CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202080Orig1s000

OTHER REVIEW(S)

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: 06-17-11

To: Bob Rappaport, MD, Director
Division of Anesthesia, Analgesia, and Addiction Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff (CSS)

From: Silvia N. Calderon, Ph.D.
Team Leader, CSS

Subject: Oxecta NDA 20-2080 CSS Labeling Recommendations

This memorandum addresses issues discussed in the June 14, 2011, telecom on Oxecta (NDA 20-2080) with the Sponsor, members of the Controlled Substance Staff (CSS), the Division of Anesthesia, Analgesia and Addiction Products (DAAAP) and the Division of Biometrics VI. Oxecta is a new immediate release oxycodone tablet in a new formulation that was developed to prevent intranasal and intravenous abuse of the product.

SUMMARY OF CSS AND BIOSTATISTICS REVIEWER CONCLUSIONS AND RECOMMENDATIONS

The following summary has been reproduced from pages 4 through 6 of Dr. Randall-Thompson's memo (DARRTS, NDA 202080, Randall Thompson, Jovita, F, 5- 24, 2011), The memo reviews and provides CSS conclusions and recommendations on Oxecta abuse liability studies[1]:

Conclusions

1. After reviewing PR-381 and PR-382 analytical lab bench-top studies, we consider the procedures and techniques to be incomplete in investigating and assessing the feasibility of preparing an injectable solution of TRADENAME (Oxycodone HCl).

[1] Study K234-10-1002 was a randomized, double-blind, active-controlled study to evaluate the relative abuse potential and safety of intranasally administered crushed Oxecta tablets in non-dependent recreational opioid users. The primary abuse potential measure was Drug Liking on the visual analog scale (VAS). Overall Drug Liking VAS and Take Drug Again VAS were considered as secondary measures. All measures were administered to subjects on a bipolar scale.

PR-381 and PR-382 did not examine the variables that increase dissolution and the yield of extractions: variables include reducing particle size of the sample, using solvents of different polarity and pHs and increasing temperatures. PR-381 did not examine use of agitation and mixing techniques in solubilization.

2. Testing of solvents for extraction was limited. PR-382 included eight extraction procedures and use of a wider array of solvents (b) (4) (b) (4)) and mixing techniques (i.e., Several common solvents that are often used in extraction studies were not examined. These include (b) (4) These solvents are readily available in retail settings. Specific cutting or grinding methods used to prepare tablets for mixing was not provided.

1. The relevance of developing an oxycodone immediate release formulation that might deter IV abuse should be considered in light of the fact that information in the public domain shows that the number of opioid users that intravenously abuse oxycodone immediate release products is very small and possibly nonexistent, depending on the geographic area examined,[2],[3] relative to the most preferred route of administration by opioid users and addicts by the oral route, followed by the intranasal route.4,5
3. Study K234-10-1002 suggests that a higher number of unique facial and oropharyngeal adverse events might be associated with IN use of TRADENAME (Oxycodone HCl) when compared to Roxicodone by the same route.
4. Although a higher incidence of adverse events related to oral and pharyngeal discomfort was observed in Study K234-10-1002 for subjects snorting TRADENAME (Oxycodone HCl), subjects still report liking TRADENAME (Oxycodone HCl). The significance of these findings in evaluating the IN abuse potential of the formulation is unknown.
5. It is difficult to assess if the potential deterrent properties of the formulation are related to the specific product composition, or if they are related to the number and amount of excipients in the formulation. Study K234-10-1002 was not designed to address the contribution of the individual excipients of the formulation in deterring IN abuse.
6. Data presented in the NDA do not support the inclusion of explicit language in the label related to the deterrent IN abuse, because Study K234-10-1002 was not designed to:
    a. Address whether it is the quality or the quantity of each or all of the excipients of the formulation that contributes to deterring IN abuse.

    b. Evaluate the effect of reducing the particle size of the sample and of longer snorting times. Subjects were given 5 minutes to snort crushed tablets. The

[2] Katz, N.P.; Adams, E.H.; Chilcoat, H.; Colucci, R.D.; Comer, S.D.; Goliber, P.; Grudzinskas, C.; Jasinski, D.; Lande,S.D.; Passik, S.D.; Schnoll, S.H; Sellers, E, Travers, D. ; Weiss, R (2007) . Challenges in the development of prescription opioid abuse-deterrent formulations. *Clin. J. Pain 23*, 648-660.

[3] Davis, W.R.; Johnson, B.D. Prescription opioid use, misuse, and diversion among street users in New York City (2008). *Drug and Alcohol Dependence 92*, 267-276.

question that still remains unanswered is, whether the study findings would remain the same if subjects were given either a sample with a smaller particle size or were given more than 5 minutes to snort the whole sample.

7. Study K234-10-1002 does not provide data that (b) (4) of TRADENAME (Oxycodone HCl). Study K234-10-1002 does not provide data to rule out the deterrent effects that might be associated with the weight and mass of the tablets. Each tablet of TRADENAME (Oxycodone HCl) contains 7.5 mg of oxycodone hydrochloride and 482.5 mg of mixed excipients (see 3.2.P.1 Description and Composition of the Drug Product: Table 3.2P.1-2, pg 2).

In summary, the deficiencies noted in the methodology and data collection from K234-10-1002 include the following:

a. Sequence effect halves the sample size (Differences in the crushed material weight or API/excipient concentration ratio between TRADENAME (Oxycodone HCl) and Roxicodone may have impacted blinding conditions such that participants during testing were able to identify one treatment from another)
b. High drop-out rate makes evaluation difficult
c. Potential unblinding of treatments causes bias
d. Validity of Subjected-Rated Scale for Nasal Effects is unknown
e. Selection and validity of measurements is uncertain
f. Concept of functional excipients is unknown
g. Crushed tablet consistency (particle size, uniformity, sample appearance) between TRADENAME (Oxycodone HCl) and Roxicodone was not verified
h. Difference in the weight/mass of crushed material and differences in excipient concentration between TRADENAME (Oxycodone HCl) and Roxicodone is not experimentally controlled in the study and thus may impact study results.

Recommendations

1. The Sponsor should consider conducting additional in-vitro and clinical studies that address and eliminate the study design deficiencies described above, to support specific formulation-related deterrent (b) (4) for IN or IV abuse.
2. A possible claim that TRADENAME (Oxycodone HCl) (b) (4) would need to be supported by an additional study that reassesses the physicochemical characteristics of TRADENAME (Oxycodone HCl). If a new in-vitro study were to be conducted, the following general principles should be considered:
   - Extraction studies should explore the effect of several experimental conditions known to affect dissolution. These experimental variables include: particle size,

the use of solvents that explore a wide polarity and pH range, the effect of varying conditions of agitation, and the effect of increasing temperatures on extraction.

- Suggested solvents may include (b) (4) Temperatures, extraction times and multi-step extraction procedures for tested solvents should be explored.

3. If the Sponsor considers repeating the human abuse potential study to explore IN abuse of TRADENAME (Oxycodone HCl), the above described study design issues of K234-10-1002 should be addressed to support a "functional role" for the excipients, so that we can know whether deterrent effects derive from any excipient or any combination of two or three of them, and explores whether deterrent effects derive from the overall relative quantity or quality of crushed material or any of the excipients.

The following Executive Summary was extracted from Dr. Ling Chen's review (DARRTS, NDA 202080, Chen, Ling, Biometrics Review, 4-01-2011)

1. Executive Summary

Study K234-10-1002 in NDA 202080 was a randomized, double-blind, active-controlled crossover study to evaluate the relative abuse potential and safety of intranasally administered crushed Acurox® Tablets in comparison with crushed Roxicodone Tablets in non-dependent recreational opioid users.

There were two treatments in the study. These treatments were 2 crushed Acurox® Tablets each containing oxycodone HCl 7.5 mg, and 3 crushed Roxicodone® Tablets each containing oxycodone HCl 5 mg. The primary abuse potential measure was Drug Liking on the visual analog scale (VAS). Overall Drug Liking VAS and Take Drug Again VAS were considered as secondary measures. All measures were on a bipolar scale.

After Naloxone Challenge Phase (ensuring that subjects were not physically dependent on opioids) and Drug Discrimination Phase (ensuring that subjects could differentiate between intranasally self-administered crushed Roxicodone® Tablets 15 mg and placebo (weight-equivalent crushed Lactose tablets)), 40 eligible subjects were enrolled in the Treatment Phase and completed the study as planned.

Because 2 crushed Acurox® Tablets (weight 980 mg) had more than 3 times the weight of 3 crushed Roxicodone® Tablets (weight 300 mg), the study was not truly blind to opioid users. Serious sequence effects were found in this study. Thus, only data collected in the first period were used in this reviewer's analysis.

The reviewer's analysis showed that for crushed Acurox® Tablets, 11 subjects (>50%) had scores 90 to 100 for Emax of Drug Liking VAS. For Overall Drug Liking VAS and Take Drug Again VAS, 40% of subjects had scores between 90 and 100. In addition, 65%, 55% and 45% of subjects in Acurox® group had scores 80 or above for Emax of Drug Liking VAS, Overall Drug Liking VAS, and Take Drug Again VAS, respectively. Even though these percentages were similar to or lower than those of crushed Roxicodone® Tablets, the median response of crushed Acurox® Tablets was not significantly lower than that of crushed Roxicodone® Tablets in the Wilcoxon-Mann-Witney test for the primary and secondary measures based on data from the first period.

In conclusion, the study did not demonstrate that Acurox® Tablets have a lower abuse potential than Roxicodone® Tablets when crushed and administered intranasally to non-dependent recreational opioid users.

Analysis of the data collected in Study K234-10-1002 indicates that a serious sequence effect was observed. More subjects gave lower Drug Liking scores to crushed Oxecta tablets when taken intranasally in the second period than in the first period (See DARRTS, NDA 202080, Chen, Ling, Biometrics Review, 4-01-2011). Due to the sequence effects, the FDA statisticians only included data from the first period in the analysis. The reasons for causing the sequence effect are not known, however, it might be related to the weight differences between crushed Roxicodone (positive

control in the study) and crushed Oxecta; or because subjects were unblinded due to their previous knowledge that one of the treatments was potentially irritating as explained in the informed consent form. The Biometrics review reports that when considering data from the first period, the median response of crushed Oxecta tablets was not significantly lower than that of crushed Roxicodone tablets in the Wilcoxon-Mann-Witney test for the primary and secondary measures.

The following data Table (Table 19) has been extracted from the Sponsor's submission dated June 10, 2011, Rationale for Revisions to Section 9.2 Abuse Liability located in the EDR.,

Table 19. Summary of Mean (SD) Primary Endpoint Results by Treatment Sequence – Evaluable Population (N = 39)

Parameter		Mean (SD)		
Sequence	N	Acurox® Tablets N = 39	Roxicodone® Tablets N = 39	P-value
Drug Liking VAS E_{max}				
Acurox® Tablets followed by Roxicodone® Tablets	19	80.9 (25.2)	96.8 (6.9)	0.0130
Roxicodone® Tablets followed by Acurox® Tablets	20	60.8 (28.3)	90.2 (14.4)	0.0008
Overall Drug Liking VAS E_{8h}				
Acurox® Tablets followed by Roxicodone® Tablets	19	62.8 (36.8)	95.2 (8.9)	0.0018
Roxicodone® tablets followed by Acurox® Tablets	20	32.9 (32.2)	79.6 (24.0)	0.0005
Take Drug Again VAS E_{8h}				
Acurox® Tablets followed by Roxicodone® Tablets	19	61.3 (42.1)	96.8 (7.5)	0.0022
Roxicodone® Tablets followed by Acurox® Tablets	20	30.4 (40.8)	85.8 (25.1)	0.0002

E_{max} = maximum effect or greatest liking; E_{8h} = effect at 8 hours; SD = standard deviation; VAS = visual analogue scale.
Mean differences were tested by paired t-test.
Abstracted from: Table 14.2.2.6

Table 19 shows that the mean values for the primary measure, Drug Liking, reported by subjects receiving Oxecta first was 80.9 with a standard deviation of 25.2, whereas for subjects taking Roxicodone tablets first the mean value was 90.2 with a standard deviation of 14.4. The mean values for Take Drug Again reported by subjects receiving Oxecta first was 61.3 with a standard deviation of 42.1, whereas the mean reported value for subjects receiving Roxicodone first was of 85.8 with a standard deviation of 25.1 in a bipolar Take Drug Again VAS scale measured 8 hours after drug administration.

CSS 's Conclusions and Recommendation

The proposed label submitted by the Sponsor on June, 10 2011, has addressed two out of three of CSS's recommendations, (b) (4) As pointed out by CSS reviewers and accepted by the Sponsor, in vitro studies did not provide a definitive answer to this point. In

addition, the currently proposed label does not include unsubstantiated claims (b) (4) [redacted] Thus, the main unresolved labeling issue is related to CSS's recommendation to (b) (4) [redacted]

Research in the area of abuse potential assessment indicates that a drug of known abuse potential shows on average a 15 point difference in a bipolar scale for drug liking when compared to placebo, depending on the drug class and dose of the tested drug.[4] However, there is a lack of data that indicate what would constitute a clinically meaningful difference in drug liking when comparing the liking effects of (b) (4) [redacted] abuse deterrent formulations of the same drug of abuse and taken in equal doses. Research in this area to correlate differences in drug liking and other measures with postmarketing data indicative of incremental improvements in decreasing opioid pharmaceutical abuse is much needed.

The difference of means between the Oxecta and immediate release oxycodone tablet is of the order of 10 points for the Drug Liking VAS and 24 points for the Take Drug Again VAS, representing a 20 % and 49 % difference for their respective measures. These differences coupled with the fact that subjects in the abuse potential study failed to take the whole dose of Oxecta might be indicative of a meaningful difference between the Oxecta and Roxicodone formulations. These differences may be attributed to reported blockage of the nasal passages and that the intranasal intake of Oxecta was associated with a higher incidence of facial and oropharingeal discomfort. Thus, inclusion of this information in the label is acceptable.

Considering the review issues summarized above:

1) I agree that general and descriptive language under the *Drug Abuse and Dependence* section is acceptable if qualified by the statement that the clinical significance of the difference in drug liking and difference in response to taking the drug again reported in this study has not yet been established and that there is no evidence that Oxecta has a reduced abuse liability compared to immediate-release oxycodone.

Thus, I agree that it is acceptable for the label to point to the numerical differences in the mean and median observed in the Drug Liking VAS and the Take Drug Again VAS between Oxecta and immediate release oxycodone tablets.

2) I also agree with the following language as proposed by DAAAP and acceptable to the Sponsor (see EDR NDA 202080, Draft labeling,submission, 6-17-2011), because the statement does not claim tha (b) (4) [redacted] and because it

[4] Millovan, D. *et al*., 2009, CPDD 71st Annual Meeting, http://www.cpdd.vcu.edu/Pages/Meetings/CPDD09AbstractBook.pdf

addresses differences observed in the Drug Liking and Take Drug Again scales in the clinical context:

> In a double-blind, active-comparator, crossover study in 40 non-dependent recreational opioid users, "drug liking" responses and single-dose safety of crushed OXECTA tablets were compared with crushed immediate-release Oxycodone tablets when subjects self-administered the drug intranasally. The presence of sequence effects resulted in questionable reliability of the second period data. First period data demonstrated small numeric differences in the median and mean drug liking scores, lower in response to OXECTA than immediate-release oxycodone. Thirty percent of subjects exposed to OXECTA responded that they would not take the drug again compared to 5% of subjects exposed to immediate-release oxycodone. Study subjects self-administering OXECTA reported a higher incidence of nasopharyngeal and facial adverse events and a decreased ability to completely insufflate two crushed tablets within a fixed time period (21 of 40 subjects). The clinical significance of the difference in drug liking and difference in response to taking the drug again reported in this study has not yet been established. There is no evidence that OXECTA has a reduced abuse liability compared to immediate-release oxycodone.

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/s/

SILVIA N CALDERON
06/17/2011

MICHAEL KLEIN
06/17/2011

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: An epidemiological study to address whether this formulation of Oxycodone HCl results in a decrease in misuse and abuse, and their consequences: overdose, death and addiction.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	09-2012
Study/Trial Completion:	09/2015
Final Report Submission:	06/2016
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Formulation purported to be abuse deterrent - this is a concept that can only be tested once the product is on the market.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

An epidemiological study to address whether this formulation of Oxycodone HCl results in a decrease in misuse and abuse, and their consequences: overdose, death and addiction.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An epidemiological study to address whether this formulation of Oxycodone HCl results in a decrease in misuse and abuse, and their consequences: overdose, death and addiction.

Required

☒ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☐ Has the applicant adequately justified the choice of schedule milestone dates?
☐ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

SHARON H HERTZ
06/17/2011

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

DATE: June 10, 2011

TO: Bob Rappaport, M.D.
Director
Division of Anesthesia, Analgesic and Addiction Products(DAAAP)
Office of Drug Evaluation II

Chandrahas Sahajwalla, Ph.D.
Director,
Division of Clinical Pharmacology II (DCPII)

FROM: Arindam Dasgupta, Ph.D., Staff Fellow
Abhijit Raha, Ph.D., Pharmacologist
GLP & Bioequivalence Investigations Branch
Office of Scientific Investigations

THROUGH: Martin K. Yau, Ph.D.
Acting Team Leader – Bioequivalence
GLP & Bioequivalence Investigations Branch
Office of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 202080, Oxycodone HCl 5 and 7.5 mg sponsored by King Pharmaceuticals

At the request of the DAAAP, Office of New Drugs (OND), OSI (formerly DSI) audited the clinical and analytical portions of the following bioequivalence (BE) study.

OSI previously provided our evaluation of inspectional findings at the bioanalytical site for this study. This addendum evaluates the inspectional findings **(Attachment 1)** at the clinical site inspection, conducted at Worldwide Clinical Trials Drug Developments Solutions CRS (formerly CEDRA Clinical Research LLC), San Antonio, TX between 6/07 and 6/10/2011. We describe the firm's verbal response at the close of the inspection, and we will update this evaluation to report their written response when we receive it.

Study Number: AP-ADD-100

Study Title: "A single dose, 3-period, open-label, randomized, 3-treatment, 3-way crossover pharmacokinetic comparison between Acurox® 2 x 7.5 mg/30 mg Tablets and Acurox® DD 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"

Clinical Site: Worldwide Clinical Trials Drug Development Solutions CRS (formerly CEDRA Clinical Research LLC), San Antonio, Texas

OBSERVATION 1

> **An investigation was not conducted in accordance with the investigational plan. Respiration rates were not recorded at several times after dosing with naloxone or oxycodone. (See Attachment 1 for specific examples.)**

Although there were no indications of significant sequelae for these subjects, the firm should correct their practices to protect human subject safety during future studies.

In addition, the inspection revealed a number of time deviations in blood sampling **(See Attachment 2)**. The biopharmaceutics reviewer should evaluate whether these deviations impact pharmacokinetic parameters.

Worldwide Clinical Trials acknowledged the finding and promised corrective action.

Conclusion:

Following the above inspection, the Office of Scientific Investigations recommends that the clinical data of study **AP-ADD-100** can be accepted for Agency review.

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

Arindam Dasgupta, Ph.D.

Abhijit Raha, Ph.D.

Final Classification:

Clinical

Worldwide Clinical Trials Drug Development Solutions (formerly CEDRA Clinical Research LLC), San Antonio, TX – VAI

cc: DARRTS
OND/ODEII/DAAAP/Rappaport/Lisa Basham
OTS/OCP/DCPII/Sahajwalla/Suresh Naraharisetti

OC/OSI/Haidar/Ball/Dasgupta/Raha/Yau/Dejernett
SW-FO/DAL-DO/INV/Ngai/Martinez

cc: email
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Draft: AD AR 06/10/2011
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Attachment 1

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Attachment 2

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/s/

ARINDAM DASGUPTA
06/10/2011

ABHIJIT RAHA
06/10/2011

MICHAEL F SKELLY
06/10/2011
on behalf of Martin K. Yau, Ph.D.

MEMORANDUM

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

DATE: June 03, 2011

TO: Bob Rappaport, M.D.
Director
Division of Anesthesia, Analgesic and Addiction Products(DAAAP)
Office of Drug Evaluation II

Chandrahas Sahajwalla, Ph.D.
Director,
Division of Clinical Pharmacology II (DCPII)

FROM: Arindam Dasgupta, Ph.D., Staff Fellow
Abhijit Raha, Ph.D., Pharmacologist
GLP & Bioequivalence Branch
Division of Scientific Investigations

THROUGH: Sam. H. Haidar, Ph.D., R.Ph.
Chief, GLP and Bioequivalence Branch
Division of scientific Investigations

Martin K. Yau, Ph.D.
Acting Team Leader – Bioequivalence
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Division of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 202080, Oxycodone HCl 5 and 7.5 mg sponsored by King Pharmaceuticals

At the request of the Division of Anesthesia, Analgesic and Addiction Products (DAAAP), Office of New Drugs (OND), the Division of Scientific Investigations (DSI) audited the analytical portion of the following bioequivalence (BE) study.

Study Number: AP-ADD-100 ((b) (4) Study #0242491)

Study Title: "A single dose, 3-period, open-label, randomized, 3-treatment, 3-way crossover pharmacokinetic comparison between Acurox® 2 x 7.5 mg/30 mg

Tablets and Acurox® DD 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"

The audit of the analytical portion of this study was [redacted] (b) (4) Following inspection of the analytical site (May 9-18, 2011), Form FDA-483 was issued (**Attachment 1**). DSI is yet to receive the firm's written response to the inspectional findings. **Please note that the audit of the clinical portion of the study has been postponed (see attached email, Attachment 2).** Our evaluation of the inspectional findings of the clinical site inspection will be provided after audit of the clinical portion of the study.

The Form FDA-483 observations for study AP-ADD-100 (analytical), firm's response during the inspection and our evaluations follow:

Analytical Site: [redacted] (b) (4)

1. Samples from m[redacted]nalytical runs for oxycodone (5 of 16 runs in [redacted] (b) (4) study 0242491 were injected in advance of acquir[redacted]inal reported data of the analytical runs. [redacted] (b) (4) SOP PS-104 (revision 4) at the time the study was conducted failed to describe selection, evaluation, and reporting of 'pre-injection samples'.

Although, t[redacted]les used for pre-injection were not pre-defined in [redacted] (b) (4) SOP PS-104, audit of both paper and electronic [redacted]records revealed that the samples injected prior to the actual analytical run were usually the eight calibration curve standards, one blank, and one low QC sample processed in the actual run. No actual study samples were used as pre-injection samples and pre-injections did not occur in every analytical run; only about 31.25 % of the analytical runs had pre-injection samples. Moreover, audit trails of [redacted]re-injection and analytical runs were maintained by [redacted] (b) (4) and were audited

during the inspection. DSI found that selection or changes to automatic integration parameters during the "pre-injection run" did not bias run acceptance. Thus the above observation should not impact study outcome.

(b) (4) acknowledged the findings. Since the completion of AP-ADD-100, an SOP for the selection of pre-injection samples was implemented. As per the new SOP, a batch of samples independent of the study batch is prepared and processed to be used for pre-injection and instrument stabilization.

2. Failure to document all aspects of study conduct:

Specifically, documentation for individual calibrator and Quality Control (QC) sets used in oxycodone study 0242491 during sample processing were not maintained. QC samples were not uniquely identified and tracked along with samples from study 0242491.

(b) (4) acknowledged the observation and stated that since t 2010, individual calibrators and QCs are uniquely identified and tracked along with study samples.

The above finding is not likely to impact outcome of the current study.

Conclusion:

Following the above inspection, the Division of Scientific Investigations recommends that the analytical data of study 0242491 can be accepted for Agency review.

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

Arindam Dasgupta, Ph.D.

Abhijit Raha, Ph.D.

Final Classification:

Analytical

(b) (4)

cc: DARRTS
OND/ODEII/DAAAP/Rappaport/Lisa Basham
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Draft: AD AR 06/03/2011
Edits: MKY 06/03/2011; MFS 06/03/2011; SHH 06/03/2011
DSI: 6175; O:\BE\EIRCOVER\202080kin.oxy.doc
FACTS:1262952

Attachment 1

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Attachment 2

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/s/

ARINDAM DASGUPTA
06/03/2011

MARTIN K YAU
06/03/2011

SAM H HAIDAR
06/03/2011

505(b)(2) ASSESSMENT

Application Information		
NDA # 202080	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Oxecta (review pending) Established/Proper Name: Oxycodone Hydrochloride Dosage Form: Tablets Strengths: 5 & 7.5 mg		
Applicant: King (Pfizer)		
Date of Receipt: December 17, 2010		
PDUFA Goal Date: June 17, 2011	Action Goal Date (if different):	
Proposed Indication(s): management of moderate to severe pain when use of an opioid analgesic is appropriate		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 021011 Roxicodone	Previous findings of safety and effectiveness
Published Literature	Nonclinical data to qualify excipients

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Applicant bridged the proposed Oxycodone HCl Tablets with the reference product, Roxicodone Tablets by submitting the data from a Bioequivalence study. The study evaluated the Bioequivalence between Oxycodone HCl Tablets (2 x 7.5 mg) and Roxicodone Tablets (15 mg).

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☒

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Roxicodone (Xanodyne)	NDA 021011	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☒ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application: Roxicodone Tablets

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a change in the excipients that purportedly render that formulation abuse resistant. In addition, 7.5 mg is a new strength of Oxycodone HCl.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☒ NO ☐

*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☐
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES ☐ NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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/s/

LISA E BASHAM
05/31/2011

PARINDA JANI
05/31/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: May 25, 2011

To: Lisa Basham – Regulatory Project Manager
Division of Anesthesia, and Analgesia Products (DAAP)

From: Mathilda Fienkeng – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments**
NDA 202080 Oxycodone Hydrochloride tablets CII

DDMAC has reviewed the proposed product labeling (PI), Carton and Container label for Oxycodone Hydrochloride tablets CII submitted for DDMAC review on February 23, 2010.

Comments regarding the proposed PI are provided directly on the updated proposed PI sent via email on May 13, 2011, by Lisa Basham. If you have any questions about DDMAC's comments, please do not hesitate to contact me at 301 796 3692 or Mathilda.fienkeng@fda.hhs.gov. .

Carton and Container Labeling

DDMAC is concerned about the prominence and disparate font styles of the trade name and established names in the presentations. We recommends revising the proposed established name on the carton labeling to be in accordance with 21 CFR 201.10 (g)(2) which states that, "[t]he established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features."

DDMAC notes that the carton labeling states that TRADENAME tablets, "are to be swallowed whole (b) (4) while the PI states, "TRADENAME tablets must be swallowed whole and is not amenable to crushing or dissolution." DDMAC recommends revising the carton labeling for consistency with the full PI.

18 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

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/s/

MATHILDA K FIENKENG
05/25/2011

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Controlled Substance Staff

Date: 05-24-11

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Addiction Products (DAAAP)

Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff (CSS)

From: Jovita Randall-Thompson, Ph.D., Pharmacologist, CSS
Stephen Sun, M.D., Medical Officer, CSS

Subject: Acurox (immediate-release oxycodone) NDA 20-2080
Indication: Treatment for the (b) (4) of moderate to severe pain when the use of an (b) (4) opioid analgesic tablet is appropriate
Dosages: Oxycodone hydrochloride immediate release 5 mg and 7.5 mg tablet
Sponsor: King Pharmaceuticals

Materials reviewed: NDA 20-2080 - Acurox, submission date of 12/17/2010 in the EDR
1) "Randomized, Double-Blind, Active-Controlled Study to Evaluate the Relative Abuse Potential and Safety of Intranasally Administered Crushed Acurox Tablets in Non-Dependent Recreational Opioid Users." (Study K234-10-1002, dated 11/04/2010) (\\cdsesub5\EVSPROD\NDA202080\0000\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\k234-10-1002)
2) "Report for the Demonstration of the Ability of Acurox® (oxycodone HCl, USP) Tablets to Resist Direct Conversion into an Injectable Solution" (Protocol PR-381, dated 10/21/2010) (\\cdsesub5\EVSPROD\NDA202080\\0000\m3\32-body-data\32p-drug-prod\acurox-tablet\32p2-pharm-dev\syringe-report-pr-381.pdf)
3) "Report for the Evaluation of the Potential for Extraction of Oxycodone HCl from Dissolved Acurox® (Oxycodone HCl, USP) Tablets for the Preparation of an Intravenous Solution Suitable for Injection in Humans" (Protocol PR-382, dated 10/11/2010) (\\cdsesub5\EVSPROD\NDA202080\\0000\m3\32-body-data\32p-drug-prod\acurox-tablet\32p2-pharm-dev\extraction-report-pr-382.pdf)
4) Division of Pulmonary, Allergy, and Rheumatology Products Medical Officer Consultation 03/02/2011 (DARRTS, 03/07/2011)
(http://darrts fda.gov:9602/darrts/ViewDocument?documentId=090140af8021a743)
5) Statistical Review and Evaluation, NDA 202080 - Acurox, Study K234-10-1002 (DARRTS, 04/01/2011)
(http://darrts fda.gov:9602/darrts/ViewDocument?documentId=090140af802207a3)

6) NDA 22-451- Acurox, submission date of 12/17/2010 in the EDR (12/30/2008), "A Phase I Single-Center, Single-Blind Study in Recreational Opioid Users to Evaluate the Safety, Tolerability and Pharmacokinetics of Crushed and Intranasally Administered Acurox® (oxycodone HCl and niacin) Tablets (Study *AP-ADF-106, 12/02/2008) (\\Cdsesub1\EVSPROD\NDA022451\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain\5354-other-stud-rep)*
7) Pre-NDA 202080 Meeting Package (06/11/10, paper copy), Pre-NDA 202080 Preliminary Responses, 09/23/2010 (http://darrts fda.gov:9602/darrts/ViewDocument?documentId=090140af801f47d4);
8) Pre-NDA 202080 Meeting Minutes 9/27/2010 (DARRTS, 11/05/2010) (http://darrts fda.gov:9602/darrts/ViewDocument?documentId=090140af801fffe6)
9) Filing Issues Identified 2/02/2011, NDA 202080 - Acurox (DARRTS, 2/02/2011) (http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af80215cf5)

Table of Contents

I. Summary

A. Background

The Division of Anesthesia, Analgesia and Addiction Products (DAAAP) consulted the Controlled Substance Staff (CSS) to review the NDA 202080, Acurox (TRADENAME (Oxycodone HCl)) (immediate release oxycodone tablets). The principle active pharmaceutical ingredient of TRADENAME (Oxycodone HCl) is oxycodone, a Schedule II opioid that has a significant abuse potential.[1,2,3] The proposed recommended dosage of TRADENAME (Oxycodone HCl) is one or two tablets of 5 mg or 7.5 mg oxycodone, taken every 6 hrs as needed.

Current FDA approved immediate release drugs containing oxycodone with therapeutic doses similar to those of TRADENAME (Oxycodone HCl) include Roxicodone® (Xanodyne Pharms), Percocet® (Endo) and Oxycodone HCl tablets (Mallinckrodt and various generics).

CSS reviewed the abuse liability of NDA 22-451 (Acurox) submitted 12/30/2008. This formulation contained 5 mg/30 mg or 7.5 mg/30 mg of oxycodone/niacin, and the excipients sodium lauryl sulfate (SLS), (b) (4), crospovidone NF and microcrystalline cellulose NF (b) ( ) The current formulation, renamed "TRADENAME (Oxycodone HCl)," (NDA 202080), is Acurox without niacin. (b) (4)

TRADENAME (Oxycodone HCl) tablets contain the following excipients: colloidal silicon dioxide NF, crospovidone NF, magnesium stearate, microcrystalline cellulose, polyethylene oxide and sodium lauryl sulfate. (b) (4) Though (b) ( ) is listed as a functional excipient in some parts of the NDA, it is not listed in others (see 3.2.P.2 Pharmaceutical Development, Extraction Report PR-382, pg. 9). TRADENAME (Oxycodone HCl) tablets (b) (4) . TRADENAME (Oxycodone HCl) tablets, however, do not (b) (4) The Sponsor offers that the

[1] Comer, S.D.; Sullivan, M.A.; Whittington, R.A.; Vosburg, S.K. and Kowalczyk, W.J. (2008) Abuse liability of prescription opioids compared to heroin in morphine-maintained heroin abusers. *Neuropsychopharmacology 33, 1179-1191.*

[2] Leri, F. and Burns, L. (2005). Ultra-low-dose naltrexone reduces the rewarding potency of oxycodone and relapse vulnerability in rats. *Pharmacology, Biochemistry and Behavior 82, 25 -262.*

[3] Zhang, Y.; Picettti, R.; Butelman, E.R.; Schlussman, S.D.; Ho, A. and Kreek, M.J. (2009). Behavioral and Neurochemical changes induced by oxycodone differ between adolescent and adult mice. *Neuropsychopharmacology (2009) 34, 912-922.*

"functional excipients" are impediments to IN and IV abuse (see Common Technical Document Summaries, 2.2 Introduction to Summary, pg 1).

To characterize [redacted] abuse deterrent properties of the TRADENAME (Oxycodone HCl) formulation the Sponsor conducted the following three experimental studies:

- Study PR-381 - "Report for the Demonstration of the Ability of Acurox [TRADENAME (Oxycodone HCl] Tablets to Resist Direct Conversion into an Injectable Solution"
- Study PR-382 - "Report for the Evaluation of the Potential for Extraction of Oxycodone HCl from Dissolved Acurox [TRADENAME (Oxycodone HCl)] Tablets for the Preparation of an Intravenous Solution Suitable for Injection in Humans"
- Study K234-10-1002 - "Randomized, Double-Blind, Active-Controlled Study to Evaluate the Relative Abuse Potential and Safety of Intranasally Administered Crushed Acurox [TRADENAME (Oxycodone HCl)] Tablets in Non-Dependent Recreational Opioid Users."

B. Conclusions

1. After reviewing PR-381 and PR-382 analytical lab bench-top studies, we consider the procedures and techniques to be incomplete in investigating and assessing the feasibility of preparing an injectable solution of TRADENAME (Oxycodone HCl). PR-381 and PR-382 did not examine the variables that increase dissolution and the yield of extractions: variables include reducing particle size of the sample, using solvents of different polarity and pHs and increasing temperatures. PR-381 did not examine use of agitation and mixing techniques in solubilization.
2. Testing of solvents for extraction was limited. PR-382 included eight extraction procedures and use of a wider array of solvents [redacted] and mixing techniques (i.e., [redacted]. Several common solvents that are often used in extraction studies were not examined. These include [redacted] These solvents are readily available in retail settings. Specific cutting or grinding methods used to prepare tablets for mixing was not provided.

   The relevance of developing an oxycodone immediate release formulation that might deter IV abuse should be considered in light of the fact that information in the public domain shows that the number of opioid users that intravenously abuse oxycodone immediate release products is very small and possibly nonexistent, depending on the geographic area examined,[4,5] relative to the most preferred route of administration by opioid users and addicts by the oral route, followed by the intranasal route.[4,5]

[4] Katz, N.P.; Adams, E.H.; Chilcoat, H.; Colucci, R.D.; Comer, S.D.; Goliber, P.; Grudzinskas, C.; Jasinski, D.; Lande,S.D.; Passik, S.D.; Schnoll, S.H; Sellers, E, Travers, D. ; Weiss, R (2007) . Challenges in the development of prescription opioid abuse-deterrent formulations. *Clin. J. Pain 23*, 648-660.

[5] Davis, W.R.; Johnson, B.D. Prescription opioid use, misuse, and diversion among street users in New York City (2008). *Drug and Alcohol Dependence 92*, 267-276.

3. Study K234-10-1002 suggests that a higher number of unique facial and oropharyngeal adverse events might be associated with IN use of TRADENAME (Oxycodone HCl) when compared to Roxicodone by the same route.
4. Although a higher incidence of adverse events related to oral and pharyngeal discomfort was observed in Study K234-10-1002 for subjects snorting TRADENAME (Oxycodone HCl), subjects still report liking TRADENAME (Oxycodone HCl). The significance of these findings in evaluating the IN abuse potential of the formulation is unknown.
5. It is difficult to assess if the potential deterrent properties of the formulation are related to the specific product composition, or if they are related to the number and amount of excipients in the formulation. Study K234-10-1002 was not designed to address the contribution of the individual excipients of the formulation in deterring IN abuse.
6. Data presented in the NDA do not support the inclusion of explicit language in the label related to the deterrent IN abuse, because Study K234-10-1002 was not designed to:
    a. Address whether it is the quality or the quantity of each or all of the excipients of the formulation that contributes to deterring IN abuse.

    b. Evaluate the effect of reducing the particle size of the sample and of longer snorting times. Subjects were given 5 minutes to snort crushed tablets. The question that still remains unanswered is, whether the study findings would remain the same if subjects were given either a sample with a smaller particle size or were given more than 5 minutes to snort the whole sample.
7. Study K234-10-1002 does not provide data that (b) (4) of TRADENAME (Oxycodone HCl). Study K234-10-1002 does not provide data to rule out the deterrent effects that might be associated with the weight and mass of the tablets. Each tablet of TRADENAME (Oxycodone HCl) contains 7.5 mg of oxycodone hydrochloride and 482.5 mg of mixed excipients (see 3.2.P.1 Description and Composition of the Drug Product: Table 3.2P.1-2, pg 2).

In summary, the deficiencies noted in the methodology and data collection from K234-10-1002 include the following:

a. Sequence effect halves the sample size (Differences in the crushed material weight or API/excipient concentration ratio between TRADENAME (Oxycodone HCl) and Roxicodone may have impacted blinding conditions such that participants during testing were able to identify one treatment from another)
b. High drop-out rate makes evaluation difficult
c. Potential unblinding of treatments causes bias
d. Validity of Subjected-Rated Scale for Nasal Effects is unknown
e. Selection and validity of measurements is uncertain
f. Concept of functional excipients is unknown

g. Crushed tablet consistency (particle size, uniformity, sample appearance) between TRADENAME (Oxycodone HCl) and Roxicodone was not verified
h. Difference in the weight/mass of crushed material and differences in excipient concentration between TRADENAME (Oxycodone HCl) and Roxicodone is not experimentally controlled in the study and thus may impact study results.

C. Recommendations

1. The Sponsor should consider conducting additional in-vitro and clinical studies that address and eliminate the study design deficiencies described above, to support specific formulation-related deterrent (b) (4) for IN or IV abuse.
2. A possible claim that TRADENAME (Oxycodone HCl) (b) (4) would need to be supported by an additional study that reassesses the physicochemical characteristics of TRADENAME (Oxycodone HCl). If a new in-vitro study were to be conducted, the following general principles should be considered:
   - Extraction studies should explore the effect of several experimental conditions known to affect dissolution. These experimental variables include: particle size, the use of solvents that explore a wide polarity and pH range, the effect of varying conditions of agitation, and the effect of increasing temperatures on extraction.
   - Suggested solvents may include (b) (4) Temperatures, extraction times and multi-step extraction procedures for tested solvents should be explored.
3. If the Sponsor considers repeating the human abuse potential study to explore IN abuse of TRADENAME (Oxycodone HCl), the above described study design issues of K234-10-1002 should be addressed to support a "functional role" for the excipients, so that we can know whether deterrent effects derive from any excipient or any combination of two or three of them, and explores whether deterrent effects derive from the overall relative quantity or quality of crushed material or any of the excipients.

CSS is available to review protocols prior to the start of in-vitro studies and clinical studies, if the Sponsor proposes to conduct studies to address the deficiencies described above.

D. Discussion

-In-vitro Data

Study PR-381 was intended to assess whether a suitable solution for injection could be obtained by simply dissolving crushed TRADENAME (Oxycodone HCl) in a solvent (b) (4) The objective of the study was to simulate a process for preparing a drug solution for human

IV injection from TRADENAME (Oxycodone HCl) in comparison to generic oxycodone hydrochloride tablets.

(b) (4)

instead of generic oxycodone. Thus, TRADENAME (Oxycodone HCl) may be less attractive for IV abuse than Roxicodone assuming that the study captures the behavior of street IV drug abusers.

Study PR-381 did not evaluate the effect of decreasing the particle size of the sample

(b) (4)

(b) (4)

The objective of Study PR-382 was to measure the ease of extracting oxycodone from a tablet into a solution suitable for injection, and to provide expert opinion (from a chemist

(b) (4)

Study PR-382 results included the *extraction time*, in addition to *a rating of difficulty to obtain extraction materials* (1 = readily available, 10 = difficult to obtain) and *a rating of relative difficulty to extract oxycodone* (1 = easy to an untrained person, 10 complex and requires a trained chemist).

Results summarized in tables (Study PR-382, Table 4.1 and 4.2) submitted by the Sponsor illustrated that when attempting to extract oxycodone from 8 TRADENAME (Oxycodone HCl) tablets (supposedly whole, halved and grinded, though not clearly described in the study report) (b) (4)

Though some of the findings are questionable, this Study seems to show that it is easier to obtain a solution for injection when using Roxicodone tablets (generic oxycodone tablets) than when using TRADENAME (Oxycodone HCl). In addition, this study does not rule out the possibility that a solution for injection from TRADENAME (Oxycodone HCl) could be obtained.

The Sponsor's goal was to demonstrate that TRADENAME (Oxycodone HCl) is resistant to extraction methods used to extract oxycodone relative to a generic oxycodone product (Roxicodone) which has no resistant properties, and that TRADENAME (Oxycodone HCl) potentially is less likely abused by the IV route. TRADENAME (Oxycodone HCl) (b) (4), a possible advantage over the generic oxycodone

formulation. However, the findings reported in Study PR 382 do not characterize the magnitude or degree of the resistance or confirm results.

- Clinical Data

Study K234-10-1002 is intended to show the potential for abuse of crushed Acurox tablets when taken intranasally.

The study objectives were to compare the relative abuse potential of crushed Acurox® Tablets with crushed Roxicodone® tablets when administered IN to non-dependent recreational opioid users, and to evaluate the single-dose safety of crushed and IN administered Acurox® Tablets in non-dependent recreational opioid abusers. Study was conducted by an independent company (b) (4) and performed at a single, inpatient study facility.

Results for Study K234-10-1002 included three primary assessments: *Drug Liking*, *Take Drug Again Assessment* (TDAA), and *Global Assessment of Overall Drug Liking* scores. A bipolar-VAS scale of 0 to 100 was used (0: "strong dislike" or "definitely not", 100: "strong like" or "definitely so", 50: neutral). An *adverse event nasal scoring* system based on a 6-point scale (0: no problem, 5: as bad as it can be) was also offered to participants to assess the nasal tolerability of the drug.

The Sponsor grouped excipients (b) (4) Individual contributions as functional excipients are not described and, the term "functional excipient" is not fully characterized and defined by the Sponsor. There is a discrepancy in the listing of "functional excipients," in various parts of the NDA. The general Summary section includes (b) (4) in the "functional excipients" group whereas in section 3.2.P2 Pharmaceutical Development, Extraction Report PR-382, Page 9, (b) (4) is not included.

Study K234-10-1002 shows a decrease in the abuse potential of intranasally administered TRADENAME (Oxycodone HCl), but it remains unclear whether it is a result of the weight/volume and the excipient to API ratios of the TRADENAME (Oxycodone HCl) formulation or due to the inclusion of (b) (4) or any of the other specific excipients and its (b) (4).

Differences in the weight and volume of TRADENAME (Oxycodone HCl) crushed material is greatly (~3 times more) different when compared to the weight and volume of crushed material of the positive control, Roxicodone.

Differences in excipient to API ratios were not considered or factored into the methodology of the study and possibly caused a dilution effect.

Differences in the crushed material weight or API/excipient ratio between TRADENAME (Oxycodone HCl) and Roxicodone may have impacted blinding conditions such that participants during testing were able to identify one treatment from another. This confound may be reflected by the sequence effect, which was revealed when analyzing data.

Specifically, analysis of data (including scores of Drug liking, Overall Drug Liking and Take Drug again) revealed a sequence effect, between Treatment Day 5 and Treatment

Day 7, with those subjects given TRADENAME (Oxycodone HCl) on Treatment Day 5 demonstrating higher Emax scores than those subjects given TRADENAME (Oxycodone HCl) on Treatment Day 5.

As a result, data was reanalyzed using Treatment Day 5 scores only. A Wilcoxon-Mann-Witney Test was conducted, comparing Day 5 scores for TRADENAME (Oxycodone HCl) to Day 5 scores for Roxicodone.

Statistical comparisons revealed no significant differences between TRADENAME (Oxycodone HCl) and Roxicodone for Drug Liking, Overall Drug Liking and Take Drug again subjective measures (See DARRTS, NDA 202080, Ling Chen, Biometrics Review, 4/01/11).

As indicated, in Study K234-10-1002, 53% (N = 21) of the 40 participants did not completely intranasally administer crushed TRADENAME (Oxycodone HCl) (2 tablets in the 5 minutes given, 7.5 mg/tablet) (see. Study Report K234-10-1002, page 63 -64). Based upon this study design, it is unclear whether the methodology of the study is flawed due to a high drop-out rate with a low sample size for comparison against a positive control or is an indication of the deterrent's effectiveness resulting in study subject intolerability to complete the dose in the given time. If it is the latter, inability to self-administer an "abusable" active ingredient due to intolerability is a possible scientific finding consistent with a formulation that is intended to be abuse-deterrent.

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/s/

JOVITA F RANDALL-THOMPSON
05/24/2011

STEPHEN W SUN
05/24/2011

SILVIA N CALDERON
05/24/2011

MICHAEL KLEIN
05/24/2011

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

Date:	April 8, 2011
Application Type/Number:	NDA 202080
To:	Bob Rappaport, MD Director, Division of Anesthesia and Analgesia Products (DAAP)
Through:	Melina Griffis, RPh, Team Leader Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Jamie Wilkins Parker, Pharm.D., Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name(s) & Strengths:	Acurox (Oxycodone HCl) Tablets, 5 mg and 7.5 mg
Applicant/sponsor:	King Pharmaceuticals, Inc.
OSE RCM #:	2011-72

CONTENTS

1 INTRODUCTION

This review evaluates the revised labels and labeling for Acurox (Oxycodone HCl) Tablets, submitted December 17, 2010 in response to previous DMEPA recommendations (see OSE Review #2008-1716).

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis (FMEA),[1] and principles of human factors, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the revised container labels, and insert labeling submitted by the applicant as part of an NDA amendment. See Appendix A for images of proposed container labels. We also evaluated our recommendations made in OSE Review #2008-1716.

3 CONCLUSION AND RECOMMENDATIONS

The Applicant has revised the labeling to incorporate all of the previous recommendations provided by DMEPA, however there are additional areas of needed improvement in order to minimize the potential of mediation errors. We request the recommendations for the container labels in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Danyal Chaudhry, at 301-796-3813.

3.1 COMMENTS TO THE DIVISION

We have the following recommendations for changes to the proposed package insert:

A. Comments on the Prescribing Information:

1. Patient Counseling Information

a. The statement [redacted] (b) (4) should be changed to read "ACUROX tablets must be swallowed whole (not crushed, dissolved, broken or chewed)" to remain consistent with container labels and provide a positive statement.

3.2 COMMENTS TO THE APPLICANT

1. Acurox Container Label (All Strengths)

a. Revise your established name presentation to be in accordance with 21 CFR 201.10(g)(2) which states "The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate which such proprietary name or designation appears taking into account all pertinent factors, including typography, layout, contrast and other printing features."

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

b. Although you utilize a blue and yellow color on the top of your labels the different strengths appear in the same black font. To ensure adequate differentiation between the two strengths, we request the blue and yellow color be utilized in conjunction with the strength presentation statement (5 mg and 7.5 mg) on the principal display panel. Ensure the strength is presented in a color that will be legible against the colored background.

c. Decrease the prominence of the King Pharmaceuticals symbol, so that it does not compete with the prominence of the proprietary name, established name, or strength presentation.

d. Relocate the phrase "Acurox tablets are to be swallowed whole (b) (4) (b) (4) to the principal display panel, to increase the prominence of this important statement.

e. Unbold the text of the Rx Only and container size statements.

f. Reduce the size of the graphic above the proprietary name so that it does not compete with its prominence.

1 page of draft labeling has been withheld in full as CI/TS immediately following this page

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

/s/

JAMIE C WILKINS PARKER
04/08/2011

MELINA N GRIFFIS
04/11/2011

CAROL A HOLQUIST
04/11/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 202080 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Acurox Established/Proper Name: Oxycodone Hydrochloride Tablets Dosage Form: Tablets Strengths: 5 mg & 7.5 mg		
Applicant: King (Pfizer) Agent for Applicant (if applicable):		
Date of Application: December 17, 2010 Date of Receipt: December 17, 2010 Date clock started after UN:		
PDUFA Goal Date: June 17, 2010	Action Goal Date (if different):	
Filing Date: February 15, 2011	Date of Filing Meeting: February 2, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): management of moderate to severe pain where use of an opioid analgesic is appropriate		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s):	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☐ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***		X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:		X		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	**X**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	X			

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*: 1/4/11			**X**	**Schedule II opioid**

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		X		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?				

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***				
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***				
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?[4]	X			

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☐ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	X			
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	X			
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	X			
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	X			
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	X			DSI BE audit request 1-6-11
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***			X	

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 9/17/11 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 2-1-11

NDA #: 202080

PROPRIETARY NAME: Acurox

ESTABLISHED/PROPER NAME: Oxycodone Hydrochloride

DOSAGE FORM/STRENGTH: Tablets, 5 mg & 7.5 mg

APPLICANT: King (Pfizer)

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): management of moderate to severe pain where the use of an opioid analgesic is appropriate

BACKGROUND: Purportedly abuse-deterrent formulation of IR oxycodone. Formulation contains SLS (b) (4). Prior efforts by the company include Acurox with Niacin (NDA 022451) which possessed the above attributes as well as contained niacin which was intended to cause flushing when the product is taken in excess of the recommended dose. Issues with the niacin component (flushing can be mitigated with food, and flushing occurred in patients) caused the sponsor to propose a formulation without niacin. This is that formulation.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Lisa Basham	Y
	CPMS/TL:	Parinda Jani	N
Cross-Discipline Team Leader (CDTL)	Robert Shibuya		Y
Clinical	Reviewer:	Frank Pucino	Y
	TL:	Rob Shibuya	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		

Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Suresh Naraharisetti	Y
	TL:	Suresh Doddapaneni	Y
Biostatistics	Reviewer:	Katherine Meaker	Y
	TL:	Dionne Price	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jay Chang	Y
	TL:	Adam Wasserman	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Julia Pinto (Danae Christodoulou covered filing)	Y
	TL:	Prasad Peri	Y
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		N
	TL:		N
OSE/DMEPA (proprietary name)	Reviewer:	Anne Crandall	N
	TL:		N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		N
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	Jovita Randall-Thompson	Y
	TL:	Silvia Calderon	Y
Other reviewers DMEPA C&C CSS Stats CMC Biopharm DPV/OSE DDMAC	 Anne Crandall/Melina Griffis Ling Chen/Yi Tsong Houda Mahayni Alex Winiarski/Lauron Choi Mathilda Fienkeng		 N/N Y/N Y N/Y N
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**:	☐ YES Date if known: ☒ NO ☐ To be determined

If no, for an original NME or BLA application, include the reason. For example: o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	Reason:
• Abuse Liability/Potential **Comments**: Issues with studies to evaluate abuse-deterrence. Will request DSI inspection of study sites	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	☐ Not Applicable ☒ FILE

Comments:	☐ REFUSE TO FILE ☒ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: TDB (Division level) **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☐ Standard Review ☒ Priority Review
ACTIONS ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☒	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

	• notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

LISA E BASHAM
03/07/2011

PARINDA JANI
03/07/2011

DIVISION OF PULMONARY, ALLERGY, and RHEUMATOLOGY PRODUCTS MEDICAL OFFICER CONSULTATION

Date:	March 2, 2011
To:	Corinne P. Moody, Science Policy Analyst – Controlled Substance Staff
From:	Sofia Chaudhry, MD, Medical Officer
Through:	Susan Limb, MD, Medical Team Leader
Through:	Badrul Chowdhury, MD, PhD, Division Director
Subject:	Assessment and validity of nasal toxicity measures and the known effects of sodium lauryl sulfate on the respiratory tract.

General Information

NDA/IND#:	NDA 202080
Sponsor:	King Pharmaceuticals Research Development, Inc.
Drug Product:	Acurox® (Immediate Release Oxycodone without Niacin)
Request From:	Corinne P Moody, Science Policy Analyst – Controlled Substance Staff
Date of Request:	February 18, 2011
Date Received:	February 18, 2011
Materials Reviewed:	NDA 202080 Sections: 2.4, 2.5, 2.7, 5.2, 5.3.4.1,

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Executive Summary

This is a medical officer review in response to a consultation request from the Controlled Substance Staff (CSS) regarding Acurox®, an oral immediate release (IR) oxycodone HCL product. This formulation of IR oxycodone is unique as it specifically includes excipients to discourage potential intravenous and intranasal abuse. CSS has consulted DPARP with questions regarding the assessment and validity of measuring nasal irritation, as well as a request for any information about the known effects of sodium lauryl sulfate (SLS) on the respiratory tract.

Introduction

Acurox®, IR oxycodone HCL with niacin, was initially submitted to the Agency under NDA 022451 on December 30, 2008. Niacin was included in this immediate release opioid product to induce flushing and warmth thereby discouraging abuse. However, the Agency felt the evidence to support the opioid abuse deterrence effect of niacin was insufficient to offset the presence of adverse events related to niacin in patients being treated for pain. A complete response letter detailing this was sent on June 30, 2009.

The sponsor has subsequently submitted NDA 202080 for a new Acurox® product, IR oxycodone without niacin, for priority review by the Agency. Priority review was

requested based on the need for opioid products that deter abuse and misuse. The NDA is submitted under section 505(b)(2) with Roxicodone® as the reference listed drug. The sponsor is proposing two dosage strengths: 5 mg and 7.5 mg. In addition to the active ingredient, oxycodone, Acurox® contains the following excipients.

Table 1: Acurox® Tablet Excipients

Excipient Name	**Quantity (mg) base on a daily dose of 16 Acurox® tablets**
Microcrystalline Cellulose, NF	(b) (4)
Crospovidone, NF	
Polyethylene Oxide, NF	
Sodium Lauryl Sulfate, NF	
Colloidal Silicon Dioxide, NF	
Magnesium Stearate, NF	

Data obtained from Section 2.4 Nonclinical Overview of NDA 202080

For comparison, 5 mg Roxicodone® tablets contain two excipients: microcrystalline cellulose and stearic acid.

The sponsor has included certain excipients to deter abuse and misuse. (b) (4)

(b) (4)

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Referen

Trial K234-10-1002: Intranasal administration of crushed Acurox® tablets

The sponsor has conducted a single randomized, double-blind, active control trial to evaluate the relative abuse potential and safety of intranasally administered crushed Acurox® tablets (K234-10-1002).

After the initial screening and naloxone challenge, subjects underwent a double-blind drug discrimination test to ensure their ability to differentiate between intranasal crushed Roxicodone® and placebo. This was followed by a treatment phase where subjects were sequentially administered 2 crushed 7.5 mg Acurox® tablets (15 mg oxycodone HCL) or 3 crushed 5 mg Roxicodone® tablets (15 mg oxycodone HCL). Following a 48 hour washout period, the other treatment was administered. No placebo dose was incorporated into this phase of the trial, so the effects of the excipients without oxycodone HCL remain unknown. Forty eligible healthy subjects were enrolled in the treatment phase and completed the trial as planned.

Nasal effects were rated by subjects using the 6-point Subject Rated Scale

- 1 = very mild problem
- 2 = mild/slight problem
- 3 = moderate problem
- 4 = severe problem
- 5 = problem "as bad as can be"

On the following 5 categories:

- Burning
- Need to blow nose
- Runny nose/nasal discharge
- Facial pain/pressure
- Nasal congestion

At the following times:

- Pre-dose
- 0.5 hour
- 1 hour
- 2 hour
- 4 hour

Using the results from the subject rated scale, the sponsor calculated the maximum effect (E_{max}), time to maximum effect (T_{Emax}),and the area under the effect curve from 0 to x hours post dose (AUE_{0-xh}).

Table 2: Subject-Related Scale for Nasal Effects Assessments

Endpoint	**Crushed Acurox® Mean N = 39**	**Crushed Roxicodone® Mean N = 39**	**LS-mean Difference**	**P-value**
Burning				
E_{max}	1.5	0.2	1.3	<0.0001
T_{emax} (hours)	0.4	0.5	-0.03	0.0769
AUE_{0-1h}	0.7	0.1	0.6	<0.0001
AUE_{0-2h}	1.2	0.2	0.9	0.0004
AUE_{0-4h}	1.3	0.3	1.0	0.0080
Facial Pain Pressure				
E_{max}	0.6	0.1	0.3	0.1234
T_{emax} (hours)	0.4	0.5	-0.02	1.159
AUE_{0-1h}	0.2	0.1	0.2	1.1523
AUE_{0-2h}	0.5	0.1	0.2	0.3464
AUE_{0-4h}	0.5	0.3	0.1	0.6949
Nasal Congestion				
E_{max}	2.4	0.3	2.1	<0.0001
T_{emax} (hours)	0.4	0.5	-0.03	0.0923
AUE_{0-1h}	1.3	0.1	1.1	<0.0001
AUE_{0-2h}	2.2	0.3	1.8	<0.0001
AUE_{0-4h}	2.6	0.5	2.0	0.0001
Need to Blow Nose				
E_{max}	2.0	0.2	1.8	<0.0001
T_{emax} (hours)	0.5	0.5	-0.1	0.5295
AUE_{0-1h}	1.0	0.1	0.9	<0.0001
AUE_{0-2h}	1.6	0.2	1.5	<0.0001
AUE_{0-4h}	1.8	0.3	1.6	<0.0001
Runny Nose/Nasal Discharge				
E_{max}				
T_{emax} (hours)	1.9	0.2	1.7	<0.0001
AUE_{0-1h}	0.5	0.5	0.01	0.6672
AUE_{0-2h}	1.0	0.1	0.8	<0.0001
AUE_{0-4h}	1.6	0.2	1.4	<0.0001
	1.7	0.2	1.5	<0.0001

Source: Data obtained from Section 5.4.1 K234-10-1002 Study Report Body Table 26 and Table 27

Adverse events were coded using system organ class and preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA®). The sponsor reported the following respiratory tract related treatment emergent adverse events.

Table 3: Incidence of Respiratory, Thoracic and Mediastinal disorders Treatment-Emergent Adverse Events (≥5%) in the Treatment Phase

MedDRA® Preferred Term	Crushed Acurox® N = 40	Crushed Roxicodone® N = 40
Nasal Congestion	32 (80%)	11 (28%)
Rhinorrhea	32 (80%)	5 (13%)
Nasal Discomfort	29 (73%)	12 (30%)
Throat Irritation	19 (48%)	3 (8%)
Lacrimation Increased	14 (35%)	2 (5%)

Source: Data obtained from Section 5.4.1 K234-10-1002 Study Report Body Table 24

Subjects reported a greater degree of nasal irritation with Acurox® versus intranasal Roxicodone® when analyzing data obtained from the 6 point patient rated scale. Consistent with these findings, subjects had a greater number of nasal adverse events and increased lacrimation with intranasal Acurox® versus intranasal Roxicodone®.

DPARP Responses to CSS Questions:

1. In NDA 202080, study # K234-10-1002 (IR oxycodone w/o niacin), is the 6-point Subject-Rated Scale for Nasal Effects for burning, need to blow nose, runny nose/nasal discharge, facial pain/pressure, and nasal congestion (at pre-dose, 0.5, 1, 2, 4h) considered a validated assessment tool?

DPARP Response:
No, the 6-point Subject-Related Scale for Nasal Effects utilized by the sponsor is not considered a validated assessment tool. The clinical relevance of the reported differences in the 6-Point Subject-Rated Scale for Nasal Effects is uncertain.

The Division is not aware of any validated assessment tools to assess local nasal toxicity. For safety assessment, nasal toxicity is typically evaluated by comparison of adverse event rates and serial visual examination for nasal mucosal irritation, ulceration, and septal perforation. While a variety of scoring systems have also been used in clinical trials to grade nasal symptoms for the purpose of efficacy assessment, none of the scoring systems have been validated, and the minimum clinically meaningful difference remains undetermined.

2. If not, what are the appropriate measures for evaluating nasal absorption irritancy and toxicity, e.g. are there any validated tools?

DPARP Response: See response to question 1.

3. What are the thresholds for concern and can such "intranasal" events simply be accommodated over repeated exposure (exhibit only first-time irritancy if mild degree)

DPARP Response:
As noted above, there are no validated measures that DPARP uses to assess local toxicity of nasal inhalation products. As such, we do not have predetermined "thresholds for concern". However, accommodation to local nasal toxicity does not

generally occur. Instead, nasal mucosal irritation tends to worsen over time and may progress to ulceration and septal perforation.

Mucosal ulceration and septal perforation would not be expected to occur with single dose administration, and, therefore, cannot be ruled out in the absence of long-term, repeat use data. We acknowledge that it may not be feasible to conduct a repeat-use trial for intranasal Acurox. In the absence of repeat-use data and based on the Division's experience with other intranasal products, we assume that local toxicity from intranasal administration of Acurox will increase with repeat exposure.

(b) (4)

We are not aware of any nasal or oral inhalation products that contain SLS. Furthermore, a literature search did not reveal any human studies specifically evaluating its effects on the nasal mucosa or respiratory tract. However, there are studies that indicate that the effects of sodium lauryl sulfate, as a cutaneous irritant, appear to worsen, not diminish, with higher doses and repeat exposure[1]*. Given the known irritant properties of intranasal* (b) (4) *we suspect that mucosal ulceration and septal perforation may occur in some individuals with chronic intranasal administration of Acurox.*

4. Sodium lauryl sulfate is listed as an inactive excipient. What are the known effects of sodium lauryl sulfate on nasal inhalation and/or the respiratory tract?

DPARP Response:
We are not aware of any nasal or oral inhalation products that contain SLS. SLS is a common ingredient in widely available topical and oral hygiene products; at these doses and through these routes of exposure, SLS is a known cutaneous irritant in some individuals but does not appear to cause irreversible or extreme levels of toxicity. Preclinical data indicates the potential for more severe effects upon inhalation of high doses, including upper respiratory edema and respiratory distress, but we are not aware of any reported cases nor of any human studies that specifically assessed the inhalation route of exposure. Given the known general irritant properties of SLS, we expect at a minimum that SLS will cause local irritation of the nasal mucosa in some individuals. This irritation may progress to ulceration or septal perforation upon chronic exposure, especially when (b) (4)

[1] Beyer et al. "Final Report on the Safety Assessment of Sodium Lauryl Sulfate and Ammonium Lauryl Sulfate" *Journal of the American College of Toxicology.* 1983 2(7).

[2] Hazardous Substances Data Bank, a database of the National Library of Medicine's TOXNET system. Queried term: Sodium Lauryl Sulfate on February 23, 2011.

[3] Rantanen I et al, "The Effects of Two Sodium Lauryl Sulphate-Containing Toothpastes with and without Betaine on Human Oral Mucosa In Vivo" *Swed Dent. J.* 2003 27(1):31-34.

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/s/

SOFIA S CHAUDHRY
03/07/2011

SUSAN L LIMB
03/07/2011

BADRUL A CHOWDHURY
03/07/2011

M E M O R A N D U M
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: February 9, 2011

To: Bob Rappaport, M.D., Director
Division of Anesthesia and Analgesia Products (DAAP)

Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff (CSS)

From: Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff (CSS)

CC: Jovita Randall-Thompson, Ph.D., Pharmacologist
Stephen Sun, MD., Medical Officer
Controlled Substance Staff (CSS)

Yi Tsong, Ph.D., Deputy Division Director
Ling Chen, Ph.D., Statistical Reviewer
Office of Translational Science/
Office of Biostatistics/ Division of Biometrics IV, (OTS/OB/DBVI)

Subject: Filing Review Addendum - NDA 202080 - Acurox (IR oxycodone and the excipient sodium lauryl sulfate) Tablets
Sponsor: King Pharmaceuticals

This memorandum is an addendum to the CSS' Filing Review placed in DARRTS February 8, 2010.

The following two additional potential review issues were added to the filing communication letter to be conveyed to the Sponsor as per consultation with the Clinical Pharmacology and the Biostatistics reviewers.

1. For Study K234-10-1002, pharmacokinetic parameters such as oxycodone plasma concentration, Cmax and Tmax were not provided. Therefore, PK/PD (Drug Liking) cannot be correlated.

2. There is no sufficient reason for excluding Subject ID 9028 from the statistical analysis. Subject ID 9028 was not included in the statistical analysis because of vomiting during Acurox® treatment. This subject had a moderate vomiting during Acurox® treatment recorded at hour 0 (resolved less than 1 minute), and also had a mild vomiting

during Roxicodone® treatment at hour 0.9 (resolved at 0 minute). The subject responded to Drug liking VAS at all planned time points. The Emax of Drug Liking, Overall Drug Liking and Take Drug Again for Acurox® were scored at 100, 93 and 100, respectively.

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/s/

SILVIA N CALDERON
02/09/2011

MICHAEL KLEIN
02/09/2011

M E M O R A N D U M
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: 02/08/2011

To: Bob Rappaport, M.D., Director
Division of Anesthesia and Analgesia Products (DAAP)

Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff (CSS)

From: Jovita Randall-Thompson, Ph.D., Pharmacologist, CSS

CC: Yi Tsong, Ph.D., Deputy Division Director
Ling Chen, Ph.D., Statistical Reviewer
Office of Translational Science/
Office of Biostatistics/ Division of Biometrics IV, (OTS/OB/DBVI)
Stephen Sun, M.D., Medical Officer, CSS

Subject: NDA 202080 - Acurox (IR oxycodone and the excipient sodium lauryl sulfate) Tablets
Sponsor: King Pharmaceuticals
Dosage Form and Strengths: Oxycodone, 5 mg, 7.5 mg per tablet, formulated with the excipient sodium lauryl sulfate
Indication: Treatment for the (b) (4) of moderate to severe pain when the use of an (b) (4) opioid analgesic tablet is appropriate
Submission: NDA 20-2080-Acurox, submission date of 12/17/2010
Materials Reviewed: NDA 20-2080-Acurox, submission dated of 12/17/2010: Study K234-10-1002 (date of 11/04/2010) (\\cdsesub5\EVSPROD\NDA202080\0000\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\k234-10-1002)
NDA 22-451- Acurox with niacin, submission date of 12/30/2008, which included study *AP-ADF-106* (*\\Cdsesub1\EVSPROD\NDA022451\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pain\5354-other-stud-rep*), Pre-NDA 202080 Meeting Package (06/11/10, paper copy), Pre-NDA 202080 Preliminary Responses, 09/23/2010 (http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af801f47d4) and Pre-NDA 202080 Meeting Minutes 9/27/2010 (DARRTS, 11/05/2010) (http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af801fffe6)

Background

The Division of Anesthesia and Analgesia Products (DAAP) consulted the Controlled Substance Staff (CSS) to review NDA 202080, Acurox (06/11/10). The present memorandum provides a list of filing review issues and concerns that we identified.

We collaborated with the Division of Biometrics IV within the Office of Biostatistics on identifying deficiencies during the filing review process. A list of the deficiencies is provided below.

Potential review issues to relay to the firm

1. The proposed label describes the deterrent effects of (b) (4) owever, your study, Intranasal Abuse Liability (K234-10-1002) does not provide justification for the addition of (b) (4) (b) (4)

2. In reviewing the data of your Phase I Intranasal Abuse Liability Study (K234-10-1002) a sequence (AB/BA) effect was observed. The findings show that subjects given Roxicodone in Period 1 and Acurox in Period 2 reported much lower scores on Emax of Drug Liking VAS for Acurox than those who were given Acurox in Period 1 and Roxicodone in Period 2.

3. As presented on page 32 of K234-10-1002 Study Report (11/04/2010), you indicated that all treatment tablets were crushed (b) (4) Data on the particle size of crushed tablets, sample uniformity as well as sample appearance for Acurox and Roxicodone to validate equal sample homogeneity was not found in the submission.

Request for additional information:

1. A detailed description of the measures and standards taken during Study K234-10-1002 discrimination and treatment testing to maintain the concealment of your treatment and control for treatment bias due to subjects and caregivers becoming aware of assigned treatments.

2. For Study K234-10-1002 (discrimination and treatment phase) submit the protocol followed for study drug preparation and administration to subjects. Include a description of crushing conditions, crushed material consistency and average particle size for both administered crushed treatments.

3. For Study K234-10-1002, provide the location in the EDR for Pharmacokinetic Concentrations and Pharmacokinetic Parameters datasets.

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/s/

JOVITA F RANDALL-THOMPSON
02/08/2011

SILVIA N CALDERON
02/08/2011

MICHAEL KLEIN
02/08/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DDMAC-RPM	Lisa Basham; DAAP

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
1-11-11		202080	New NDA; Package Insert

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Acurox (Oxycodone HCl) Tablets	high	Opioid analgesic	May 13, 2011

NAME OF FIRM:	
King Pharmaceuticals, Inc.	PDUFA Date: 6/17/11

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
X PACKAGE INSERT (PI)
☐ PATIENT PACKAGE INSERT (PPI)
X CARTON/CONTAINER LABELING
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
X ORIGINAL NDA
☐ IND
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
X INITIAL PROPOSED LABELING
☐ LABELING REVISION

EDR link to submission: \\CDSESUB1\EVSPROD\NDA202080\202080.enx

Please forward reviewer names ASAP so that I can add them to the meetings (Mathilda, I already have you invited to the Filing meeting. The other meetings are yet to be scheduled)

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: [Insert Date] To Be Scheduled

Labeling Meetings: [Insert Dates] To Be Scheduled

Wrap-Up Meeting: [Insert Date] To Be Scheduled

SIGNATURE OF REQUESTER Lisa Basham.

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND

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/s/

LISA E BASHAM
01/11/2011

DSI CONSULT
Request for Biopharmaceutical Inspections

DATE: January 05, 2011

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

THROUGH: Bob Rappaport, M.D.
Director, Division of Anesthesia and Analgesia Products

FROM: Lisa Basham, Senior Regulatory Health Project Manager, Division of Anesthesia and Analgesia Products, HFD-170

SUBJECT: **Request for Biopharmaceutical Inspections**
NDA 202080
Oxycodone HCl, 5 and 7.5 mg
King Pharmaceuticals.

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
AP-ADD-100	PI: Mark T. Leibowitz, MD CEDRA Clinical Research, LLC 2455 N.E. Loop 410, Suite 150 San Antonio, TX 78217 Phone: 210-635-1500 Fax: 210-635-1646	(b) (4)

International Inspections:

(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)

We have requested an international inspection because:

_____ There is a lack of domestic data that solely supports approval;

_____ Other (please explain):

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **May 24, 2011.** We intend to issue an action letter on this application by, **June 17, 2011**.

Should you require any additional information, please contact Lisa Basham, Senior Regulatory Health Project Manager, at 301-796-1175.

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/s/

SURESH B NARAHARISETTI
01/06/2011

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

Date:	March 24, 2010
To:	Igor Cerny Senior Clinical Analyst Division of Anesthesia and Analgesia Products Office of New Drugs
Through:	Laura Governale, PharmD, MBA Drug Use Data Analyst Team Leader Division of Epidemiology Office of Surveillance and Epidemiology
From:	Hina Mehta, PharmD Drug Use Data Analyst Division of Epidemiology Office of Surveillance and Epidemiology
Subject:	Acurox® (oxycodone HCl, niacin) Tablets Oxycodone Utilization Review
Drug Name(s):	Immediate and Extended Release Oxycodone
Application Type/Number:	NDA 22-451, Multiple
Applicant/sponsor:	Acura Pharmaceuticals, Inc., Multiple
OSE RCM #:	2010-270

EXECUTIVE SUMMARY

Utilization data for immediate-release and extended-release oxycodone products were requested by the Division of Anesthesia and Analgesia Products in support of the FDA's Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee, and Drug Safety and Risk Management Advisory Committee meeting to be held on April 22, 2010. The focus of this meeting is to discuss the safety and efficacy of NDA 22-451, Acurox® (oxycodone and niacin) Tablets. The analysis is focused on the use of immediate- and extended-release oxycodone products as well as hydrocodone and hydromorphone products as comparators for the five year period from year 2005 to year 2009.

- Total dispensed prescriptions for single-ingredient and combination oxycodone products increased from approximately 34.3 million prescriptions to approximately 49.5 million prescriptions dispensed from year 2005 to 2009
- In year 2009, the majority of use for oxycodone containing products was combination products with approximately 32.5 million prescriptions and 13.7 million patients while single-ingredient oxycodone products accounted for approximately 17 million prescriptions and 3.4 million patients.
- Of the single-ingredient oxycodone product usage, the majority of use were for the immediate-release products with approximately 9.2 million prescriptions and 2.1 million patients while extended-release products accounted for approximately 7.7 million prescriptions and 1.5 million patients during year 2009
- "General Practice/Family Medicine" was the top prescribing specialty for combination oxycodone products as well as single-ingredient immediate- and extended-release products throughout the study period.
- For the extended-release products, roughly 54% of mentions had a BID dosing schedule and nearly a quarter of mentions had a dosing schedule frequency greater than BID (24% TID, 3% QID).
- Approximately 28% of the mentions for immediate-release products had a QID dosing schedule (e.g., "1-2 every 6 hours or q6h prn"), and approximately 20% of the mentions had a dosing schedule frequency greater than QID (e.g, "1-2 every 4 hours or q4h prn").
- Of the combination oxycodone products, approximately 27% of oxycodone/APAP mentions had a QID dosing schedule (e.g., "1-2 every 6 hours or q6h prn"). Approximately 11% of the mentions were for frequencies less than QID (e.g., "1 every 8 hours prn") and about 50% were for frequencies greater than QID (e.g., "1 every 4 hours prn").

1 INTRODUCTION

The Division of Anesthesia and Analgesia Products is conducting an Advisory Committee on April 22, 2010 to discuss the safety and efficacy of NDA 22-451, Acurox® (oxycodone and niacin) Tablets 5/30 mg and 7.5/30 mg. Acurox® is a combination immediate-release oxycodone and fixed-dose niacin product indicated for the relief of moderate to severe pain and specifically formulated for the purpose of providing abuse deterrence by causing facial flushing when taken in doses above the recommended dose. The recommended dose of Acurox® Tablets is two 5/30 mg or two 7.5/30 mg tablets every 6 hours as

needed.[1] In support of the review of this application, the Division of Epidemiology has been requested to examine the utilization patterns of currently marketed immediate- and extended-release oxycodone products to examine the extent of use by setting of care, dosage form, directions for use or signa, and prescribing specialty for years 2005 through 2009. In addition, hydrocodone and hydromorphone products were included as comparators for market share.

2 METHODS AND MATERIAL

2.1 DETERMINING SETTINGS OF CARE AND DATA SOURCES USED

IMS Health, IMS National Sales Perspectives™ data (***see Appendix 1 for detailed database descriptions***) were used to determine the setting in which oxycodone products were sold. Sales of these products by number of Eaches (bottles, packets of pills, etc.) sold from the manufacturer into the various retail and non-retail channels of distribution were analyzed for the year of 2009. For the entire market of oxycodone containing products, combination oxycodone products accounted for about 56% of sales while single-ingredient oxycodone products accounted for approximately 44% of sales.[2] Retail pharmacy settings (chain stores, independent pharmacies, and food stores) accounted for the majority of combination oxycodone (59%) product sales distribution.[3] For single-ingredient oxycodone products, 70% of these products are sold as immediate-release products and 30% as extended-release products.[4] Of these single-ingredient oxycodone products, 57% the immediate-release formulations and 79% of the extended-release formulations are sold to retail pharmacy settings.[4] Approximately 1% and 2% of sales of ER and IR products were to mail order settings, respectively, and 19% and 43% ER and IR products, respectively, were to non-retail settings. Thus, the examination of utilization patterns focused on the outpatient retail pharmacy setting. Mail order and non-retail data were not included in this analysis.

2.2 DATA SOURCES

Proprietary drug use databases licensed by the Agency were used to conduct this analysis. The estimated number of prescriptions dispensed and unique patients receiving a prescription for oxycodone products was obtained from the SDI, Vector One®: National (VONA) and SDI, Vector One®: Total Patient Tracker (TPT) databases for years 2005 to 2009. Directions for use (Signa), as mentioned by a sample of office-based physician practices around the country, were obtained from the SDI, Physician Drug and Diagnosis Audit (PDDA) (***see Appendix 1 for full database descriptions***).

3 DATA

3.1 DISPENSED PRESCRIPTIONS

Figures 1 and 2 and Table 1 in Appendix 2 shows the total number of prescriptions dispensed for single-ingredient and combination oxycodone products and comparators, hydrocodone and hydromorphone, by dosage form (immediate-release and extended-release) from outpatient retail pharmacies for years 2005 to 2009.

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[1] NDA 22-451 (Original Application), Proposed Draft Labeling, Submitted 12/30/2008.

[2] IMS Health, IMS Nationals Sales Perspectives™, Data extracted 03/10. Source Files: 1003oxy.DVR

[3] IMS Health, IMS Nationals Sales Perspectives™, Data extracted 3/10. Source File: 1003coxy.DVR

[4] IMS Health, IMS Nationals Sales Perspectives™, Data extracted 03/10. Source Files: 1003oxy2.DVR

Of these selected opioids products, hydrocodone combination products accounted for the largest proportion of prescriptions dispensed throughout the study period accounting for over 70-75% of total dispensed prescriptions. During year 2009, approximately 122 million prescriptions (70%) were dispensed for combination hydrocodone products. The combined total of combination and single-ingredient oxycodone containing products accounted for approximately 25-29% of dispensed prescriptions throughout the study period. Hydromorphone products accounted for approximately 1% of dispensed prescriptions in year 2009 or approximately 2.2 million prescriptions of single-ingredient hydromorphone products; extended-release hydromorphone products have been discontinued since year 2005.

The total dispensed prescriptions for single-ingredient and combination oxycodone products increased from approximately 34.3 million prescriptions to approximately 49.5 million prescriptions dispensed from year 2005 to 2009. In year 2009, the majority of dispensed prescriptions for oxycodone products were combination oxycodone products with approximately 66% of the market (~32.5 million TRx/~49.5 million TRx). This was a decreased from approximately 71% of the market (~24.3 million TRx/~34.3 million TRx) in year 2005. Single-ingredient oxycodone products accounted for approximately 34% (~17 million TRx/~49.5 million TRx) of the entire oxycodone product market in year 2009, an increase from 29% (~10 millionTRx/~34.3 million TRx) of the entire oxycodone product market in year 2005. Of the single-ingredient oxycodone products, dispensed prescriptions for immediate-release oxycodone accounted for approximately 54% (~9.2 million TRx/~17 million TRx) in year 2009, an increase from about 36% (~3.6 million prescriptions/~10 million TRx) of the single-ingredient market in year 2005. Approximately 46% (~7.7 million TRx/~17 million TRx) of single-ingredient oxycodone prescriptions were dispensed as extended-release oxycodone products during year 2009, a decrease from 64% (~6.4 millionTRx/~10 million TRx) of the single-ingredient oxycodone market in year 2005.

3.2 PATIENT COUNT

The number of unique patients receiving a prescription for an oxycodone containing product from outpatient retail pharmacies increased from approximately 13 million to approximately 15.8 million from year 2005 to 2009 (Table 2 and Figure 3: Appendix 2). In year 2009, combination oxycodone products had the largest proportion of patients receiving a prescription at 86% of the market (~13.7 million patients/~15.8 million patients), a decrease from 90% of the market (11.8 million patients/~13 million patients) in year 2005. Patients on single-ingredient oxycodone products accounted for about 21% of the market (~3.4 million patients/~15.8 million patients) in year 2009, an increase from 16% (~2.1 million patients/~13 million patients) of the market in year 2005. Of the single-ingredient oxycodone products, patients receiving a prescription for immediate-release oxycodone accounted for 63% of the market (~2.2 million patients/~3.4 million patients) in year 2009, an increase from 37% of the market (~783,000 patients/~2.1 million patients) in year 2005. Approximately 44% (~1.5 million/~3.4 million patients) of patients who received a prescription for single-ingredient oxycodone products received the extended-release oxycodone formulation during year 2009, a decrease from 61% (~1.3 million patients/~2.1 million patients) in year 2005.

3.3 DIRECTIONS FOR USE, SIGNA

We also examined the most common directions for use, or signa[5], associated with the use of single-ingredient and combination oxycodone products as reported by office-based physician practices in the U.S. for cumulative years 2005 through 2009 (Appendix 2: Tables 3 and 4). Similar to dispensed prescription and patient data, the majority of mentions for single-ingredient oxycodone products were for the extended-release products throughout the time period. For the extended-release products, approximately 33% of mentions for the study period were for the "twice a day" dosing schedule followed by "1 every 12 hours" and "1 every 8 hours" with approximately 17% and 13% of mentions, respectively. In general, roughly 54% of mentions had a BID dosing schedule and nearly a quarter of mentions had a dosing schedule frequency greater than BID (24% TID, 3% QID). Approximately 7% of mentions had a QD dosing schedule.

For that same period, approximately 28% of the mentions for immediate-release products had a QID dosing schedule (e.g., "1-2 every 6 hours or q6h prn"), and approximately 20% of the mentions had a dosing schedule frequency greater than QID (e.g, "1-2 every 4 hours or q4h prn"). Approximately 22% of the mentions were for frequencies less than QID (e.g., "1 every 12 hours").

Over 99% of mentions for combination oxycodone products were for the product oxycodone/APAP during cumulative years 2005 through 2009. Approximately 27% of oxycodone/APAP mentions had a QID dosing schedule (e.g., "1-2 every 6 hours or q6h prn"). Approximately 11% of the mentions were for frequencies less than QID (e.g., "1 every 8 hours prn") and about 50% were for frequencies greater than QID (e.g., "1 every 4 hours prn").

3.4 DISPENSED PRESCRIPTIONS BY PRESCRIBER SPECIALTY

Table 5 in Appendix 2 shows the number of dispensed prescriptions by top prescribing specialties for single-ingredient and combination oxycodone products for years 2005 through 2009. "General Practice/Family Medicine" was the top prescribing specialty for combination oxycodone products as well as single-ingredient immediate- and extended-release products throughout the study period. This was followed by "Internal Medicine", "Orthopedic Surgery", and "Emergency Medicine" for combination oxycodone products and "Internal Medicine," "Anesthesiology," and "Physical Medicine and Rehab" for both immediate-release and extended-release single-ingredient oxycodone products.

4 LIMITATIONS

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that the single ingredient and combination oxycodone products were distributed primarily to the retail outpatient setting based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these outpatient retail pharmacy channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

This review analyzed data from the outpatient retail pharmacy setting only, which accounts for approximately 61% of the total distribution volume of the selected sales market. Up to 39% of the total distribution volume going into mail order and non-retail settings was not analyzed.

SDI uses the term "drug occurrences" to refer to the number of times a product has been reported on a patient information form during an office-based patient visit for that period. It is important to note that a "drug occurrence" does not necessarily result in a prescription being generated. A "drug occurrence" can

[5] Signa dosing schedule: QD = once a day; BID = twice a day; TID = three times a day; QID = four times a day.

result from a prescription written, a sample given, a recommendation for OTC products, recommendation with sample, a product dispensed or administered in the office, a hospital order, a nursing home order or a combination of these.

5 CONCLUSIONS

Total oxycodone containing product use has increased since year 2005. Within the single-ingredient oxycodone product market, there has been a shift in majority use of the extended-release products in year 2005 to the immediate-release products in year 2009. More often, combination products oxycodone/APAP are written with a dosing schedule frequency that is greater than QID such as "every 4 hours." The immediate-release single-ingredient oxycodone products are more often written with a dosing schedule frequency that is QID or less; however, approximately 20% of the mentions had a dosing schedule frequency greater than QID. These findings suggest that, it is not uncommon for the dosing schedule for single-ingredient and combination oxycodone products to exceed the QID dosing schedule.

APPENDIX 1: DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

SDI Vector One®: National (VONA)

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims per year, representing over 160 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

SDI Vector One®: Total Patient Tracker (TPT)

SDI's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

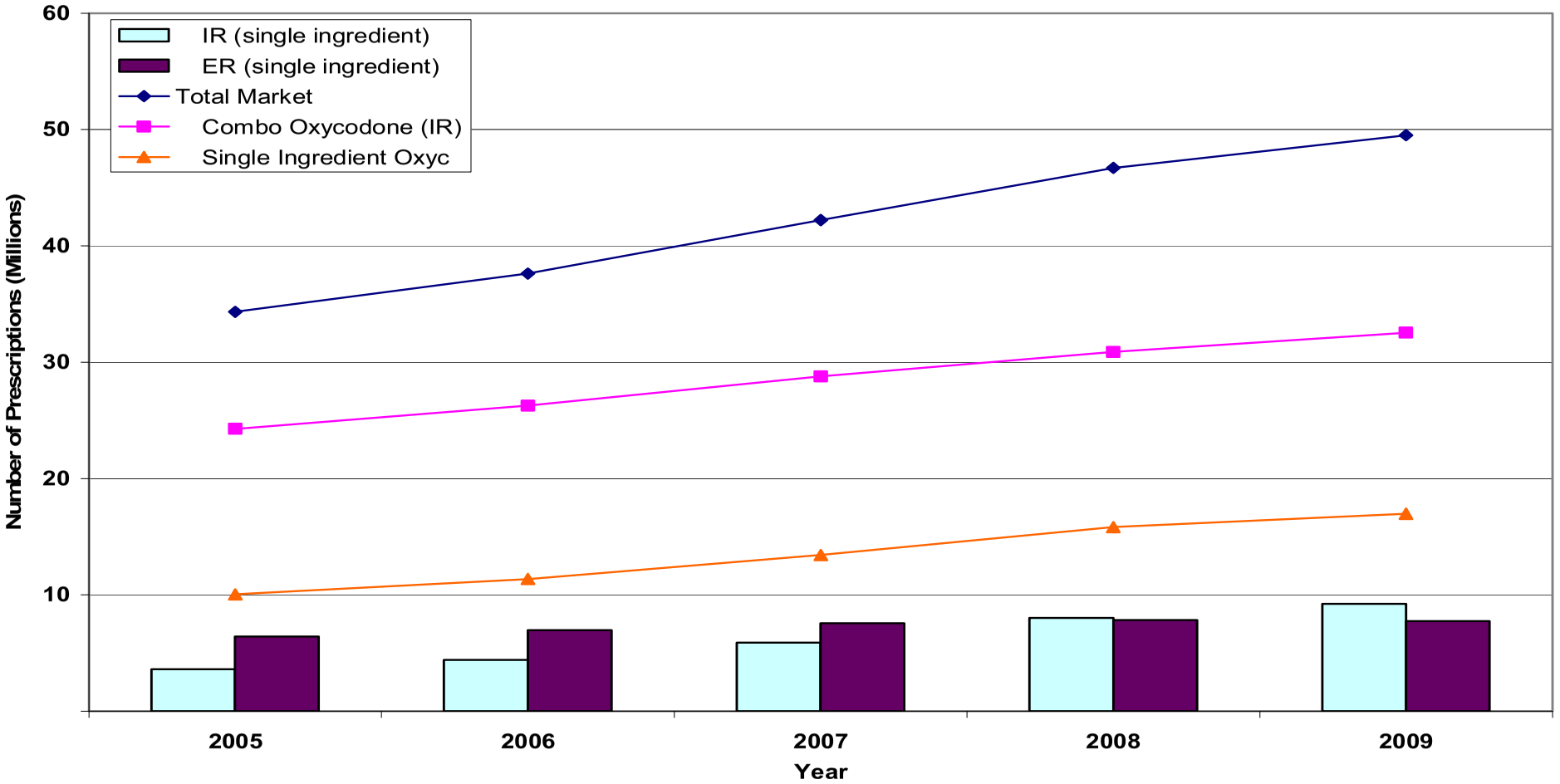
SDI Physician Drug & Diagnosis Audit (PDDA) with Pain Panel

SDI's Physician Drug & Diagnosis Audit (PDDA) with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug

products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

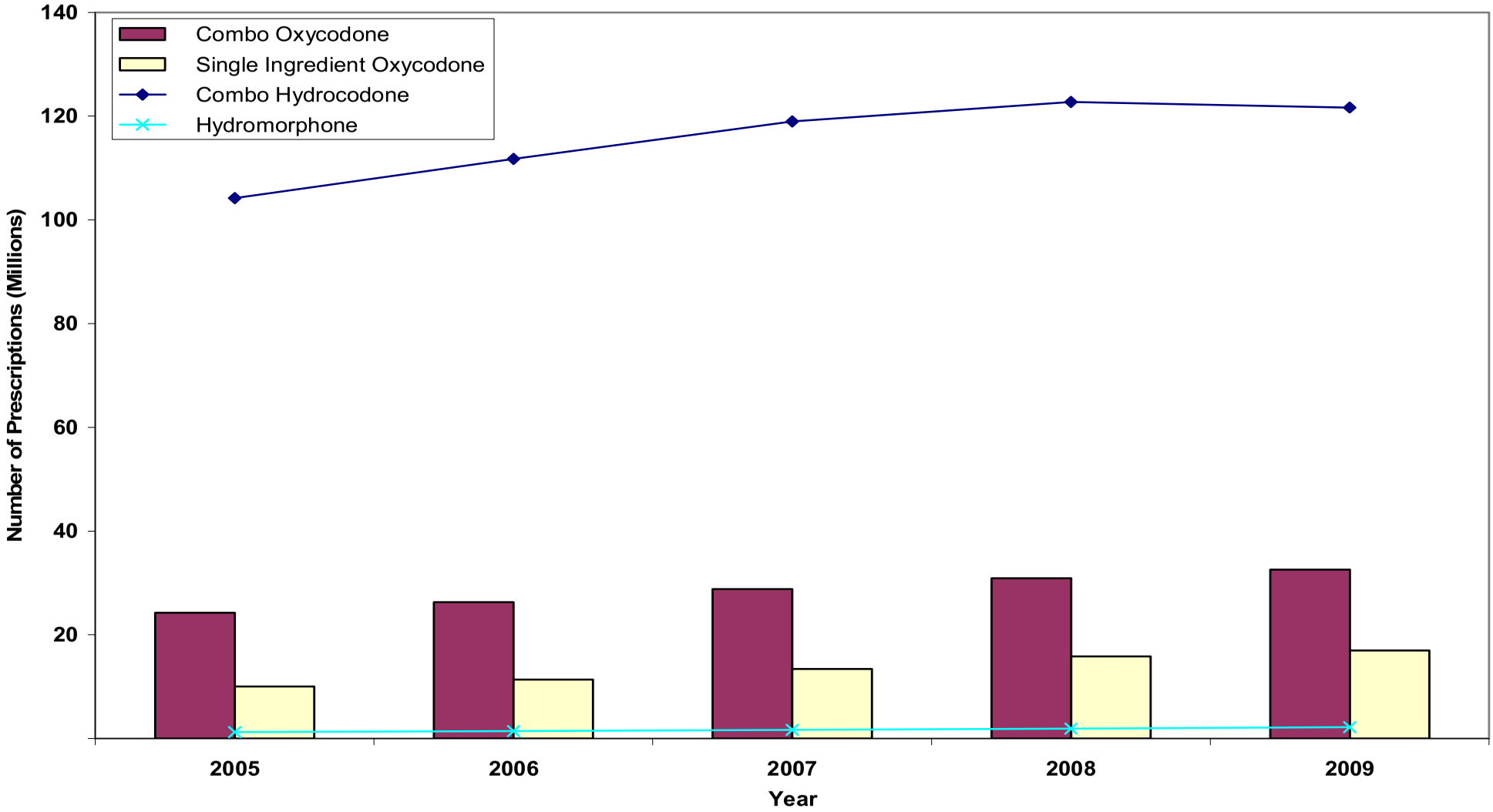
APPENDIX 2: TABLES AND FIGURES

Figure 1: Total Number of Prescriptions Dispensed for Single-Ingredient and Combination Oxycodone Through U.S. Outpatient Retail Pharmacies, Years 2005-2009



Source: SDI Vector One®: National (VONA), Extracted March2010. File: VONA 2010-270 TRx Single and Combo Oxycodone 3-11-10.xls

Figure 2: Total Number of Prescriptions Dispensed for Single-Ingredient and Combination Oxycodone and Comparators Through U.S. Outpatient Retail Pharmacies, Years 2005-2009



Source: SDI Vector One®: National (VONA), Extracted March2010. File: VONA 2010-270 TRx Oxycodone and Comparators 3-11-10.xls

Table 1: Total Number of Prescriptions Dispensed for Single-Ingredient and Combination Oxycodone and Comparators Through U.S. Outpatient Retail Pharmacies, Years 2005-2009

	2005		2006		2007		2008		2009	
	TRxs N	*Share %*	TRxs N	*Share %*	TRxs N	*Share %*	TRxs N	*Share %*	TRxs N	*Share %*
Total Market	**139,745,932**	***100.0%***	**150,787,204**	***100.0%***	**162,791,583**	***100.0%***	**171,337,783**	***100.0%***	**173,366,611**	***100.0%***
Combo Hydrocodone	104,199,302	*74.6%*	111,750,006	*74.1%*	118,944,231	*73.1%*	122,736,828	*71.6%*	121,658,608	*70.2%*
Oxycodone	34,317,673	*24.6%*	*37,628,693*	*25.0%*	42,209,209	*25.9%*	*46,711,823*	*27.3%*	49,513,701	*28.6%*
Combination Oxycodone	24,274,662	*70.7%*	26,274,997	*69.8%*	28,781,906	*68.2%*	30,884,108	*66.1%*	32,541,458	*65.7%*
Immediate Release	24,274,662	*100.0%*	26,274,997	*100.0%*	28,781,906	*100.0%*	30,884,108	*100.0%*	32,541,458	*100.0%*
Single Ingredient Oxyc	10,043,011	*29.3%*	11,353,696	*30.2%*	13,427,303	*31.8%*	15,827,715	*33.9%*	16,972,243	*34.3%*
Immediate Release	3,615,921	*36.0%*	4,393,662	*38.7%*	5,886,252	*43.8%*	8,010,875	*50.6%*	9,239,631	*54.4%*
Extended Release	6,427,090	*64.0%*	6,960,034	*61.3%*	7,541,029	*56.2%*	7,816,692	*49.4%*	7,732,612	*45.6%*
Hydromorphone	1,228,957	*0.9%*	1,408,505	*0.9%*	1,638,122	*1.0%*	1,889,018	*1.1%*	2,194,287	*1.3%*

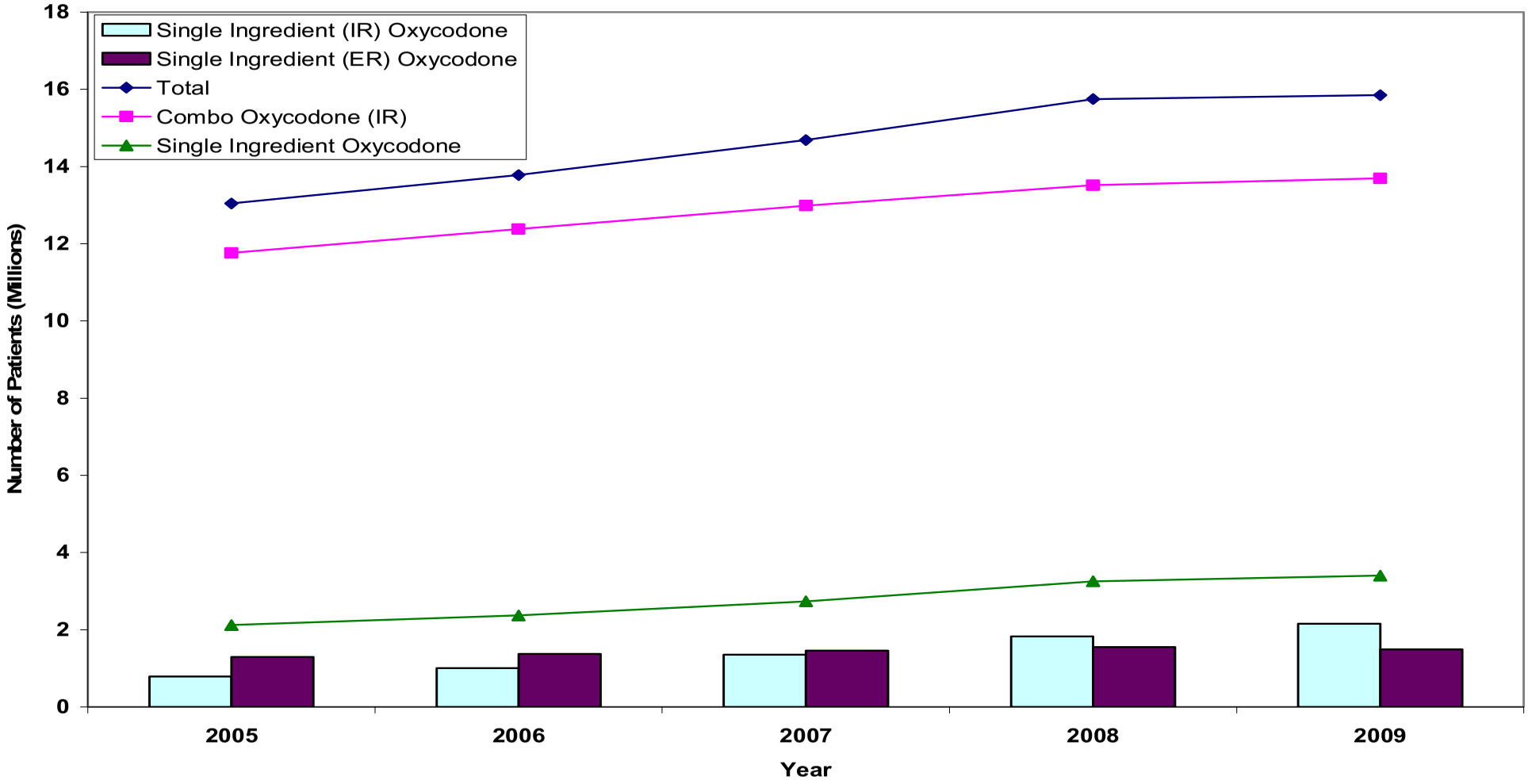
Source: SDI Vector One®: Nat ona (VONA), Extracted March2010. F es: VONA 2010-270 TRx S ng e and Combo Oxycodone 3-11-10.x s and VONA 2010-270 TRx Oxycodone and Comparators 3-11-10.x s

Table 2: Total Number of Unique Patients Receiving a Prescription for Single-Ingredient and Combination Oxycodone Through U.S. Outpatient Retail Pharmacies, Years 2005-2009

	2005		2006		2007		2008		2009	
	TRxs N	*Share %*	TRxs N	*Share %*	TRxs N	*Share %*	TRxs N	*Share %*	TRxs N	*Share %*
Total	**13,039,990**	***100.00%***	**13,775,861**	***100.00%***	**14,687,037**	***100.00%***	**15,743,201**	***100.00%***	**15,848,553**	***100.00%***
Combo Oxycodone	11,762,776	*90.21%*	12,377,214	*89.85%*	12,987,679	*88.43%*	13,519,075	*85.87%*	13,694,216	*86.41%*
Immediate Release (IR)	11,762,776	*100.00%*	12,377,214	*100.00%*	12,987,679	*100.00%*	13,519,075	*100.00%*	13,694,216	*100.00%*
Single Ingredient Oxycodone	2,120,606	*16.26%*	2,367,860	*17.19%*	2,733,837	*18.61%*	3,250,160	*20.64%*	3,399,673	*21.45%*
Immediate Release (IR)	783,033	*36.92%*	1,005,344	*42.46%*	1,354,983	*49.56%*	1,828,939	*56.27%*	2,158,186	*63.48%*
Extended Release (ER)	1,292,857	*60.97%*	1,371,254	*57.91%*	1,455,099	*53.23%*	1,549,092	*47.66%*	1,486,357	*43.72%*

Source: SDI: Vector One®: Tota Pat ent Tracker (TPT). Extracted March 2010. F es: TPT 2010-270 Tota Oxycodone Pat ent Count 3-18-10.x s, TPT 2010-270 S ng e Oxycodone Pat ent Count 3-11-10.x s, TPT 2010-270 Oxycodone IR Pat ent Count 3-11-10.x s, TPT 2010-270 Oxycodone ER Pat ent Count 3-11-10.x s, TPT 2010-270 Oxycodone Combo Pat ent Count 3-11-10.x s

Figure 3: Number of Patients Receiving a Prescription for Single Ingredient and Combination Oxycodone Through U.S. Outpatient Retail Pharmacies, 2005-2009



Source: SDI: Vector One®: Total Patient Tracker (TPT). Extracted March 2010. Files: TPT 2010-270 Total Oxycodone Patient Count 3-18-10.xls, TPT 2010-270 Single Oxycodone Patient Count 3-11-10.xls, TPT 2010-270 Oxycodone IR Patient Count 3-11-10.xls, TPT 2010-270 Oxycodone ER Patient Count 3-11-10.xls, TPT 2010-270 Oxycodone Combo Patient Count 3-11-10.xls

Table 3. Directions for Use, Signa, for Single Ingredient Oxycodone by Form as Reported by Office-Based Physicians, 2005-2009

	2005 - 2009		
	Occur (000)	*Share*	*%*
Total Market	21,173		*100.0%*
ER	13,423		*63.4%*
twice a day (BID)	4,370		*32.6%*
1 every 12 hours	2,226		*16.6%*
1 every 8 hours	1,697		*12.6%*
3 times a day (TID)	1,519		*11.3%*
once a day (QD)	965		*7.2%*
2 twice a day	323		*2.4%*
1 every 6 hours	183		*1.4%*
2 every 12 hours	163		*1.2%*
four times a day (QID)	154		*1.2%*
1 every 12 hours prn	138		*1.0%*
All Others	1,730		*12.9%*
UNSPEC.	153		*1.1%*
IR	7,750		*36.6%*
1 every 6 hours prn	740		*9.6%*
1 every 4 hours prn	699		*9.0%*
four times a day (QID)	385		*5.0%*
1 every 4 hours	350		*4.5%*
twice a day (BID)	323		*4.2%*
1 every 6 hours	308		*4.0%*
3 times a day (TID)	307		*4.0%*
2 every 4 hours prn	295		*3.8%*
3 times a day prn	263		*3.4%*
four times a day prn	254		*3.3%*
2 every 6 hours prn	242		*3.1%*
1 every 8 hours prn	166		*2.2%*
twice a day prn	164		*2.1%*
1 every 8 hours	129		*1.7%*
as directed	125		*1.6%*
2 every 6 hours	123		*1.6%*
6 per day	116		*1.5%*
2 every 4 hours	110		*1.4%*
3 every 6 hours prn	100		*1.3%*
2 every 3 hours prn	99		*1.3%*
1 every 12 hours	97		*1.3%*
2 every 8 hours prn	89		*1.2%*
2 three times a day	89		*1.1%*
5 per day	86		*1.1%*
once a day prn	79		*1.0%*
All Others	1,852		*23.9%*
UNSPEC.	206		*2.7%*

Source: SDI: Physician Drug and Diagnosis Audit. Years 2005 2009. Extracted 3 22 10.
File: PDDA 2010 270 Single Ingredient Oxycodone Sig 05 09 Cumulative 3 22 10.xls

Table 4. Directions for Use, Signa, for Combination Oxycodone Products as Reported by Office-Based Physicians, 2005-2009

	2005-2009	
	Occur (000)	Share %
Total Market	68,095	100.0%
oxycodone hcl/acetaminophen	67,949	99.8%
1 every 4 hours prn	12,966	19.1%
1 every 4 hours	7,686	11.3%
2 every 4 hours prn	7,074	10.4%
1 every 6 hours prn	6,019	8.9%
2 every 6 hours prn	3,756	5.5%
1 every 6 hours	3,094	4.6%
2 every 4 hours	2,954	4.4%
four times a day (QID)	2,816	4.1%
four times a day prn	1,765	2.6%
1 every 3 hours prn	1,497	2.2%
2 every 3 hours	1,468	2.2%
3 times a day (TID)	1,455	2.1%
twice a day (BID)	1,040	1.5%
2 every 6 hours	947	1.4%
3 times a day prn	921	1.4%
2 every 8 hours prn	921	1.4%
1 every 8 hours prn	918	1.4%
1 every 8 hours	785	1.2%
prn- as needed	755	1.1%
once a day (QD)	698	1.0%
twice a day prn	693	1.0%
2 every 3 hours prn	679	1.0%
All Others	5,643	8.3%
UNSPEC.	1,465	2.2%
oxycodone/aspirin	145	0.2%
1 every 6 hours prn	39	26.5%
1 every 4 hours prn	30	20.6%
four times a day prn	12	7.9%
2 four times a day	11	7.5%
2 four times a day prn	11	7.4%
2 five times a day	9	6.2%
3 three times a day prn	9	6.1%
2 every 4 hours prn	7	4.7%
as directed	6	4.3%
2 three times a day	5	3.6%
2 every 8 hours	2	1.5%
1 every 6 hours	2	1.4%
2 every 8 hours prn	2	1.2%
1 every 4 hours	2	1.0%

Source: SDI: Physician Drug and Diagnosis Audit. Years 2005 2009. Extracted 3 22 10.
File: PDDA 2010 270 Combination Oxycodone Sig 05 09 Culmulative 3 12 10.xls

Table 5: Total Number of Dispensed Precriptions of Single Ingredient and Combination Oxycodone by Form and Prescriber Specialty Through U.S. Outpatient Retail Pharmacies, 2005-2009

	2005		2006		2007		2008		2009	
	TRxs	*Share%*	TRxs	*Share%*	TRxs	*Share%*	TRxs	*Share%*	TRxs	*Share%*
Total Market	**34,317,694**	**100.0%**	**37,628,564**	**100.0%**	**42,209,270**	**100.0%**	**46,711,821**	**100.0%**	**49,513,701**	**100.0%**
Combo Oxycodone	24,274,669	70.7%	26,274,978	69.8%	28,781,985	68.2%	30,884,089	66.1%	32,541,458	65.7%
GP/FM/DO	4,163,980	17.2%	4,849,844	18.5%	5,344,273	18.6%	5,733,084	18.6%	6,312,548	19.4%
IM	2,979,849	12.3%	3,346,948	12.7%	3,624,140	12.6%	3,907,922	12.7%	4,208,642	12.9%
ORTH SURG	2,353,818	9.7%	2,530,854	9.6%	2,717,798	9.4%	2,785,654	9.0%	2,931,287	9.0%
EM	1,748,565	7.2%	1,942,127	7.4%	2,218,903	7.7%	2,341,498	7.6%	2,298,828	7.1%
DENT	1,555,557	6.4%	1,606,161	6.1%	1,691,131	5.9%	1,710,890	5.5%	1,729,734	5.3%
PA	715,497	2.9%	902,086	3.4%	1,138,450	4.0%	1,440,504	4.7%	1,717,354	5.3%
ANES	826,095	3.4%	1,001,043	3.8%	1,193,722	4.1%	1,305,195	4.2%	1,479,432	4.5%
UNSPEC	1,772,954	7.3%	1,260,010	4.8%	1,287,669	4.5%	1,701,533	5.5%	1,437,700	4.4%
OB/GYN	1,235,080	5.1%	1,281,120	4.9%	1,382,322	4.8%	1,389,458	4.5%	1,326,767	4.1%
PM&R	555,767	2.3%	673,955	2.6%	783,015	2.7%	956,306	3.1%	1,182,018	3.6%
NP	499,606	2.1%	651,933	2.5%	808,473	2.8%	978,728	3.2%	1,181,196	3.6%
GEN SURG	1,045,745	4.3%	1,083,749	4.1%	1,130,768	3.9%	1,132,569	3.7%	1,161,382	3.6%
AO SURG	826,496	3.4%	856,079	3.3%	896,668	3.1%	886,023	2.9%	871,709	2.7%
HOSP	687,222	2.8%	750,968	2.9%	810,999	2.8%	741,179	2.4%	649,045	2.0%
UROL	471,995	1.9%	480,356	1.8%	492,211	1.7%	485,965	1.6%	476,454	1.5%
All Others	2,836,443	11.7%	3,057,745	11.6%	3,261,443	11.3%	3,387,581	11.0%	3,577,362	11.0%
Single Ingredient Oxyc	10,043,025	29.3%	11,353,586	30.2%	13,427,285	31.8%	15,827,732	33.9%	16,972,243	34.3%
IR	3,615,924	*36.0%*	4,393,641	*38.7%*	5,886,236	*43.8%*	8,010,927	*50.6%*	9,239,631	*54.4%*
GP/FM/DO	755,632	*20.9%*	973,762	*22.2%*	1,327,287	*22.5%*	1,876,128	*23.4%*	2,342,921	*25.4%*
IM	533,728	*14.8%*	651,120	*14.8%*	892,498	*15.2%*	1,234,184	*15.4%*	1,373,423	*14.9%*
ANES	413,804	*11.4%*	495,933	*11.3%*	647,034	*11.0%*	855,188	*10.7%*	935,417	*10.1%*
PM&R	236,064	*6.5%*	306,535	*7.0%*	406,128	*6.9%*	589,812	*7.4%*	687,865	*7.4%*
UNSPEC	302,132	*8.4%*	220,689	*5.0%*	289,096	*4.9%*	478,773	*6.0%*	497,017	*5.4%*
NP	153,626	*4.2%*	215,923	*4.9%*	296,108	*5.0%*	424,428	*5.3%*	478,306	*5.2%*
PA	112,831	*3.1%*	165,829	*3.8%*	241,198	*4.1%*	346,521	*4.3%*	424,412	*4.6%*
ORTH SURG	179,161	*5.0%*	229,481	*5.2%*	284,068	*4.8%*	351,020	*4.4%*	375,736	*4.1%*
EM	54,832	*1.5%*	90,513	*2.1%*	143,938	*2.4%*	211,934	*2.6%*	298,954	*3.2%*
GEN SURG	55,082	*1.5%*	63,832	*1.5%*	83,969	*1.4%*	112,326	*1.4%*	199,753	*2.2%*
NEURO	76,816	*2.1%*	94,354	*2.1%*	133,589	*2.3%*	182,442	*2.3%*	192,144	*2.1%*
HEM	97,283	*2.7%*	116,278	*2.6%*	130,008	*2.2%*	153,220	*1.9%*	147,051	*1.6%*
All Others	742,216	*20.5%*	885,670	*20.2%*	1,141,323	*19.4%*	1,348,171	*16.8%*	1,433,683	*15.5%*
ER	6,427,101	*64.0%*	6,959,945	*61.3%*	7,541,027	*56.2%*	7,816,657	*49.4%*	7,732,612	*45.6%*
GP/FM/DO	1,698,323	*26.4%*	1,963,673	*28.2%*	2,117,327	*28.1%*	2,179,648	*27.9%*	2,138,297	*27.7%*
IM	1,101,341	*17.1%*	1,232,333	*17.7%*	1,331,799	*17.7%*	1,344,785	*17.2%*	1,344,019	*17.4%*
ANES	694,904	*10.8%*	774,851	*11.1%*	843,118	*11.2%*	838,477	*10.7%*	817,752	*10.6%*
PM&R	443,403	*6.9%*	514,175	*7.4%*	568,543	*7.5%*	638,138	*8.2%*	670,492	*8.7%*
NP	208,658	*3.2%*	260,009	*3.7%*	316,307	*4.2%*	372,219	*4.8%*	390,125	*5.0%*
UNSPEC	541,852	*8.4%*	301,604	*4.3%*	317,810	*4.2%*	384,808	*4.9%*	345,351	*4.5%*
PA	143,914	*2.2%*	183,756	*2.6%*	230,265	*3.1%*	284,616	*3.6%*	329,377	*4.3%*
ORTH SURG	280,635	*4.4%*	300,085	*4.3%*	312,670	*4.1%*	305,390	*3.9%*	304,846	*3.9%*
NEURO	199,568	*3.1%*	214,089	*3.1%*	233,230	*3.1%*	243,759	*3.1%*	222,672	*2.9%*
HEM	123,470	*1.9%*	143,081	*2.1%*	144,680	*1.9%*	146,908	*1.9%*	136,062	*1.8%*
RHEUM	143,620	*2.2%*	158,277	*2.3%*	157,584	*2.1%*	146,285	*1.9%*	130,754	*1.7%*
All Others	847,413	*13.2%*	914,012	*13.1%*	967,694	*12.8%*	931,624	*11.9%*	902,868	*11.7%*
All Others	--	--	--	--	22	*0.0%*	148	*0.0%*	--	--

Source: SDI Vector One®: National (VONA), Extracted March2010. File: VONA 2010-270 TRx Single and Combo Oxycodone by Prescriber Specialty 3-11-10.xls and and VONA 2010-270 TRx Single Ingredient Oxycodone by Form and Prescriber Specialty 3-16-10.xls

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22451	ORIG-1	ACURA PHARMACEUTICALS INC	ACUROX (IR OXYCODONE AND NIACIN)

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

/s/

HINA S MEHTA
03/24/2010

LAURA A GOVERNALE
03/24/2010
Drug use data cleared for background package.