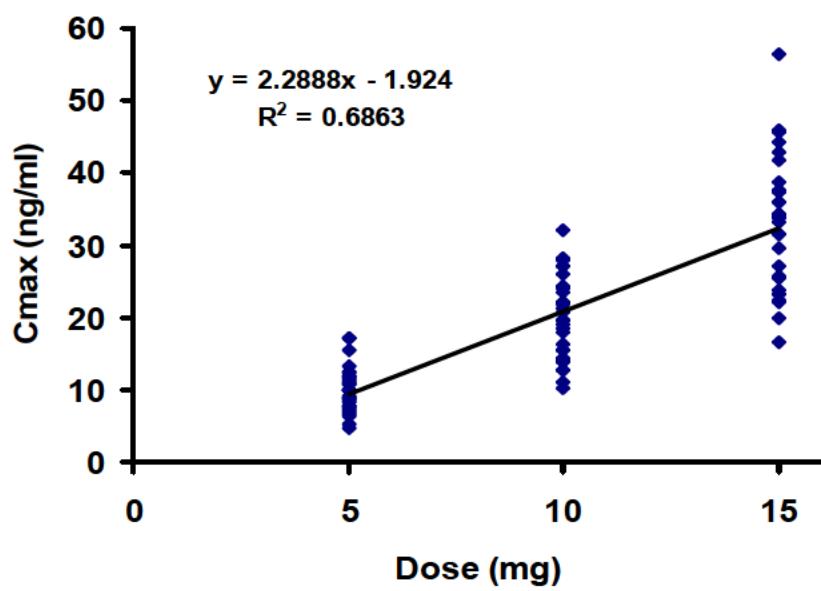
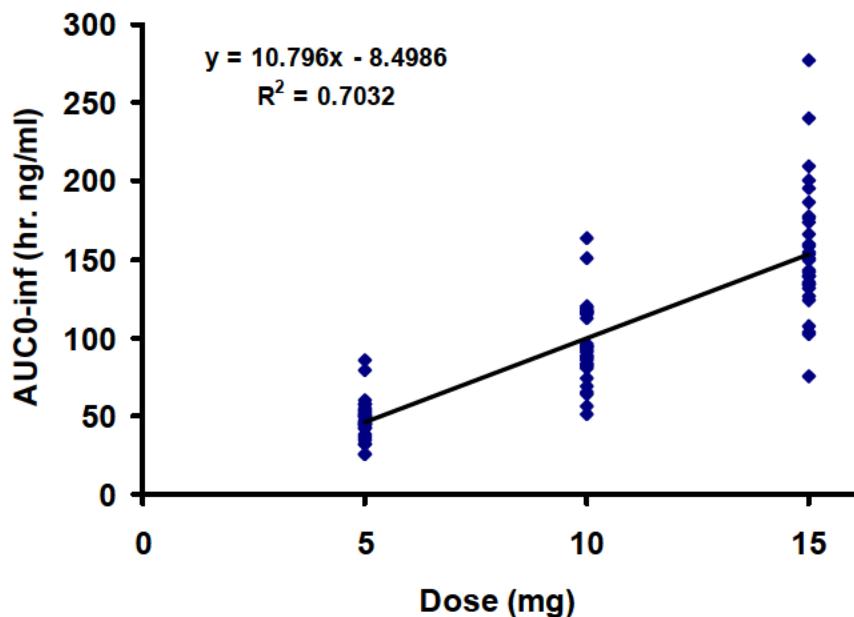


Table 2.2.3: Mean pharmacokinetic parameters of Oxycodone HCl Tablets 5, 10 and 15 mg under fasted conditions.

Parameter	Oxycodone HCl Tablet 1 x 5 mg Fasted (n=31)		Oxycodone HCl Tablets 2 x 5 mg Fasted (n=30)		Oxycodone HCl Tablets 2 x 7.5 mg Fasted (n=30)	
	Mean	SD	Mean	SD	Mean	SD
Tmax (h)	1.40	0.67	1.21	0.37	1.23	0.58
Cmax (ng/mL)	10.0	3.08	19.9	5.64	32.9	9.09
AUClast (h*ng/mL)	45.38	12.65	93.19	25.46	152.9	41.11
AUCinf (h*ng/mL)	47.40	13.07	95.50	25.64	155.4	41.57
T1/2 (h)	3.24	0.61	3.38	0.60	3.57	0.58
Tlast (h)	15.23	2.40	18.67	3.84	21.87	3.60
Clast (ng/mL)	0.431	0.107	0.478	0.184	0.495	0.241

Figure 2.2.3b: Dose proportionality assessment using linear regression for oxycodone AUC_{0-inf} and Cmax when administered as Oxycodone HCl Tablets.



2.3. Intrinsic Factors

2.3.1. What is the pediatric plan?

The Sponsor requested for a waiver of pediatric studies for the following age groups.

- a. Neonates (age < 1 month)
- b. Infants and toddlers (ages 1 month to < 2 years)
- c. Preschool children (ages 2 to < 6 years)
- d. School-age children (ages 6 to 17 years)

The primary reasons cited for waiving the pediatric assessments was that the Oxycodone HCl Tablets does not represent a meaningful therapeutic benefit over existing opioid therapies for pediatric patients. From the regulatory point of view, this NDA does not trigger PREA as it does not qualify for any of the following that required for PREA assessments:

- o New ingredient
- o New indication
- o New dosage form
- o New dosing regimen
- o New route of administration

2.4 Extrinsic Factors

There are recent articles related to drug-drug interactions with oxycodone were published subsequent to the approval of the reference Roxicodone® Tablets Product.

These articles are:

1. Kummer O et al. Effect of the inhibition of CYP3A4 or CYP2D6 on the pharmacokinetics and pharmacodynamics of oxycodone. Eur J Clin Pharmacol. 2011; 67:63-71.
2. Nieminen et al. Oxycodone concentrations are greatly increased by the concomitant use of ritonavir or lopinavir/ritonavir. Eur J Clin Pharmacol. 2010; 66:977-85.
3. Hagelberg NM et al. Voriconazole drastically increases exposure to oral oxycodone. Eur J Clin Pharmacol. 2009;65:263-271
4. Nieminen TH et al. Rifampin greatly reduces the plasma concentrations of intravenous and oral oxycodone. Anesthesiology. 2009; 110:1371-1378.

Since the findings from these studies are relevant to all oxycodone products, Agency has been incorporating these findings into oxycodone package inserts as appropriate. As such, package insert of this product will also be updated with these metabolism and drug-drug interaction data.

2.5. General Biopharmaceutics

2.5.1. Is the Oxycodone HCl Tablets bioequivalent to the reference immediate release oral tablet following single dose administration in fasting conditions?

The BE comparison between Oxycodone HCl Tablets and Roxicodone® Tablets (Reference-1) and Oxycodone HCl Tablets and Acurox® Tablets (N22451) (Reference - 2) was evaluated in the study AP-ADD-100. A total number of 36 healthy subjects under

fasting conditions completed the all three treatments. The final to-be-marketed formulation was used for Oxycodone HCl Tablets.

Treatments:

- Test : Oxycodone HCl Tablets - (2 x 7.5 mg) - Lot: 57219
- Reference 1 : Roxicodone® Tablets (1 x 15 mg) Lot: 956688A
- Reference 2 : Acurox® Tablets (2 x 7.5 mg/30 mg) - Lot: 55422

The three single dose treatments were administered with at least a 7-day washout period between doses. All the subjects were given three doses of naltrexone (at -12 hr, -30 min and +12 hr) to block the occurrence of unacceptable adverse effects associated with oxycodone.

Results:

From the Figure 2.5.1a it is evident that plasma concentration-time profiles of Oxycodone HCl Tablets overlap with Roxicodone® Tablets or Acurox® Tablets. The mean \pm SD of the PK parameters for oxycodone is presented in Table 2.5.1a. The means, ratios of geometric means and the 90% confidence intervals for the log-transformed PK parameters comparing Oxycodone HCl Tablets (Test) with Roxicodone® (Reference 1) and Oxycodone HCl Tablets (Test) with Acurox® Tablets (Reference 2) is presented in the Tables 2.5.1b and 2.5.1c, respectively. The assessment of BE between Oxycodone HCl Tablets and Roxicodone® Tablets and Oxycodone HCl Tablets and Acurox® Tablets is shown in the Figure 2.5.1b

Figure 2.5.1a: Mean oxycodone concentration-time profiles after administration of Oxycodone HCl Tablets, Acurox® and Roxicodone® Tablets under fasting conditions.

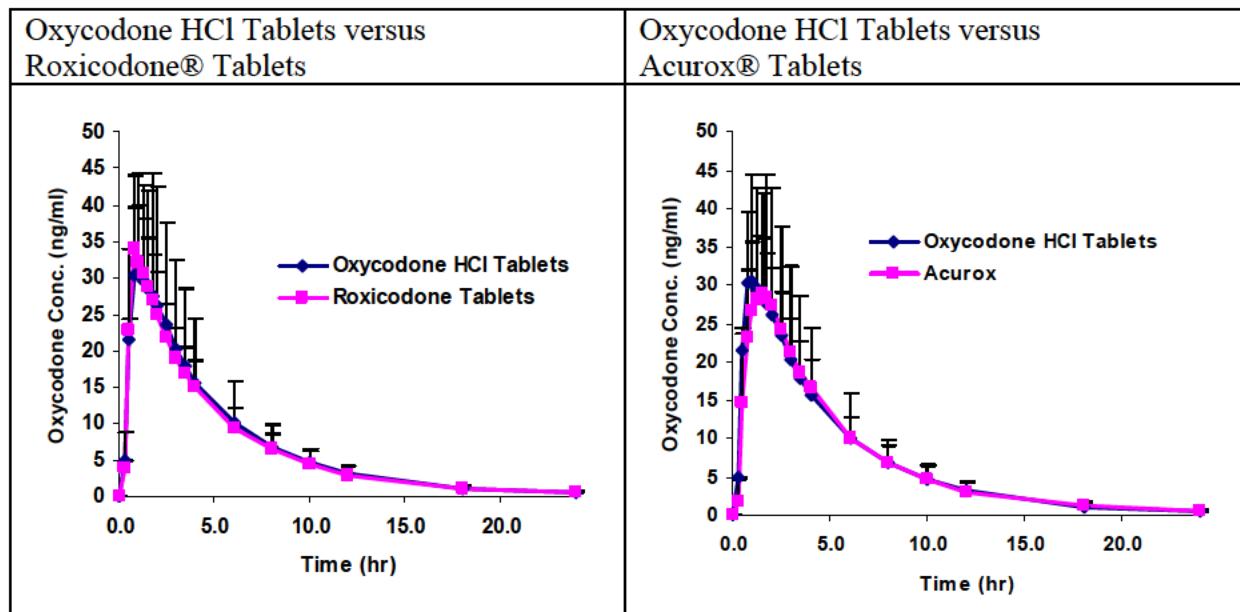


Table 2.5.1a.: Pharmacokinetic parameters of oxycodone after administration of Oxycodone HCl Tablets, Acurox® Tablets and Roxicodone® Tablets.

Parameter	Oxycodone HCl Tablets Mean ± SD	Acurox® Tablets Mean ± SD	Roxicodone® Tablets Mean ± SD
Cmax (ng/mL)	34.5 ± 7.83	32.2 ± 6.02	36.5 ± 8.78
AUClast (hr*ng/mL)	165.8± 36.5	163.8 ± 36.0	160.3 ± 40.9
AUCinf (hr*ng/mL)	168.9 ± 37.5	167.0 ± 37.2	163.4± 42.1
AUC _{Extrap} (%)	1.84 ± 0.85	1.89 ± 0.94	1.86 ± 0.90
T1/2 (hr)	3.94 ± 0.63	3.96 ± 0.73	3.99 ± 0.79
Tlast (hr)	22.5 ± 2.64	22.5 ± 3.00	22.50±3.00
Clast(ng/mL)	0.535± 0.247	0.543 ± 0.264	0.516± 0.248
Tmax (hr)	1.18 ± 0.57	1.46 ± 0.44	0.98 ±0.40

Table 2.5.1b.: The point estimates and the 90% confidence intervals of geometric means ratio for PK parameters comparing Oxycodone HCl Tablets (Test) with Roxicodone® Tablets (Reference 1)

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c	
	Oxycodone HCl Tablets (Test)	Roxicodone® Tablets (Ref)		Lower	Upper
Cmax	33.2	36.2	92.20	86.54	98.22
AUClast	162.0	156.2	103.77	99.64	108.06
AUCinf	165.0	159.1	103.78	99.66	108.08

Table 2.5.1c.: The point estimates and the 90% confidence intervals of geometric means ratio for PK parameters comparing Oxycodone HCl Tablets (Test) with Acurox® Tablets (Reference 2)

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c	
	Oxycodone HCl Tablets (Test)	Acurox® Tablets (Ref)		Lower	Upper
Cmax	33.2	31.6	105.16	97.71	113.17
AUClast	162.0	159.4	101.64	96.22	107.36
AUCinf	165.0	162.4	101.60	96.18	107.32

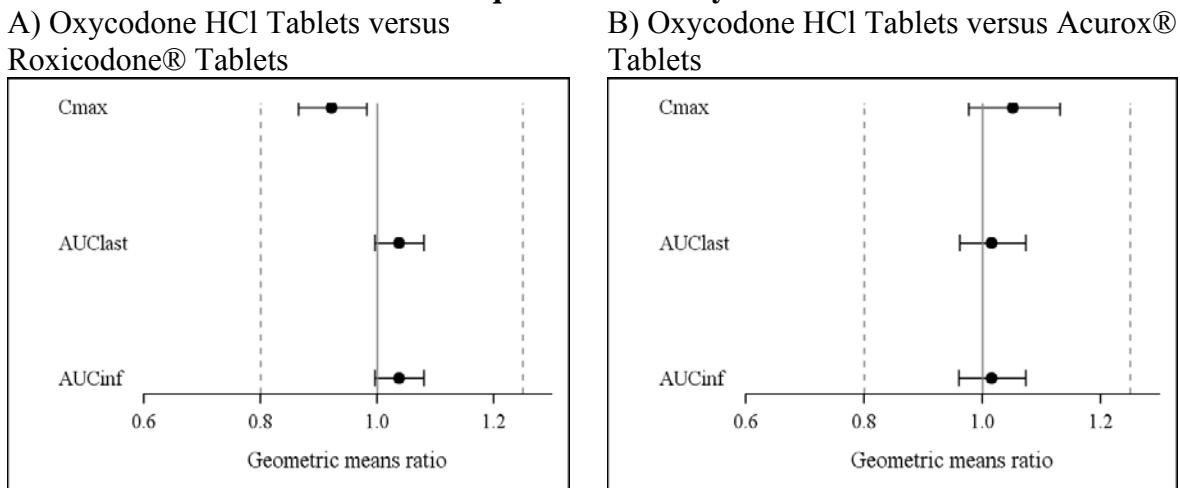
^a Geometric mean based on least squares mean of log-transformed parameter values

^b Ratio (%) = geometric mean ratio

^c 90% confidence interval

Figure 2.5.1b: The point estimates and the 90% confidence intervals of geometric means ratio for Cmax AUC_{last} and AUC_{inf} of A) Oxycodone HCl Tablets versus Roxicodone® 2) Oxycodone HCl Tablets versus Acurox® Tablets. Geometric means for the treatments were based on least squares means of log-transformed PK parameter values.

Bioequivalence Analysis



The BE analysis showed that the ratio of the geometric means for log transformed Cmax and AUC values as well as its corresponding confidence intervals fell within the range of 80% to 125%. It is concluded that the Oxycodone HCl Tablets is bioequivalent to both Roxicodone® IR Tablets and Acurox® Tablets under fasting conditions.

2.5.2 What is the effect of food on the BA of G-ER?

For Oxycodone HCl Tablets food effect was evaluated as part of the study K234-10-1001, which evaluated the dose proportionality of Oxycodone HCl Tablets.

Treatments:

- Oxycodone HCl Tablets (2 x 7.5 mg) under fasted conditions
- Oxycodone HCl Tablets (2 x 7.5 mg) under fed conditions
- Roxicodone® Tablets (1 x 15 mg) under fed conditions

The treatments were administered with at least a 7-day washout period between doses. All the subjects were given two doses of naltrexone (at -12 hr, +1 hr) to block the occurrence of opioid effects associated with oxycodone.

Results:

The Figure 2.5.2a shows the plasma concentration-time profiles of Oxycodone HCl Tablets under fasted and fed conditions. The Figure 2.5.2b shows the plasma concentration-time profiles for Oxycodone HCl Tablets and Roxicodone® Tablets under fed conditions. The PK parameters for oxycodone are presented in Table 2.5.2a.

Figure 2.5.2: Oxycodone plasma concentration time profiles after administration of Oxycodone HCl Tablets (2x 7.5 mg) under fasting and fed conditions and Roxicodone® Tablets (1x 15 mg) under fed conditions.

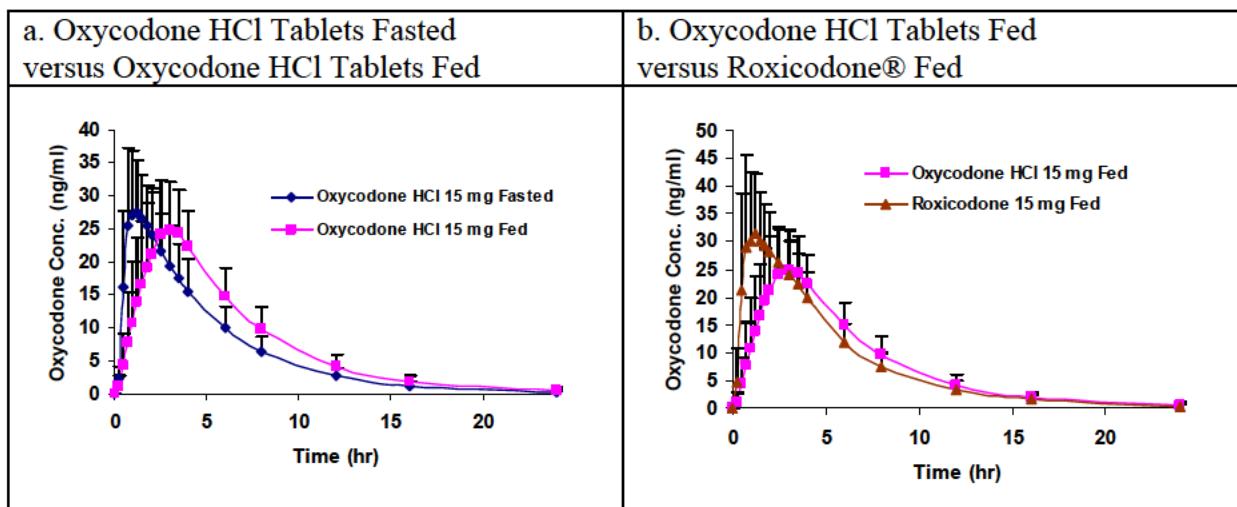


Table 2.5.2a.: Pharmacokinetic parameters of oxycodone after administration of Oxycodone HCl Tablets (2x 7.5 mg) under fasting and fed conditions and Roxicodone® Tablets (1x 15 mg) under fed conditions.

Parameter	Oxycodone HCl Tablets Fasted Mean ± SD	Oxycodone HCl Tablets Fed Mean ± SD	Roxicodone® Fed Mean ± SD
Tmax (hr)	1.23 ± 0.58	3.04 ± 1.14	1.33 ± 0.89
Cmax (hr)	32.9 ± 9.09	28.5 ± 7.37	37.7 ± 11.3
AUClast (hr*ng/mL)	152.9 ± 41.1	178.8 ± 44.6	186.3 ± 50.1
AUCinf (hr*ng/mL)	155.4 ± 41.6	184.1 ± 45.0	189.2 ± 51.2
T1/2 (hr)	3.57 ± 0.63	3.71 ± 0.73	3.74 ± 0.79

Administration of Oxycodone HCl Tablets with food resulted in a 21% increase in AUCinf, a 14% decrease in Cmax, and an approximately 1.75-hour delay in oxycodone Tmax (3.00 hours vs 1.25 hours) compared to under fasted conditions. The food effect, observed for Oxycodone HCl Tablets formulation was similar to that observed with the previously submitted Acurox® Tablet formulation. For Acurox® formulation, food increases AUC and Cmax by 19%, and 5%, respectively and delays Tmax from 1.3 hours when fasting to 2.9 hours with food.

Food effect study in the Roxicodone® package insert also shows a similar effect, in which, food increases the oxycodone oral solution's AUC by 27%, decreases Cmax by 7% and delays Tmax from 1.25 h to 2.54 h. For Roxicodone® Tablets, no dose adjustments with food were warranted (Roxicodone® package insert).

Under fed conditions (in this study), in comparison to Roxicodone® Tablets, Oxycodone HCl Tablets showed similar AUC and 17% decrease in Cmax and a delayed Tmax (3 hours versus 1.3 hours).

Reviewers Comments: Over all, the observed food effect for Oxycodone HCl Tablets does not warrant any dosing adjustments for Oxycodone HCl Tablets. The following labeling comments for the food effect are proposed by this reviewer. Deletion is shown by **Strike-through text** and addition is shown by **underline text**.

(b) (4)

2.6.Analytical Section

2.6.1 Are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? What is the QC sample plan? What are the accuracy, precision and selectivity of the method?

Plasma samples were analyzed for oxycodone using a liquid chromatography with tandem mass spectrometry (LC-MS-MS) procedure developed by (b) (4)

The assay development validation in terms of specificity, precision accuracy short-and long term stability is summarized in the Clin Pharm Review (DARRTS dated 06/01/2009) for the previous Acurox® submission.

In brief, human plasma samples containing ethylenediaminetetraacetic acid (EDTA) were analyzed for oxycodone and the internal standard (oxycodone D6) following extraction with an organic solvent. The organic layer was removed, evaporated, reconstituted, and injected onto a SCIEX PI 3000 LC-MS-MS in positive ion multiple-reaction-monitoring (MRM) mode equipped with a high performance liquid chromatography (HPLC) column. The peak area of the m/z 316→298 oxycodone product ion was measured against the peak area of the m/z 322→304 product ion of the internal standard.

The range of calibrators and QCs used for studies were:

- Calibrators: 0.25, 0.5, 1.25, 5.0, 12.5, 25, 45, and 50 ng/mL
- Quality controls: 0.75, 10.0, 18.8 and 37.5 ng/ml

The intraday and interlay accuracy and precision for QCs that were run with the samples were within the acceptable range of $100 \pm 15\%$.

4.2.2 Study Synopses

Study AP-ADD-100

Important Note – Name Changes

During the conduct of this study, the name Acurox® (oxycodone HCl/niacin) Tablets was changed to Acurox® with Niacin (oxycodone HCl/niacin) Tablets (05/05/2010) and is referred to by its former name in the protocol and title and by its new name in this study report.

During the conduct of this study, [REDACTED] (oxycodone HCl) Tablets was changed to Acurox® (oxycodone HCl) Tablets (05/05/2010) and is referred to by its former name in the protocol and title and by its new name in this study report.

Name of Sponsor/Company: Acura Pharmaceutical Technologies, Inc.	Individual Study Table Referring to Part of the Dossier: Volume: Page:	(For National Authority Use Only)		
Name of Finished Product: Acurox® (oxycodone HCl, USP) Tablets				
Name of Active Ingredient: Oxycodone hydrochloride				
Title of Study: "A Single-Dose, 3-Period, 3-Treatment, 3-Way Crossover Pharmacokinetic Comparison between Acurox® 2 x 7.5 mg/30 mg tablets and [REDACTED] (b)(4) 2 x 7.5 mg/0 mg tablets, both from Acura Pharmaceutical Technologies, Inc., and Roxicodone® (1 x 15 mg tablet) from Xanodyne Pharmaceuticals, Inc. under Fasting Conditions"				
Investigators: Mark T. Leibowitz, M.D.; Cynthia A. Zamora, M.D.; Majin Miguel Castillo, M.D., MBA; Steven Hinitt, M.D., MPH, MPA; Nancy K. Hinitt, M.D.; Joe H. Juren, M.D.; Mary C. Clarke, MSN, FNP-BC				
Study Center(s): CEDRA Clinical Research, LLC, 2455 N.E. Loop 410, Suite 150, San Antonio, Texas 78217				
Number of Subjects: Enrolled: 40 Completed: 37	Planned: 40	Analyzed: 36		
Publication (reference): None				
Study Period (days): 15 days	Phase of Development: 1			
Objectives: <ol style="list-style-type: none">1. To compare the pharmacokinetic characteristics of oxycodone in Acurox® Tablets (Test Product) with Acurox® with Niacin Tablets (Reference Product 1) and Roxicodone® tablets (Reference Product 2).2. To evaluate the bioequivalence of the test and reference products with regard to oxycodone exposure: Bioequivalence would be established if the 90% confidence intervals for $\ln(C_{max})$, $\ln(AUC_{last})$, and $\ln(AUC_{inf})$ were within the accepted 80% to 125% limits.				
Study Design (Methodology): This was a single-dose, open-label, randomized, three-period, three-treatment, crossover study. Forty (40) healthy subjects who successfully completed the screening process were enrolled in the study and checked into the research center the night before first dose of study medication. Subjects who continued to meet inclusion/exclusion criteria the morning of dosing were randomly assigned to a treatment sequence to receive three separate single-dose administrations of study medication, one treatment per period, according to the randomization schedule. Dosing days were separated by a washout period of at least 7 days.				
Diagnosis and Main Criteria for Inclusion: Healthy male or female subjects 18-55 years of age				
Test Product, Dose and Mode of Administration, Lot Number: Acurox® (oxycodone HCl, USP) Tablets (2 x 7.5 mg) for oral administration - Lot: 57219				
Reference Product, Dose and Mode of Administration, Lot Number: Acurox® with Niacin (oxycodone HCl, USP/niacin, USP) Tablets (2 x 7.5 mg/30 mg) for oral administration - Lot: 55422				

Reference Product, Dose and Mode of Administration, Lot Number: Roxicodone® (oxycodone hydrochloride, USP), Tablets (1 x 15 mg) for oral administration - Lot: 956688A

Duration of Treatment: Three single-dose treatments were administered with at least a 7-day washout period between doses.

Criteria for Evaluation:

Efficacy: Efficacy was not evaluated in this study.

Safety: Safety was evaluated based on the following parameters: physical examinations, vital signs, clinical laboratory evaluations, ECGs, and reported or observed adverse events.

Statistical Methods:

Data were analyzed by noncompartmental methods in WinNonlin. Concentration-time data that were below the limit of quantification (BLQ) were treated as zero (0.00 ng/mL) in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as "missing". Full precision concentration data (not rounded to three significant figures) and actual sample times were used for all pharmacokinetic and statistical analyses.

The following pharmacokinetic parameters were calculated: peak concentration in plasma (C_{max}), time to peak concentration (T_{max}), elimination rate constant (λ_z), terminal half-life ($T_{1/2}$), area under the concentration-time curve from time-zero to the time of the last quantifiable concentration (AUC_{last}), and area under the plasma concentration time curve from time-zero extrapolated to infinity (AUC_{inf}).

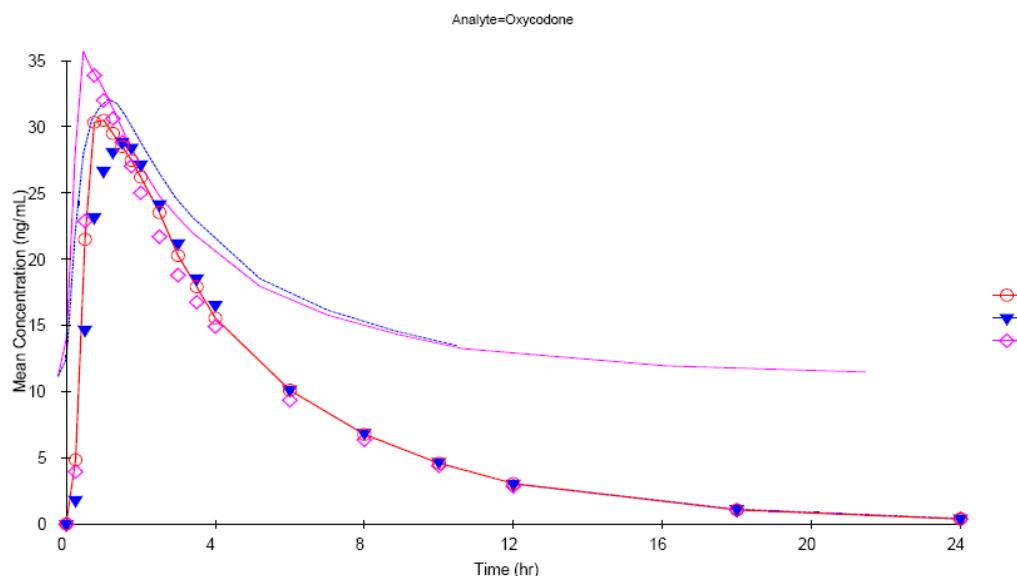
Analysis of variance (ANOVA) and the Schuirmann's two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C_{max} , AUC_{last} , and AUC_{inf} . The 90% confidence interval for the ratio of the geometric means (Test/Reference) was calculated. Bioequivalence was declared if the lower and upper confidence intervals of the log-transformed parameters were within 80% to 125%.

SUMMARY – CONCLUSIONS

Pharmacokinetic Results:

Thirty-seven (37) of the 40 subjects completed the study; however, data from 36 subjects were used for the pharmacokinetic and statistical analyses. One subject of the 37 was excluded from the data analysis data set due to vomiting 2 hours and 1 minute after dosing with Acurox® in Period 3. Mean concentration-time data are shown in [Figure 1](#). Results of the pharmacokinetic and statistical analyses are shown in [Tables 1 through 3](#).

Figure 1. Mean Oxycodone Concentration-Time Profiles after Administration of Acurox® Tablets (Treatment A), Acurox® with Niacin Tablets (Treatment B), and Roxicodone (Treatment C)



Source data: [Tables 14.2.1 - 14.2.3](#)

Synopsis Table 1. Pharmacokinetic Parameters of Oxycodone

Parameter	Acurox®				Acurox® with Niacin				Roxicodone®			
	n	Mean	SD	CV%	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (hr)	36	1.18	0.57	48.62	36	1.46	0.44	29.91	36	0.98	0.40	40.61
C _{max} (ng/mL)	36	34.5	7.83	22.67	36	32.2	6.02	18.71	36	36.5	8.78	24.05
AUC _{last} (hr*ng/mL)	36	165.8	36.46	21.99	36	163.8	36.02	21.99	36	160.3	40.85	25.49
AUC _{inf} (hr*ng/mL)	36	168.9	37.53	22.22	36	167.0	37.23	22.29	36	163.4	42.08	25.76
AUC _{Extrap} (%)	36	1.84	0.85	46.37	36	1.89	0.94	49.83	36	1.86	0.90	48.71
λ _z (hr ⁻¹)	36	0.1806	0.0298	16.51	36	0.1811	0.0361	19.95	36	0.1813	0.0426	23.50
T _{1/2} (hr)	36	3.94	0.63	16.10	36	3.96	0.73	18.38	36	3.99	0.79	19.73
T _{last} (hr)	36	22.50	2.64	11.71	36	22.50	3.00	13.33	36	22.50	3.00	13.33
C _{last} (ng/mL)	36	0.535	0.247	46.19	36	0.543	0.264	48.54	36	0.516	0.248	47.96

Note: Full precision data used in pharmacokinetic analysis

Source data: [Tables 14.2.4 - 14.2.6](#)

Synopsis Table 2. Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Oxycodone Comparing Acurox® (Test) with Acurox® with Niacin (Ref)

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		ANOVA Power	CV%
	Test	Ref		Lower	Upper		
C _{max}	33.2	31.6	105.16	97.71	113.17	0.999	17.60
AUC _{last}	162.0	159.4	101.64	96.22	107.36	1.000	13.08
AUC _{inf}	165.0	162.4	101.60	96.18	107.32	1.000	13.08

^a Geometric mean for Acurox® and Acurox® with Niacin based on least squares mean of log-transformed parameter values

^b Ratio (%) = geometric mean (Acurox®)/geometric mean (Acurox® with Niacin)

^c 90% confidence interval

Source data: [Listings 16.4.3.1 - 16.4.3.2](#)

Synopsis Table 3. Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Oxycodone Comparing Acurox® (Test) with Roxicodone® (Ref)

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		ANOVA	
	Test	Ref		Lower	Upper	Power	CV%
C _{max}	33.4	36.2	92.20	86.54	98.22	1.000	15.14
AUC _{last}	162.0	156.2	103.77	99.64	108.06	1.000	9.67
AUC _{inf}	165.1	159.1	103.78	99.66	108.08	1.000	9.67

^a Geometric mean for Acurox® and Roxicodone® based on least squares mean of log-transformed parameter values

^b Ratio (%) = geometric mean (Acurox®)/geometric mean (Roxicodone®)

^c 90% confidence interval

Source data: [Listing 16.4.3.3 - 16.4.3.4](#)

The 90% confidence interval for comparing the maximum exposure to oxycodone, based on ln(C_{max}), is within the accepted 80% to 125% limits for both Acurox® Tablets vs. Acurox® with Niacin Tablets and Acurox® Tablets vs. Roxicodone®. The 90% confidence intervals for comparing total systemic exposure to oxycodone, based on ln(AUC_{last}) and ln(AUC_{inf}), are within the accepted 80% to 125% limits for both Acurox® Tablets vs. Acurox® with Niacin Tablets and Acurox® Tablets vs. Roxicodone®.

SAFETY RESULTS:

This study in healthy volunteers included a naltrexone HCl block to minimize the occurrence of unacceptable adverse effects associated with oxycodone. A total of 34 treatment-emergent AEs were reported by 19 of the 40 subjects over the course of the study. Twenty-seven of the 34 treatment-emergent AEs were mild and 7 were moderate in intensity. Nineteen of the 34 treatment-emergent AEs were considered probably related to the study treatment and 11 were considered possibly related to the study treatment; the remaining 4 treatment-emergent AEs were unrelated to study treatment.

The most commonly reported treatment-emergent AEs were flushing (n=9 [24%]; all following Acurox® with Niacin and nausea (n=6; 3 following Acurox®, 1 following Acurox® with Niacin, and 2 following Roxicodone®). In total, 12 AEs were reported following Acurox®, 13 AEs were reported following Acurox® with Niacin, and 9 AEs following Roxicodone®.

An abnormal laboratory result at the end-of-study evaluation indicated moderate neutropenia in one subject with a history of chronic leukopenia. The neutropenia was determined to be unrelated to the study treatment. The subject returned to the site for repeat clinical laboratory evaluations and was followed up until test results were determined to be non-clinically significant by the Investigator. The subject was referred to his primary physician for further follow up.

There were no severe or serious treatment-emergent AEs and no safety concerns arose during the study. No clinically significant abnormalities in ECGs, vital signs, or physical exams were observed.

CONCLUSION:

Acurox® Tablets are bioequivalent to Acurox® with Niacin Tablets and Roxicodone® under fasted conditions.

Date of Report: 26 August 2010

Study K234-10-1001:

Name of Company: King Pharmaceuticals Research and Development, Inc. 4000 CentreGreen Way, Suite 300 Cary, NC 27513	Individual Study Table Referring to Part of the Dossier Volume:	(For National Authority <i>Use only</i>)										
Name of Finished Product: Acurox® (oxycodone HCl, USP) Tablets	Page:											
Name of Active Ingredient: Oxycodone hydrochloride												
Title of Study: Open-Label, Single-Dose, Randomized, 5-Period, 5-Way Crossover Study to Evaluate the Dose Proportionality and the Effects of Food on the Bioavailability of Acurox® Tablets in Healthy Volunteers												
Investigators: Cynthia A. Zamora, M.D.; Mark T. Leibowitz, M.D.; Steven Hinitt, M.D., MPH, MPA; Nancy K. Hinitt, M.D.; Joe H. Juren, M.D.; Mary C. Clarke, MSN, FNP-BC; and Michael R. Natalino, M.D., P.A.												
Study Center: Worldwide Clinical Trials Drug Development Solutions, 2455 NE Loop 410, Suite 150, San Antonio, Texas 78217												
Publication (reference): None												
Studied Period: 14 July 2010 through 20 September 2010	Phase of Development: 1											
Objectives: The primary objective of this study was: <ul style="list-style-type: none">• To determine the pharmacokinetic dose proportionality of oxycodone in Acurox® Tablets in healthy volunteers under fasted conditions The secondary objectives of this study were: <ul style="list-style-type: none">• To determine the effects of food on the bioavailability of oxycodone in Acurox® Tablets in healthy volunteers• To evaluate the effects of food on the bioavailability of oxycodone in Acurox® Tablets compared with oxycodone in Roxicodone® Tablets in healthy volunteers• To evaluate the single-dose safety of different doses of Acurox® Tablets following administration to healthy volunteers administered a naltrexone block												
Methodology: This was an open-label, single-dose, randomized, 5-period, 5-way crossover study. Thirty-five (35) healthy subjects, who successfully completed the screening process were enrolled in the study. Subjects completed a Screening Phase, a Treatment Phase consisting of 5 Dosing Periods, and an End-of-Study Phase. The Screening Phase was conducted on an outpatient basis within 30 days prior to the start of the Treatment Phase. During the Treatment Phase, Subjects were to receive the following 5 treatments in random order: <table><tr><td>Treatment A:</td><td>One (1) Acurox® Tablet containing 5 mg oxycodone HCl under fasted conditions</td></tr><tr><td>Treatment B:</td><td>Two (2) Acurox® Tablets each containing 5 mg oxycodone HCl under fasted conditions</td></tr><tr><td>Treatment C:</td><td>Two (2) Acurox® Tablets each containing 7.5 mg oxycodone HCl under fasted conditions</td></tr><tr><td>Treatment D:</td><td>Two (2) Acurox® Tablets each containing 7.5 mg oxycodone HCl under fed conditions immediately following ingestion of a standard high-fat breakfast</td></tr><tr><td>Treatment E:</td><td>One (1) Roxicodone® Tablet containing 15 mg oxycodone HCl under fed conditions immediately following ingestion of a standard high-fat breakfast</td></tr></table>			Treatment A:	One (1) Acurox® Tablet containing 5 mg oxycodone HCl under fasted conditions	Treatment B:	Two (2) Acurox® Tablets each containing 5 mg oxycodone HCl under fasted conditions	Treatment C:	Two (2) Acurox® Tablets each containing 7.5 mg oxycodone HCl under fasted conditions	Treatment D:	Two (2) Acurox® Tablets each containing 7.5 mg oxycodone HCl under fed conditions immediately following ingestion of a standard high-fat breakfast	Treatment E:	One (1) Roxicodone® Tablet containing 15 mg oxycodone HCl under fed conditions immediately following ingestion of a standard high-fat breakfast
Treatment A:	One (1) Acurox® Tablet containing 5 mg oxycodone HCl under fasted conditions											
Treatment B:	Two (2) Acurox® Tablets each containing 5 mg oxycodone HCl under fasted conditions											
Treatment C:	Two (2) Acurox® Tablets each containing 7.5 mg oxycodone HCl under fasted conditions											
Treatment D:	Two (2) Acurox® Tablets each containing 7.5 mg oxycodone HCl under fed conditions immediately following ingestion of a standard high-fat breakfast											
Treatment E:	One (1) Roxicodone® Tablet containing 15 mg oxycodone HCl under fed conditions immediately following ingestion of a standard high-fat breakfast											

For each Dosing Period, subjects were admitted to the clinical research unit (CRU) on the evening before dosing (Day -1). Venous blood samples were collected at specified times pre- and post-dose on an inpatient basis on Study Days 1-2 during each Dosing Period. Likewise, vital signs, adverse event (AE) assessments, clinical laboratory assessments, and pulse oximetry readings were performed at specified times during each Dosing Period. Subjects were discharged from the CRU after collection of the 24-hour post-dose plasma sample on Day 2 of each Dosing Period provided that all available clinical assessments were complete and acceptable to the Investigator. Subjects were to return to the CRU for subsequent Dosing Periods after a washout period of at least 7 days.

A final safety assessment was to be performed at the end of Dosing Period V (24 hours after the last dose), representing the end of the study.

Number of Subjects (Planned and Analyzed): Up to 40 planned in order to complete 26; 35 enrolled; 33 analyzed

Diagnosis and Main Criteria for Inclusion: Healthy male or female subjects 18-55 years of age

Test Products, Dose and Mode of Administration, Batch Number:

- Acurox® (oxycodone HCl, USP) Tablets
(1 x 5 mg) for oral administration; fasted - Lot: 57218
- Acurox® (oxycodone HCl, USP) Tablets
(2 x 5 mg) for oral administration; fasted - Lot: 57218
- Acurox® (oxycodone HCl, USP) Tablets
(2 x 7.5 mg) for oral administration; fasted - Lot: 57219
- Acurox® (oxycodone HCl, USP) Tablets
(2 x 7.5 mg) for oral administration; fed - Lot: 57219

Duration of Treatment: Five single-dose treatments were administered with at least a 7-day washout period between doses.

Reference Therapy, Dose and Mode of Administration, Batch Number: Roxicodone® (oxycodone hydrochloride, USP), Tablets (1 x 15 mg) for oral administration; fed - Lot: 956688A

Criteria for Evaluation:

Efficacy: Efficacy was not evaluated in this study.

Pharmacokinetics: The Pharmacokinetic Population was defined as all subjects who had at least 1 pharmacokinetic sample taken following administration of study drug. The following pharmacokinetic parameters were calculated: peak concentration in plasma (C_{max}), time to peak concentration (T_{max}), elimination rate constant (λ_z), terminal half-life ($T_{1/2}$), area under the concentration-time curve from time-zero to the time of the last quantifiable concentration (AUC_{last}), and area under the plasma concentration time curve from time-zero extrapolated to infinity (AUC_{inf}).

Safety: The following safety endpoints were evaluated in this study:

- Incidence, intensity, and seriousness of AEs
- Changes in 12-lead electrocardiograms (ECG)
- Changes in vital signs (blood pressure, heart rate, and respiratory rate)
- Oxygen saturation of hemoglobin (SpO_2) measured by pulse oximetry
- Changes in clinical chemistry, hematology, and urinalysis values

Statistical Methods:

Efficacy: Not applicable

Pharmacokinetics: Concentration-time data were analyzed by noncompartmental methods in WinNonlin.

The following pharmacokinetic parameters were calculated: C_{max} , T_{max} , λ_z , $T_{1/2}$, AUC_{last} , and AUC_{inf} .

The dose proportionality (i.e. proportionality of a change in systemic exposure with a change in dose) of oxycodone in Aurox® Tablets under fasting conditions was assessed using (1) a confidence interval (CI) approach, (2) linear regression, and (3) a power model. For the CI approach and linear regression analysis, the C_{max} , AUC_{last} , and AUC_{inf} values for individual subjects were normalized (i.e., dose-adjusted) to the 5 mg dose (Treatment A), by dividing the parameter values by 2 for Treatment B and by 3 for Treatment C, prior to performing comparisons.

The effect of food on the pharmacokinetic profile of oxycodone in Aurox® Tablets was assessed using the ln-transformed pharmacokinetic exposure parameters of oxycodone (C_{max} , AUC_{last} , and AUC_{inf}) following administration of 2 x 7.5 mg tablets under fed and fasted conditions. The 90% CIs about the ratios of the geometric means were calculated.

The bioavailability of oxycodone in Aurox® (2 x 7.5 mg tablets) relative to that in Roxicodone® (1 x 15 mg tablet) was assessed under fed conditions using the ln-transformed pharmacokinetic exposure parameters of oxycodone (C_{max} , AUC_{last} , and AUC_{inf}). The 90% CIs about the ratios of the geometric means were calculated.

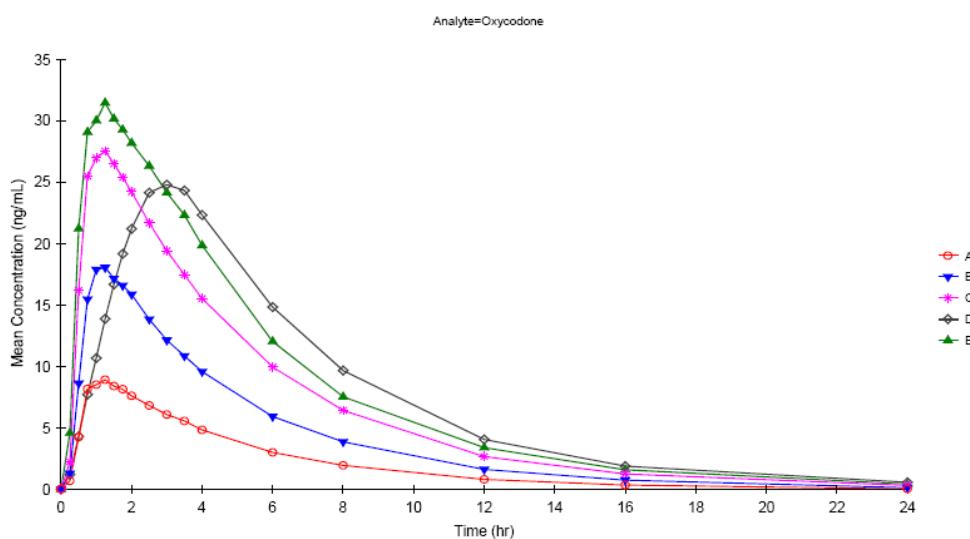
Safety: All summaries and analyses of safety data were conducted on the Safety Population defined as subjects who received at least one dose of study drug. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA® Version 13.0) preferred terms and summarized by treatment. Descriptive summaries of treatment-emergent clinically significant abnormalities in ECG, vital signs, pulse oximetry, and clinical laboratory data were provided.

SUMMARY OF RESULTS

Efficacy: Not applicable

Pharmacokinetics: Mean concentration-time data are shown in Synopsis Figure 1. Results of the pharmacokinetic and statistical analyses are shown in [Synopsis Table 1](#) (pharmacokinetic parameters), [Synopsis Table 2](#) (dose proportionality), [Synopsis Table 3](#) (dose proportionality), [Synopsis Table 4](#) (Food Effect), and [Synopsis Table 5](#) (Relative Bioavailability).

Synopsis Figure 1. Mean Oxycodone Concentration-Time Profiles after Administration of Acurox® 1 x 5 mg Fasted (A), Acurox® 2 x 5 mg Fasted (B), Acurox® 2 x 7.5 mg Fasted (C), Acurox® 2 x 7.5 mg Fed (D), and Roxicodone® 1 x 15 mg Fed (E)



Source data: [Tables 14.2.1](#) through [14.2.5](#)

Synopsis Table 1. Pharmacokinetic Parameters of Oxycodone by Treatment

Parameter	TREATMENT A Acurox® 1 x 5 mg Fasted				TREATMENT B Acurox® 2 x 5 mg Fasted			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (h)	31	1.40	0.67	47.98	30	1.21	0.37	30.80
C _{max} (ng/mL)	31	10.0	3.08	30.81	30	19.9	5.64	28.25
AUC _{last} (h*ng/mL)	31	45.38	12.65	27.88	30	93.19	25.46	27.32
AUC _{inf} (h*ng/mL)	31	47.40	13.07	27.57	30	95.50	25.64	26.85
AUC _{Extrap} (%)	31	4.36	1.19	27.39	30	2.53	1.09	42.99
T _{1/2} (h)	31	3.24	0.61	18.94	30	3.38	0.60	17.74

Parameter	TREATMENT C Acurox® 2 x 7.5 mg Fasted				TREATMENT D Acurox® 2 x 7.5 mg Fed			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (h)	30	1.23	0.58	47.74	29	3.04	1.14	37.33
C _{max} (ng/mL)	30	32.9	9.09	27.61	29	28.5	7.37	25.85
AUC _{last} (h*ng/mL)	30	152.9	41.11	26.88	29	178.8	44.58	24.94
AUC _{inf} (h*ng/mL)	30	155.4	41.57	26.75	28	184.1	45.02	24.45
T _{1/2} (h)	30	3.57	0.58	16.27	28	3.71	0.55	14.75

Parameter	TREATMENT E Roxicodone® 1 x 15 mg Fed			
	n	Mean	SD	CV%
T _{max} (h)	30	1.33	0.89	67.42
C _{max} (ng/mL)	30	37.7	11.3	29.90
AUC _{last} (h*ng/mL)	30	186.3	50.13	26.91
AUC _{inf} (h*ng/mL)	30	189.2	51.23	27.07
T _{1/2} (h)	30	3.74	0.59	15.90

Note: Full precision data used in pharmacokinetic analysis

Source data: [Tables 14.2.6 through 14.2.10](#)

Synopsis Table 2. Statistical Analysis of the Dose-Normalized, Natural Log-Transformed Systemic Exposure Parameters of Oxycodone Comparing Acurox® 2 x 5 mg Fasted (Test) with Acurox® 1 x 5 mg Fasted (Reference)

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
C _{max}	10.1263	10.2645	98.65	92.74	104.95	0.9999	13.02
AUC _{last}	47.8522	47.0572	101.69	96.80	106.83	1.0000	10.36
AUC _{inf}	49.0234	49.0616	99.92	95.10	104.99	1.0000	10.41

Note: Pharmacokinetic parameters (C_{max}, AUC_{last}, and AUC_{inf}) for Acurox® 2 x 5 mg were dose-normalized to the 5 mg dose of Acurox® (1 x 5 mg) by dividing the parameter values by 2 prior to performing comparisons.

^a Geometric Mean for Acurox® 2 x 5 mg Fasted (Test) and Acurox® 1 x 5 mg Fasted (Ref) based on Least Squares Mean of log-transformed parameter values

^b Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

^c 90% Confidence Interval

Source data: [Appendices 16.4.20 and 16.4.21](#)

Synopsis Table 3. Statistical Analysis of the Dose-Normalized, Natural Log-Transformed Systemic Exposure Parameters of Oxycodone Comparing Acurox® 2 x 7.5 mg Fasted (Test) with Acurox® 1 x 5 mg Fasted (Reference)

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
C _{max}	10.9429	10.0949	108.40	101.49	115.78	0.9998	14.42
AUC _{last}	50.5041	45.5402	110.90	105.47	116.61	1.0000	10.97
AUC _{inf}	51.3901	47.5657	108.04	102.77	113.58	1.0000	10.92

Note: Pharmacokinetic parameters (C_{max}, AUC_{last}, and AUC_{inf}) for Acurox® 2 x 7.5 mg were dose-normalized to the 5 mg dose of Acurox® (1 x 5 mg) by dividing the parameter values by 3 prior to performing comparisons.

^a Geometric Mean for Acurox® 2 x 7.5 mg Fasted (Test) and Acurox® 1 x 5 mg Fasted (Ref) based on Least Squares Mean of log-transformed parameter values

^b Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

^c 90% Confidence Interval

Source data: [Appendices 16.4.22 and 16.4.23](#)

Synopsis Table 4. Statistical Analysis of the Natural Log-Transformed Systemic Exposure Parameters Comparing Acurox® 2 x 7.5 mg Fed (Test) with Acurox® 2 x 7.5 mg Fasted (Reference)

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
C _{max}	28.7442	33.3062	86.30	79.34	93.88	0.9952	16.71
AUC _{last}	181.1176	149.6582	121.02	113.41	129.14	0.9998	12.86
AUC _{inf}	184.3175	151.9725	121.28	113.72	129.35	0.9998	12.75

^a Geometric Mean for Acurox® 2 x 7.5 mg Fed (Test) and Acurox® 2 x 7.5 mg Fasted (Ref) based on Least Squares Mean of log-transformed parameter values

^b Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

^c 90% Confidence Interval

Source data: [Appendices 16.4.24 and 16.4.25](#)

Synopsis Table 5. Statistical Analysis of the Natural Log-Transformed Systemic Exposure Parameters Comparing Acurox® 2 x 7.5 mg Fed (Test) with Roxicodone® 1 x 15 mg Fed (Reference)

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b (Test/Ref)	90% CI ^c		Power	ANOVA CV%
	Test	Ref		Lower	Upper		
C _{max}	28.5363	34.1786	83.49	76.66	90.93	0.9945	17.21
AUC _{last}	174.3790	175.6501	99.28	94.43	104.37	1.0000	10.05
AUC _{inf}	177.3905	178.3980	99.44	94.56	104.56	1.0000	10.10

^a Geometric Mean for Acurox® 2 x 7.5 mg Fed (Test) and Roxicodone® 1 x 15 mg Fed (Ref) based on Least Squares Mean of log-transformed parameter values

^b Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

^c 90% Confidence Interval

Source data: [Appendices 16.4.26 and 16.4.27](#)

Safety: All subjects received 50 mg naltrexone HCl, a mu-opioid receptor antagonist, approximately 12 hours before and 1 hour before study drug administration in order to minimize the occurrence of untoward pharmacological effects of oxycodone.

A treatment-emergent AE (TEAE) was defined as any AE where the onset was after dosing with a study medication (Acurox®, Roxicodone®, or naltrexone) but prior to receipt of the next dose of a different study medication.

There were no serious AEs.

A total of 115 TEAEs were reported over the course of the study. Of the 115 TEAEs reported over the course of the study, a total of 101 were reported following administration of a study treatment (Acurox® or Roxicodone®). There were 14 TEAEs reported following administration of naltrexone and prior to administration of a study treatment.

A total of 16 TEAEs were reported by 10 subjects after dosing with Acurox® (oxycodone HCl, USP) Tablet (1 x 5 mg) under fasted conditions. The most commonly reported AEs were nausea (n=7) and dizziness (n=3).

A total of 17 TEAEs were reported by 7 subjects after dosing with Acurox® (oxycodone HCl, USP) Tablet, (2 x 5 mg) under fasted conditions. The most commonly reported AEs were nausea (n=6), dizziness (n=2), and headache (n=2).

A total of 23 TEAEs were reported by 8 subjects after dosing with Acurox® (oxycodone HCl, USP) Tablet (2 x 7.5) under fasted conditions. The most commonly reported AEs were nausea (n=7) and headache (n=4).

A total of 25 TEAEs were reported by 13 subjects after dosing with Acurox® (oxycodone HCl, USP) Tablet, (2 x 7.5 mg) under fed conditions. The most commonly reported AEs were nausea (n=6) and headache (n=6).

A total of 20 TEAEs were reported by 10 subjects after dosing with Roxicodone® (1 x 15 mg tablet) under fed conditions. The most commonly reported AEs were nausea (n=5), abdominal pain (n=4), and headache (n=4).

Of the 101 TEAEs reported following study treatment administration, 63 were mild and 38 were moderate in intensity. There were no severe AEs. Eighty-three (83) of the AEs were judged by the Investigator as related to the study drug and the remaining 18 were judged as not related to the study drug.

None of the AEs were related to abnormal laboratory evaluations.

No clinically significant changes in clinical laboratory values, vital signs or physical examinations were observed.

CONCLUSIONS:

Efficacy: Not applicable

Pharmacokinetics: Thirty-five (35) healthy subjects were enrolled in the study. Twenty-eight (28) subjects completed the study. Thirty-three (33) subjects were included in the pharmacokinetic analysis.

Dose Proportionality

- Acurox® Tablets are dose proportional between 5 mg and 15 mg using all three statistical analyses performed (CI approach, linear regression, and power model).
- Based on the results from the CI approach and linear regression, a proportional change in exposure (C_{max} , AUC_{last} , and AUC_{inf}) with dose was observed for Acurox® Tablets between 5 mg and 15 mg under fasted conditions.
- The results of the power model analysis suggested that Acurox® Tablets would be dose-proportional between 5 mg and approximately 49 mg in terms of maximum exposure based on C_{max} , between 5 mg and approximately 42 mg in terms of total exposure based on AUC_{last} , and up to approximately 68 mg based on AUC_{inf} .
- There were no statistically significant differences in T_{max} values between 1 x 5 mg, 2 x 5 mg, and 2 x 7.5 mg Acurox® Tablets under fasted conditions ($p > 0.05$, Wilcoxon signed rank test).

Food Effect

- Administration of Acurox® Tablets with food resulted in a 14% decrease in oxycodone peak exposure based on C_{max} , a 21% increase in total exposure based on AUC_{last} and AUC_{inf} , and an approximately 1.75-hour delay in oxycodone T_{max} (3.00 hours vs 1.25 hours) compared with an equivalent dose of Acurox® Tablets administered under fasted conditions.
- The 90% confidence intervals for the primary pharmacokinetic parameters were not within the accepted 80% to 125% range for bioequivalence indicating the presence of a food interaction. Overall, the presence of a high-fat, high-calorie meal during the time of Acurox® administration appeared to affect the rate of absorption of oxycodone from Acurox® Tablets more than the extent of absorption. There was no evidence that taking Acurox® Tablets with food reduced the overall bioavailability of the drug.

Relative Bioavailability

- Acurox® Tablets and Roxicodone® have comparable oral bioavailability (based on AUC) when the two products are administered under fed conditions. Based on the ratios of the geometric means for AUC_{last} and AUC_{inf} , the oral bioavailability of oxycodone from Acurox® Tablets relative to Roxicodone® was approximately 99%. The 90% CIs for comparing total exposure based on AUC_{last} and AUC_{inf} were within the accepted 80% to 125% limits.
- The 90% CI for comparing C_{max} was not within the 80% to 125% limit suggesting that Acurox® Tablets and Roxicodone® are not bioequivalent under fed conditions.
- The rate of absorption of oxycodone from 2 x 7.5 mg Acurox® Tablets was significantly slower than that from Roxicodone® based on a comparison of T_{max} (3.00 hours vs 1.00 hour).

Safety:

- There were no SAEs.
- The most commonly reported TEAEs (occurring in $\geq 10\%$ of subjects) were nausea, headache, abdominal pain, dizziness, and abdominal distention.
- Most treatment-emergent AEs were mild in intensity; no AEs were considered severe.
- No clinically significant treatment-related changes in clinical laboratory values, vital signs, or 12-lead ECG results were observed.
- Overall, single oral doses of Acurox® and Roxicodone® were generally safe and well tolerated by the healthy adult subjects in this study who had received a naltrexone block. The adverse events reported or observed following administration of Acurox® Tablets and Roxicodone® were similar, and consistent with the known safety profile of oxycodone HCl following blockade with naltrexone HCl.

Date of the Report: 20 October 2010

4.3 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology				
New Drug Application Filing and Review Form				
<u>General Information About the Submission</u>				
NDA/BLA Number	Information NDA-202080		Information Acurox ®	
OCP Division (I, II, III, IV, V)	II		Generic Name Oxycodone	
Medical Division			Drug Class Opioids	
OCP Reviewer	Suresh B Naraharisetti		Indication(s) [REDACTED] (b) (4) of moderate to severe pain	
OCP Team Leader	Suresh Doddapaneni		Dosage Form Immediate-release tablet	
Pharmacometrics Reviewer			Dosing Regimen 5 to 15 mg every 4 – 6 hrs as needed for pain. Dose should be titrated based on individual patient's response to the initial dose	
Date of Submission	12/17/2010		Route of Administration Oral	
Estimated Due Date of OCP Review			Sponsor King Pharmaceuticals	
Medical Division Due Date			Priority Classification	
PDUFA Due Date				
<i>Clin. Pharm. and Biopharm. Information</i>				
	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods	X	1		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				

single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:		1 (K-234-10-1001)		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -		1		Abuse liability study
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -		1		
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	X	1 (K-234-10-1001)		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan		1		Sponsor is requesting a waiver
Literature References				
Total Number of Studies		6	5	

On initial review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			

19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	
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IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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

Suresh Babu Naraharisetti
2011

January 28,

Reviewing Clinical Pharmacologist

Date

Suresh Doddapaneni
2011

January 28,

Team Leader/Supervisor

Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SURESH B NARAHARISETTI

05/16/2011

YUN XU

05/16/2011

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment					
Application No.:	NDA 202-080 (000)				
Submission Date:	December 17, 2010 and March 9, 2011	Reviewer: Houda Mahayni, Ph.D.			
Division:	DAAP	Team Leader: Angelica Dorantes, Ph.D.			
Sponsor:	King Pharmaceuticals	Supervisor: Patrick J. Marroum, Ph.D.			
Trade Name:	Acurox®	Date Assigned:	December 27, 2010		
Generic Name:	Oxycodone HCl	Date of Review:	May 2, 2011		
Indication:	Management of moderate to severe pain where the use of an opioid analgesic is appropriate	Type of Submission: Original NDA under section 505 (b)(2)			
Formulation/strengths	Immediate-Release Tablet/ 5 mg and 7.5 mg				
Route of Administration	Oral				
<u>SUBMISSION:</u>					
<p>Acurox® Tablets are an abuse deterrent formulation of immediate-release oxycodone hydrochloride tablets utilizing Aversion® Technology. Aversion® Technology uses a unique combination of inactive ingredients that function to discourage misuse or abuse. This technology is designed to deter nasal snorting of crushed tablets and intravenous (IV) injection of crushed and dissolved tablets.</p>					
<p>Acurox® Tablets contains either 5 mg or 7.5 mg oxycodone HCl per tablet as the active analgesic ingredient. The proposed indication for Acurox® Tablets is for the (b) (4) of moderate to severe pain where the use of an (b) (4) opioid analgesic tablet is appropriate.</p>					
<p>This NDA is being submitted under section 505(b) (2) of the Food, Drug and Cosmetic Act with Roxicodone® (Oxycodone Hydrochloride Tablets USP) (NDA 021011) as the reference listed drug (RLD).</p>					
<p>The clinical development program for Acurox® Tablets consisted of 3 prospective studies:</p> <ul style="list-style-type: none"> • a pivotal bioequivalence (BE) study with the RLD Roxicodone® Tablets in healthy volunteers (AP-ADD-100) • a dose-proportionality and food-effect study in healthy volunteers (K234-10-1001) • an intranasal abuse liability study in non-dependent recreational opioid users to assess the limits and impediments to abuse of Acurox® Tablets when crushed and administered intranasally (K234-10-1002) 					
<p>This review focuses on the evaluation of the dissolution method and the biowaiver request.</p>					

BIOPHARMACEUTIC INFORMATION:

The quantitative composition for both tablet strengths and the function of each component is provided in Table 1. The theoretical tablet weight for both the 5 mg and 7.5 mg tablets is 490 mg. The theoretical quantity of oxycodone hydrochloride is listed. However, the actual amount used varied depending upon the potency of the drug substance.

The sponsor stated that the two strengths of tablets meet the definition of *proportionally similar* as described in the March 2003 FDA "Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations."

Table 1: Acurox Tablet Composition

Component	Quality Standard	Function	IIG Levels	Strength			
				5 mg	%	7.5 mg	%
Oxycodone Hydrochloride USP	USP	Active pharmaceutical ingredient	Not applicable	5*	(b) (4)	7.5*	(b) (4)
Polvethylene Oxide NF (b) (4)	NF						(b) (4)
Sodium Lauryl Sulfate NF (b) (4)	NF						
Microcrystalline Cellulose NF (b) (4)	NF						
Crospovidone NF (b) (4)	NF						
Colloidal Silicon Dioxide NF (b) (4)	NF						
Magnesium Stearate NF (b) (4)	NF						
				Total: 490	100	490	100

* Actual quantity will be corrected for potency.

Reviewer's Note:

The two strengths of tablets meet the definition of proportionally similar as described in the BA/BE guidance.

Dissolution Method and Specification

The dissolution method was developed during the development activities of another product called Acurox with Niacin Tablets. Acurox Tablets is a comparable formulation to Acurox with Niacin Tablets.

Additionally, the sponsor stated that this dissolution method demonstrated in vitro-in vivo correlation for Oxycodone HCl during the development of Acurox with Niacin Tablets. The dissolution parameters are listed below.

Apparatus:	II (Paddle)
Medium:	Purified Water
Volume:	500 mL
Rotation:	50 rpm
Temperature:	37°C
Analytical Method:	UV
Specification:	Q = 70% in 45 minutes

The sponsor conducted a bioequivalence study (Protocol #20-686-1N) using a product candidate #1 (PC1) formulations which contained (b) (4)

The BE study was conducted in thirty subjects who participated in a single-dose, fasting, open-label, randomized, two-period crossover study. The sponsor compared the pharmacokinetic characteristics of PC1 (Lot #SB-04-001) to oxycodone HCl (5mg) component in Percocet® 5/325 mg tablet (Endo Labs). PC1 was found bioinequivalent to the oxycodone HCl component of Percocet tablets. However, the sponsor expected that the test and reference product to be bioequivalent based on the in-vitro dissolution data obtained by the compendial methods for each individual product. Failure of the BE study prompted the sponsor to reevaluate the formulation and the dissolution methodology. The aim was to develop a dissolution method capable of mimicking the in-vivo response.

The above dissolution method was deemed not discriminating, as it could not be used to predict if a given formulation would be bioequivalent to a reference product. The sponsor aimed at developing a better dissolution method to guide ongoing product evaluation and reformulation efforts. The approach was to develop a dissolution method that would show a distinctly different dissolution profile between the test and reference products used in the failed bioequivalence study. Multiple media were evaluated and a new method was finalized. The new method was designated as Test Method TM1005 (Apparatus II, 50 rpm, 900 ml of 0.1N HCl). This is the method the sponsor is proposing as the regulatory dissolution method for Acurox (Oxycodone HCl). The parameters utilized for the method are those of the current USP method for Oxycodone HCl and Acetaminophen Tablets. The dissolution parameters are as follows:

Apparatus:	II (Paddle)
Medium:	0.1 N HCl
Volume:	900 mL
Rotation:	50 rpm
Temperature:	37°C

An example of the discriminating capability of this method is shown in Figure 2 below. It can be seen that the dissolution profile of the two products used in the failed BE study are significantly different. (b) (4)

Based on this wide difference in dissolution results, the sponsor felt that method TM1005 would be discriminating and useful in predicting in-vivo response for future BE studies. Therefore, the decision was made

that only method TM1005 would be utilized for dissolution testing in all future experiments and formulation evaluations.

(b) (4)

A second BE study (Protocol #20-730-1N) was conducted on twelve subjects. The study was a single-dose, fasting, open-label, randomized, two-period crossover study conducted at Cedra Corporation to compare the pharmacokinetic characteristics of Product Candidate #1 (Oxycodone HCl, 5mg, Lot #SB-04-002) with that of Oxycodone HCl tablets, 5mg (Mallinckrodt). Figure 3 shows the results from the pilot BE study.

Figure 3: Plasma Concentration Profiles (BE Study 20-730-1N)



The sponsor concluded that PCI (Lot # SB-04-002) is

(b) (4)

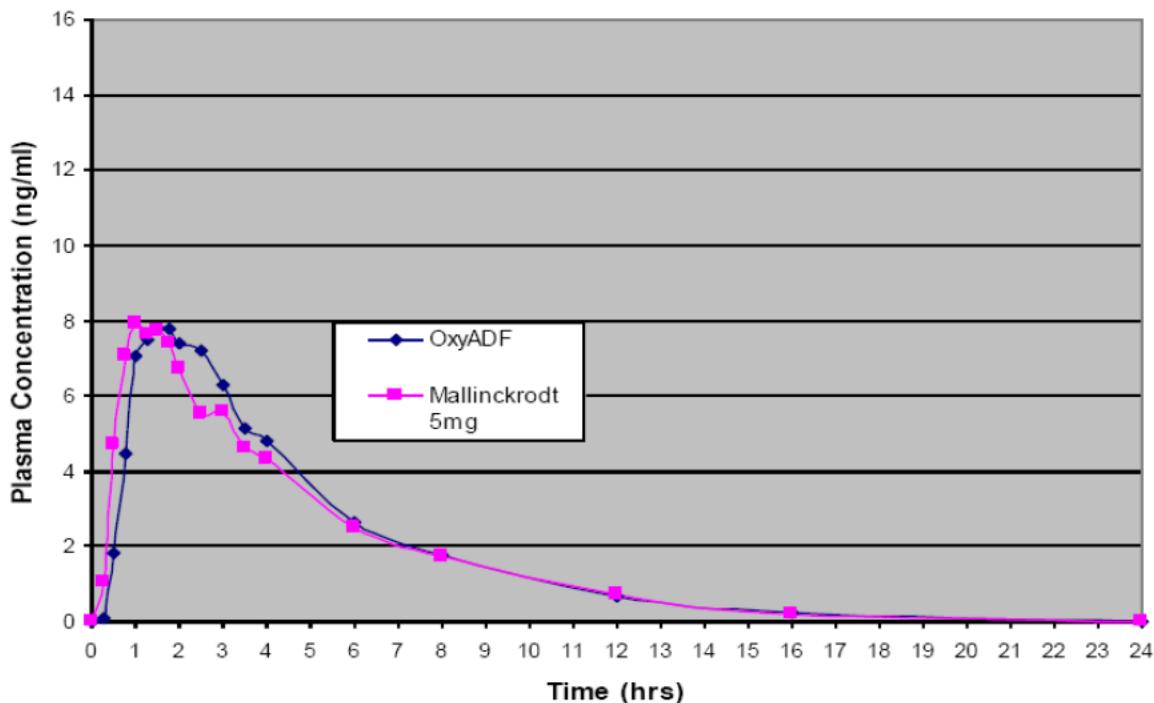
The sponsor made a strategic decision to place development activities on hold for Product Candidate #1, and to initiate development of a second product candidate containing niacin as the component designed to deter excessive oral consumption. This product candidate was designated OxyADF (later changed to Acurox™). The product is an immediate release 5mg oxycodone HCl tablet containing niacin made using the Aversion Technology.

The sponsor performed a third BE study (Protocol #20-761-1G), and decided to test Lot # 12202A05. The only formulation difference between the bioequivalent formulation of Product Candidate #1 (Lot SB-04-002) and Lot 12202A05

(b) (4)

The sponsor tested Lot # 12202A05 in a pilot BE study to see if bioequivalence could be demonstrated versus a 5mg generic oxycodone HCl tablet. Twelve subjects participated in a single-dose, fasting, open-label, randomized, two-period crossover study conducted at Cedra Corporation to compare the pharmacokinetic characteristics of the prototype Acurox™ formulation with that of generic Oxycodone HCl tablets, 5mg (Mallinckrodt). Figure 4 shows the results from the pilot BE study.

Figure 4: Plasma Concentration Profiles (BE Study 20-761-1G)



The sponsor stated that the results of this study suggested that under fasting conditions the Acurox™ test product was bioequivalent to the reference oxycodone product manufactured by Mallinckrodt.

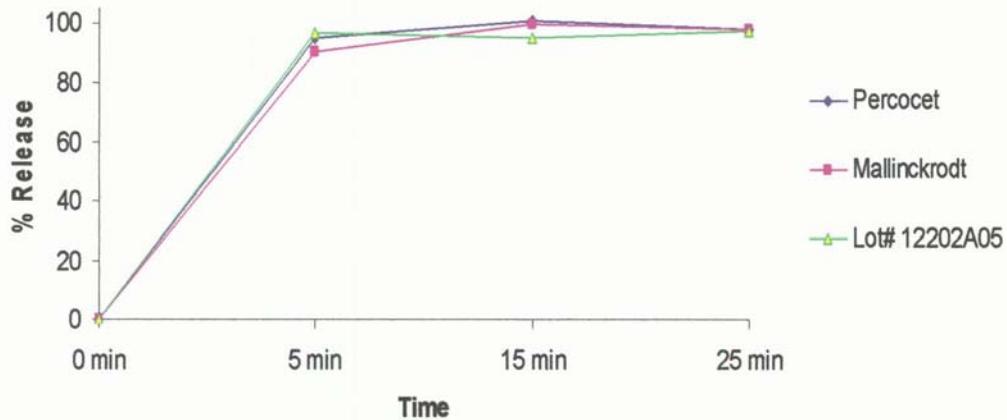
To demonstrate the discriminating capability of the dissolution method TM1005, Lot # 12202A05 representing Product Candidate #2 (PC2) was analyzed by four different dissolution methods.

(b) (4)

The profile for Method II (TM1005) shows that the product meets the (b) (4) Q at the 5 minutes time point thus predicting bioequivalence to Percocet and Mallinckrodt tablets. The data also validates the discriminating capability of TM1005 when compared to Method I, III, and IV.

Data generated from Product Candidate #2 (Lot # 12202A05) is shown in Figure 6 versus the commercial standards Percocet and Mallinckrodt tablets at selected time points. Based on the dissolution profile similarity between all three products, the sponsor predicted bioequivalence results for the third BE study.

Figure 6: Dissolution Profile of Product Candidate #2 versus Percocet and Mallinckrodt Tablets



The sponsor examined the discriminating capability of dissolution method (TM1005) (the proposed method for Acurox). Dissolution experiments were conducted to compare dissolution results between Aversion Candidates 1 and 2 and commercially available Oxycodone HCl tablet.

The sponsor used the following dissolution methods to conduct the comparison:

- **Method I - USP 28 method for 5mg, Oxycodone HCl Tablets**
Media= 500 ml of water (pH neutral)
Apparatus II
50 rpm
Temperature 37° C
- **Method II - TM1005**
Media = 900 ml of 0.1 N HCl (pH ~1.1)
Apparatus II
50 rpm
Temperature 37° C

(b) (4)

Note: All data analysis was performed using TM1006 an HPLC method suitable for the analysis of dissolution samples containing Oxycodone HCl.

The analytical method used to quantitate oxycodone is a reverse phase isocratic HPLC at 205 nm detection. The procedure for the dissolution of Oxycodone HCl was validated with respect to each of the following characteristics: specificity, system precision, linearity/range, and solution stability. Table 2 below show the validation summary of the dissolution method of Oxycodone HCl.

Table 2: Validation Summary: Dissolution (Oxycodone HCl)

Attribute	Result
Specificity	Method specificity was demonstrated.
System Precision	System precision was achieved with a %RSD of \leq 5.0% at 0.006 mg/mL.
Linearity/Range	The linearity/range was determined to be 33-167% of the 0.006 mg/mL method concentration level. A correlation coefficient of >0.9999 was achieved. The bias was determined to be well within 10%.
Solution Stability	Standard and sample solution stability was determined for a minimum of 48 hours at ambient temperature.

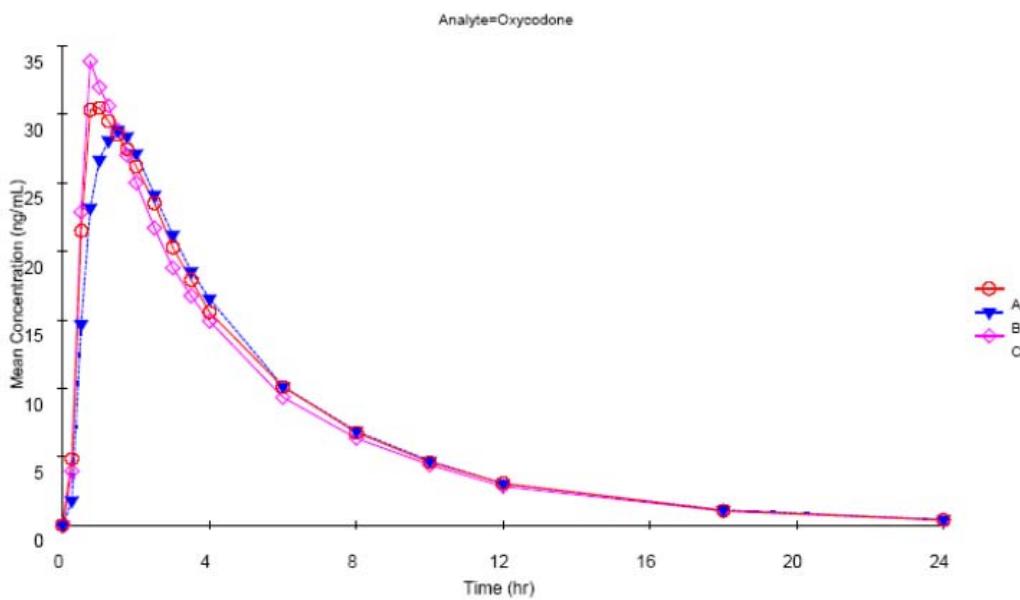
Initially, the sponsor proposed the dissolution specification of NLT [REDACTED]^{(b) (4)}. The justification provided is that this specification exceeds the compendia requirement of Q 70% in 45 minutes.

During the filing communication dated February 10, 2011, FDA requested the sponsor to [REDACTED]^{(b) (4)} the dissolution specification to NLT [REDACTED]^{(b) (4)} in 15 minutes. On March 9, 2011, the sponsor revised the dissolution specification to NLT [REDACTED]^{(b) (4)} in 15 minutes.

To further support the bridge to the development work performed on the Niacin-containing product, a three-way crossover BE study, AP-ADD-100, was conducted. The sponsor stated that the BE study demonstrated that Acurox tablets are bioequivalent to both Acurox with Niacin Tablets and the reference listed drug Roxicodone (Oxycodone HCl) Tablets USP.

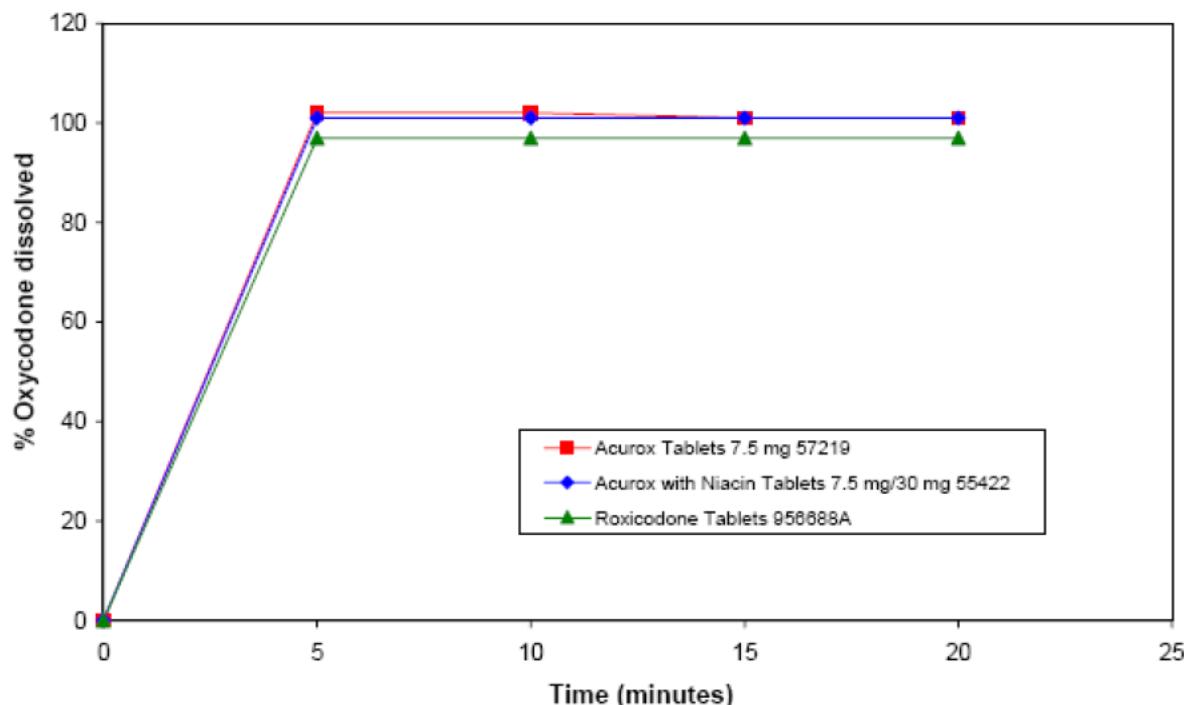
The mean oxycodone concentration-time curves after dosing with each product are shown in Figure 7.

Figure 7: AP-ADD-100: Mean Oxycodone Concentration-Time Profiles after Administration of Acurox® Tablets (A), Acurox® with Niacin Tablets (B), and Roxicodone® Tablets (C)



To demonstrate the applicability of this method for Acurox® Tablets, a dissolution profile comparison was conducted on the various tablet formulations that were studied in the BE study AP-ADD-100, including the reference listed drug Roxicodone® Tablets. This comparison shows that Acurox® Tablets have a similar profile to Acurox® with Niacin Tablets, thus concluding that the current dissolution method is acceptable as a valuable quality assurance tool. These data are presented in Figure 8.

Figure 8: Dissolution Profile Comparison of Oxycodone HCl



The sponsor stated that dissolution profiles of Acurox® Tablets 5 mg and 7.5 mg are comparable to Roxicodone® Tablets. Both tablet strengths met the f_2 (similarity factor) criteria of >50 when compared with Roxicodone® Tablets. The data are presented in Table 3 below. Also, the sponsor stated that Oxycodone is a Class 1 API based on BCS.

Table 3: Dissolution Profile Comparison of Oxycodone HCl

Time	Product Tested and Average Result (Range)			
	Acurox Tablets 5 mg Lot # 57218	Acurox Tablets 7.5 mg Lot # 57219	Acurox with Niacin Tablets 7.5 mg/30 mg Lot # 55422	Roxicodone Tablets 15 mg Lot 956688A
5 minutes	99	102	101	97 (b) (4)
10 minutes	99	102	101	97 (b) (4)
15 minutes	99	101	101	97 (b) (4)
20 minutes	98	101	101	97 (b) (4)

Reviewer's Note:

For a drug to be classified as a BCS Class 1 compound, supportive information on solubility, permeability, and dissolution should be submitted to the Agency for review. An official designation will be made by the BCS Committee once the data has been reviewed.

Biowaiver Request

The sponsor conducted a BE study using the higher strength 7.5 mg. Because the 5 mg and 7.5 mg are dose proportional. FDA waives the regulatory requirement to conduct in-vivo study on the lower strength of 5 mg if the BE study on the higher strength 7.5 mg is found acceptable.

RECOMMENDATION:

The proposed dissolution method as listed below is acceptable.

The dissolution parameters are as follows:

Apparatus: II (Paddle)
Medium: 0.1 N HCl
Volume: 900 mL
Rotation: 50 rpm
Temperature: 37°C

FDA and the sponsor agreed on the following dissolution specification: NLT ^{(b) (4)} in 15 minutes

The biowaiver request to waive the conduct of in-vivo study on the lower strength (5 mg) of Acurox is acceptable if the BE study (AP-ADD-100) is found acceptable.

Houda Mahayni, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: NDA 202080, LBasham, ADorantes, SPatwardhan, JPinto

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/s/

HOUDA MAHAYNI

05/16/2011

PATRICK J MARROUM

05/16/2011

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 202-080 (000)	Reviewer: Houda Mahayni, Ph.D.	
Division:	DAAP		
Sponsor:	King Pharmaceuticals	Team Leader: Angelica Dorantes, Ph.D	
Trade Name:	Acurox®	Supervisor: Patrick J. Marroum, Ph.D	
Generic Name:	Oxycodone HCl	Date Assigned:	December 17, 2010
Indication:	Management of moderate to severe pain where the use of an opioid analgesic is appropriate	Date of Review:	January 28, 2010
Formulation	Immediate-Release Tablet		
Route of Administration	Oral		
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	CDER Stamp Date	Date of informal/Formal Consult	PDUFA DATE
Dec 17, 2010	Dec 17, 2010	Dec 27, 2010	Jun 17, 2011
Type of Submission:	Original NDA under section 505(b)(2)		
Type of Consult:	Dissolution method and specifications		
FILING REVIEW ADDENDUM			
RECOMMENDATION: <p>The proposed dissolution specification of NLT [REDACTED] ^{(b) (4)} is not acceptable. It is recommended that the sponsor [REDACTED] ^{(b) (4)} the dissolution specification to NLT [REDACTED] ^{(b) (4)} in 15 minutes.</p>			
Houda Mahayni, Ph. D. Biopharmaceutics Reviewer Office of New Drugs Quality Assessment		Patrick J. Marroum, Ph. D. Biopharmaceutics Supervisor Office of New Drugs Quality Assessment	
cc: NDA 202080, LBasham, ADorantes, SPatwardhan, JPinto, DChristodoulou			

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/s/

HOUDA MAHAYNI

02/09/2011

PATRICK J MARROUM

02/09/2011

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 202-080 (000)	Reviewer: Houda Mahayni, Ph.D.	
Division:	DAAP		
Sponsor:	King Pharmaceuticals	Team Leader: Angelica Dorantes, Ph.D	
Trade Name:	Acurox®	Supervisor: Patrick J. Marroum, Ph.D	
Generic Name:	Oxycodone HCl	Date Assigned:	December 17, 2010
Indication:	Management of moderate to severe pain where the use of an opioid analgesic is appropriate	Date of Review:	January 28, 2010
Formulation	Immediate-Release Tablet		
Route of Administration	Oral		
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	CDER Stamp Date	Date of informal/Formal Consult	PDUFA DATE
Dec 17, 2010	Dec 17, 2010	Dec 27, 2010	Jun 17, 2011
Type of Submission:	Original NDA under section 505(b)(2)		
Type of Consult:	Dissolution method and specifications--- FILING REVIEW		
REVIEW SUMMARY:			
<p>Acurox® Tablets is an immediate-release tablet formulation. It contains either 5 mg or 7.5 mg oxycodone HCl per tablet as the active analgesic ingredient. The targeted indication for Acurox® is for the ^{(b) (4)} of moderate to severe pain where the use of an ^{(b) (4)} opioid analgesic tablet is appropriate. The composition of Acurox® Tablets is intended to introduce limits or impediments to two common methods of opioid analgesic product abuse: IV injection of opioids extracted from dissolved tablets and nasal snorting of pulverized tablets.</p>			
<p>This NDA is being submitted under section 505(b)(2) of the Food, Drug and Cosmetic Act with Roxicodone® (Oxycodone Hydrochloride Tablets USP) (NDA 021011) as the reference listed drug (RLD).</p>			
<p>The clinical development program for Acurox® Tablet consisted of 3 prospective studies:</p> <ul style="list-style-type: none"> • a pivotal bioequivalence study with the RLD Roxicodone® Tablets in healthy volunteers (AP-ADD-100) • a dose-proportionality and food-effect study in healthy volunteers (K234-10-1001) • an intranasal abuse liability study in non-dependent recreational opioid users to assess the limits and impediments to abuse of Acurox® Tablets when crushed and administered intranasally (K234-10-1002) 			
<p>The components and composition for both tablet strengths and the function of each component are provided in Table 1 below.</p>			

Table 1: Acurox Tablet Composition

Component	Quality Standard	Function	IIG Levels	Strength			
				5 mg		7.5 mg	
				Quantity per Unit mg/tab	%	Quantity per Unit mg/tab	%
Oxycodone Hydrochloride USP	USP	Active pharmaceutical ingredient	Not applicable	5*	(b) (4)	7.5*	(b) (4)
Polylethylene Oxide NF (b) (4)	NF						(b) (4)
Sodium Lauryl Sulfate NF (b) (4)	NF						
Microcrystalline Cellulose NF (b) (4)	NF						
Crospovidone NF (b) (4)	NF						
Colloidal Silicon Dioxide NF (b) (4)	NF						
Magnesium Stearate NF (b) (4)	NF						
				Total: 490	100	490	100

* Actual quantity will be corrected for potency.

Acurox® tablet formulation is nearly identical [REDACTED] to the Acurox® with Niacin [REDACTED] Tablet formulation. Acurox® Tablets is a comparable formulation, [REDACTED]

The proposed dissolution test method parameters are as follows:

Dissolution Apparatus: Apparatus II (Paddle)

Dissolution Medium: 900 mL of 0.1 N HCl

Speed: 50 rpm

Temperature: 37°C

The proposed dissolution specification is NLT [REDACTED] (b) (4). Quantitation of oxycodone is performed using reverse phase isocratic HPLC. The dissolution method of Oxycodone HCl was validated with respect to specificity, system precision, linearity/range, and solution stability.

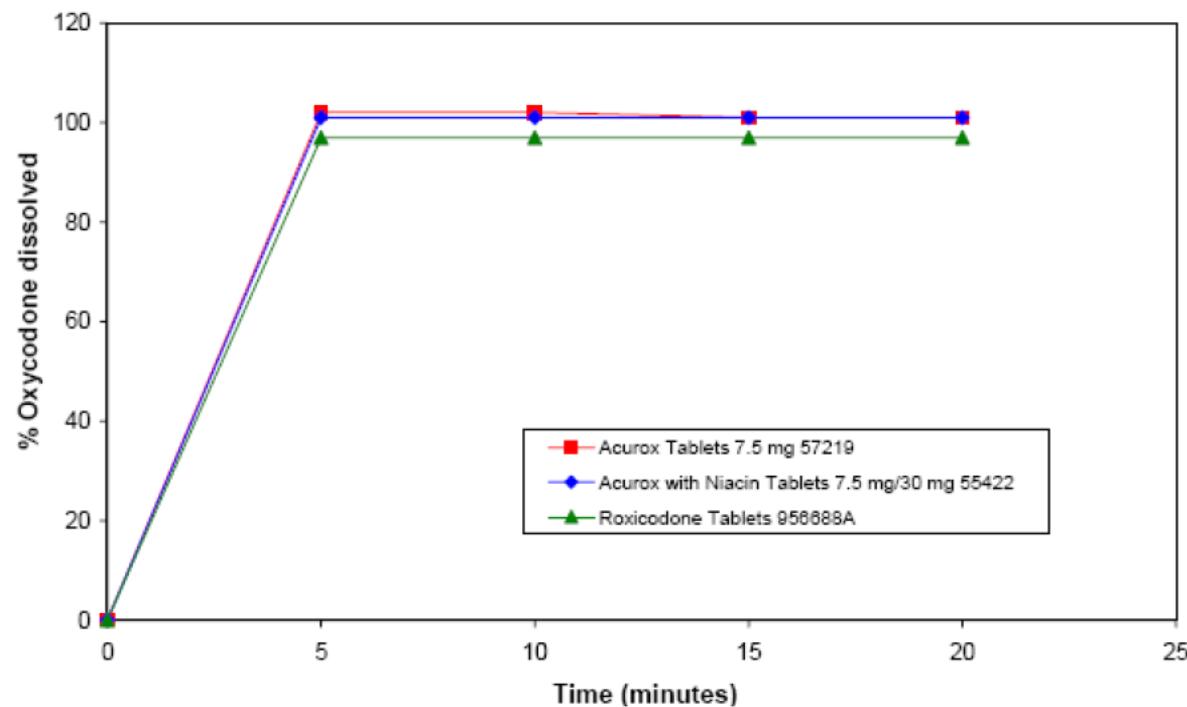
The sponsor stated that the proposed dissolution method demonstrated in vitro-in vivo capability for Oxycodone HCl during the development of Acurox® with Niacin tablets, as it was shown to be specific and discriminating. Since the Acurox® Tablet formulation is nearly identical [REDACTED] (b) (4) to the Acurox® with Niacin Tablet formulation, the sponsor believes that this method should also be applicable.

To demonstrate the applicability of this method for Acurox® Tablets, a dissolution profile comparison was conducted on the various tablet formulations that were studied in the bioequivalency study AP-ADD-100, including the reference listed drug Roxicodone® Tablets. This comparison shows that Acurox® Tablets have a similar profile to Acurox® with Niacin Tablets, thus the sponsor concluded that the current dissolution method is acceptable as a valuable quality assurance tool. These data are presented in Table 2 and Figure 1 below.

Table 2: Dissolution Profile Comparison of Oxycodone HCl

Time	Product Tested and Average Result (Range)			
	Acurox Tablets 5 mg Lot # 57218	Acurox Tablets 7.5 mg Lot # 57219	Acurox with Niacin Tablets 7.5 mg/30 mg Lot # 55422	Roxicodone Tablets 15 mg Lot 956688A
5 minutes	99	102	101	97 (b) (4)
10 minutes	99	102	101	97 (b) (4)
15 minutes	99	101	101	97 (b) (4)
20 minutes	98	101	101	97 (b) (4)

Figure 1: Dissolution Profile Comparison of Oxycodone HCl



The sponsor stated that dissolution profiles of Acurox® Tablets 5 mg and 7.5 mg are comparable to Roxicodone® Tablets. Both tablet strengths met the *f*2 (similarity factor) criteria of >50 when compared with Roxicodone® Tablets. The 5 mg batch produced an *f*2 value of 83 and the 7.5 mg

batch produced an *f*₂ value of 67.

A total of six NDA Registration/Clinical batches were manufactured at King Pharmaceuticals Inc. to support the development of Acurox® (oxycodone HCl) tablet, and to serve as the primary stability lots for the product. This consisted of three batches each of the 5 mg and 7.5 mg strength tablets. The manufacturing process and batch sizes utilized during the production of these batches are identical to that proposed for the commercial batches.

The biopharmaceutics review will focus on the proposed dissolution method and specification.

RECOMMENDATION:

The ONDQA/biopharmaceutics team has reviewed NDA 202808 for filing purposes. We found this NDA filable from biopharmaceutics perspective. The sponsor has submitted a reviewable submission. There are no comments to be conveyed to the sponsor at this time.

Houda Mahayni, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: NDA 202080, LBasham, ADorantes, SPatwardhan, JPinto, DChristodoulou

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/s/

HOUDA MAHAYNI

02/07/2011

PATRICK J MARROUM

02/07/2011

From: Suresh Babu Naraharisetti, Ph.D.

To: DOCUMENT ROOM (LOG-IN and LOG-OUT)
Please log-in this consult and review action for the
specified IND/NDA submission

DATE: 02/02/2011	IND No.: Serial No.:	NDA No. 202080	DATE OF DOCUMENT 12/17/2010	
NAME OF DRUG Oxycodone HCl (Acurox®)		PRIORITY CONSIDERATION	Date of informal/Formal Consult: 12/17/2010	

NAME OF THE SPONSOR: [King Pharmaceuticals]

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

- | | | |
|--|---|--|
| <input type="checkbox"/> PRE-IND | <input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> ANIMAL to HUMAN SCALING | <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> IN-VITRO METABOLISM | <input type="checkbox"/> IN-VIVO WAIVER REQUEST | <input type="checkbox"/> CORRESPONDENCE |
| <input type="checkbox"/> PROTOCOL | <input type="checkbox"/> SUPAC RELATED | <input type="checkbox"/> DRUG ADVERTISING |
| <input type="checkbox"/> PHASE II PROTOCOL | <input type="checkbox"/> CMC RELATED | <input type="checkbox"/> ADVERSE REACTION REPORT |
| <input type="checkbox"/> PHASE III PROTOCOL | <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> ANNUAL REPORTS |
| <input type="checkbox"/> DOSING REGIMEN CONSULT | <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS | <input type="checkbox"/> FAX SUBMISSION |
| <input type="checkbox"/> PK/PD- POPPK ISSUES | <input type="checkbox"/> MEETING PACKAGE (EOP2/Pre- | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> PHASE IV RELATED | NDA/CMC/Pharmacometrics/Others) | Filing Meeting |

REVIEW ACTION

- | | | |
|--|---|---|
| <input type="checkbox"/> NAI (No action indicated) | <input type="checkbox"/> Oral communication with
Name: [] | <input type="checkbox"/> Formal Review/Memo (attached) |
| <input type="checkbox"/> E-mail comments to:
<input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox | <input type="checkbox"/> Comments communicated in
meeting/Telecon. see meeting minutes
dated: [] | <input type="checkbox"/> See comments below |
| <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others
(Check as appropriate and attach e-mail) | | <input type="checkbox"/> See submission cover letter |
| | | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):
Filing Review |

REVIEW COMMENT(S)

- NEED TO BE COMMUNICATED TO THE SPONSOR HAVE BEEN COMMUNICATED TO THE SPONSOR

BACKGROUND/COMMENTS TO SPONSOR:

King Pharmaceuticals submitted this 505 (b) (2) application for oxycodone HCl immediate release tablets (Acurox®) of strengths 5 and 7.5 mg for the relief of moderate to severe pain. This application references NDA 021011 for Roxicodone® (Oxycodone HCl IR Tablets), and establishes safety and efficacy based on bioequivalence with Roxicodone® Tablets.

Regulatory History:

Complete Response Action on Acurox with Niacin (N22451) Submission :

In December 2008, sponsor submitted NDA 22451 for Acurox with Niacin consisting of 5 or 7.5 mg of oxycodone hydrochloride and 30 mg of niacin as an abuse deterrent opioid drug product. Niacin is included in this formulation with the intent of causing aversive effects such as flushing if the labeled dose is exceeded via the oral route of administration. However, this product was issued a Complete Response action due to 1) Relatively higher incidence of flushing in patients taking Acurox with niacin (ranging from 11% to 41% compared to 1.5% with placebo) and 2) little or no evidence that the inclusion of niacin in Acurox will deter the abuse of oxycodone.

Current Submission:

The current Acurox® Tablets is a reformulated tablet without niacin. (b) (4)

Per the sponsor, this reformulated tablet is also an abuse deterrent opioid drug product. The functional inactive ingredients such as (b) (4) in the drug product have the potential to deter oxycodone abuse and misuse by providing limits and impediments to intranasal and intravenous administration.

In support of this NDA, sponsor conducted the following Clinical/Clinical Pharmacology studies:

Two PK Studies in Healthy Volunteers:

- **BE Study (AP-ADD-100):** A Single-Dose, 3-Period, 3-Treatment, 3-Way Crossover PK Comparison between Acurox® 2 x 7.5 mg/30 mg tablets and Acurox® DD 2 x 7.5 mg/0 mg tablets, and Roxicodone® (1 x 15 mg tablet) under Fasting Conditions".
- **Dose Proportionality, Food Effect Study (K234-10-1001):** Open-Label, Single-Dose, Randomized, 5-Period, 5-Way Crossover Study to Evaluate the Dose Proportionality and the Effect of Food on the Bioavailability of Acurox® Tablets in Healthy Volunteers

Abuse Liability Study in Recreational Opioid Users:

- **Relative Abuse Liability and Safety Study (K234-10-1002):** Randomized, Double-Blind, Active-Controlled Study to Evaluate the Relative Abuse Potential and Safety of Intranasally Administered Crushed Acurox® Tablets (2 x 7.5 mg) compared with crushed and intranasally administered Roxicodone® Tablets (3 x 5 mg) in Non-Dependent Recreational Opioid Users

The pre- NDA meeting with sponsor was held for this NDA on 09/27/2010. The conducted PK studies meet the regulatory requirements for filing and this application is filable from a clinical pharmacology perspective. The clinical pharmacology filing check list is attached as attachment-1 to this review.

Since the BE study (AP-ADD-100) is pivotal to the approval of this application, a consult for Division of Scientific Investigations (DSI) Inspection of this study has been issued on 01/06/2011.

SIGNATURE OF REVIEWER: <u>Suresh Babu Naraharisetti, Ph.D.</u> SIGNATURE OF TEAM LEADER: <u>Suresh Doddapaneni, Ph.D.</u>	Date 02/02/2011 Date 02/02/2011
CC.: HFD # []; TL: []	Project Manager: _____ Date _____

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	<i>NDA-202080</i>	Brand Name	<i>Acurox ®</i>
OCP Division (I, II, III, IV, V)	<i>II</i>	Generic Name	<i>Oxycodone</i>
Medical Division		Drug Class	<i>Opioids</i>
OCP Reviewer	<i>Suresh B Naraharisetti</i>	Indication(s)	(b) (4) of moderate to severe pain
OCP Team Leader	<i>Suresh Doddapaneni</i>	Dosage Form	<i>Immediate-release tablet</i>
Pharmacometrics Reviewer		Dosing Regimen	<i>5 to 15 mg every 4 – 6 hrs as needed for pain. Dose should be titrated based on individual patient's response to the initial dose</i>
Date of Submission	<i>12/17/2010</i>	Route of Administration	<i>Oral</i>
Estimated Due Date of OCP Review		Sponsor	<i>King Pharmaceuticals</i>
Medical Division Due Date		Priority Classification	
PDUFA Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods	X	1		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:		1 (K-234-10-1001)		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for
NDA/BLA or Supplement 090808
Reference ID: 2699912

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -		1		Abuse liability study
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:		1		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	X	1 (K-234-10-1001)		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan		1		Sponsor is requesting a waiver
Literature References				
Total Number of Studies		5		

On initial review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
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Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)

Data

9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X		
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?		X	

Studies and Analyses

11	Is the appropriate pharmacokinetic information submitted?	X		
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?		X	

General

18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X		
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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

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/s/

SURESH B NARAHARISETTI
02/02/2011

SURESH DODDAPANENI
02/02/2011