

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202080Orig1s000

SUMMARY REVIEW



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA , ANALGESIA, AND ADDICTION PRODUCTS

Summary Review for Regulatory Action

Date	June 17, 2011
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia, and Addiction Products
Subject	Division Director Summary Review
NDA #	202080
Applicant Name	King Pharmaceuticals
Date of Submission	December 17, 2010
PDUFA Goal Date	June 17, 2011
Proprietary Name / Established (USAN) Name	Oxecta Oxycodone HCl
Dosage Forms / Strength	5 mg and 7.5 mg immediate-release tablets
Proposed Indication	For the management of acute and chronic moderate to severe pain where the use of an opioid analgesic is appropriate
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Frank Pucino, PharmD, MPH/Sharon Hertz, MD
CSS	Jovita Randall-Thompson, PhD/Silvia Calderon, PhD/Michael Klein, PhD
CSS Statistics	Ling Chen, PhD/Stella Machado, PhD
Pharmacology Toxicology Review	Jay H. Chang, PhD/Adam Wasserman, PhD
CMC/Quality Review	Julia C. Pinto, PhD/Danae Christodoulou, PhD/Prasad Peri, PhD
ONDQA-Biopharmaceutics Review	Houda Mahayni, PhD/Angelica Dorantes, PhD/Patrick J. Marroum, PhD
Clinical Pharmacology Review	Suresh B. Naraharisetti, PhD/Yun Xu, PhD
DDMAC	Mathilda Fienkeng, Pharm.D.
DSI	(analytical site): Arindam Dasgupta, PhD/Abhijit Raha, PhD/Sam. H. Haidar, PhD, RPh/Martin K. Yau, PhD (clinical site): Arindam Dasgupta, PhD/Abhijit Raha PhD/Martin Yau, PhD/Michael Skelly, PhD
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OSE/DMEPA (Trade Name)	Anne C. (Crandall) Tobenkin, PharmD/Melina Griffiths, RPh/Carol Holquist, RPh (Acurox) Jamie Wilkins Parker, PharmD/Lubna Merchant, MS, PharmD/Carol Holquist, RPh (Oxecta)
DPARP	Sofia Chaudhry, MD/Susan Limb, MD/ Badrul Chowdhury, MD, PhD

OND=Office of New Drugs
 CSS=Controlled Substance Staff
 DDMAC=Division of Drug Marketing, Advertising and Communication
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention
 DSI=Division of Scientific Investigations
 DPARP=Division of Pulmonary and Rheumatology Products

1. Introduction

King Pharmaceuticals has submitted this NDA for their abuse-deterrent formulation of oxycodone HCl immediate-release tablets as a 505(b)(2) application with reference to NDA 021011 for Roxicodone[®]. With the increasing misuse and abuse of opioid analgesics in the

NDA 202080

Oxecta

Division Director's Review and Summary Basis for Approval

June 17, 2011

2

U.S., many companies are developing products which are intended to be abuse-deterrent by reformulating the opioid in such a manner as to make it less easy to abuse by one route or another. In this case, Oxecta has been formulated to prevent intravenous injection of oxycodone (b) (4)

to reduce abuse by nasal insufflation (b) (4)

2. Background

The applicant provided data establishing the bioequivalence of their product to the listed drug and, as such, no new clinical or safety studies were required for this application. In addition to the CMC and clinical pharmacology data submitted, the applicant submitted data intended to support the safety of some of the excipients which would reach levels of exposure at the maximum daily dose that are above the levels that have previously been found to be safe by Agency criteria, and abuse liability studies intended to document the tamper-resistant features of the formulation.

3. CMC

The following summary of the CMC data has been reproduced from pages 1 through 3 of Dr. Peri's review:

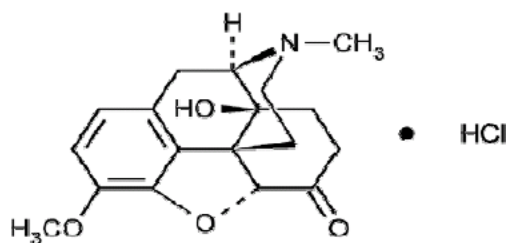
Drug Substance:

The drug substance is made by (b) (4) and is referenced to DMF (b) (4). This DMF was found adequate in a review dated Jan-4-2011. The drug substance is a white crystalline powder with a melting point between 220°C. Release specifications for Oxycodone HCl by the supplier comply with the USP monograph and include appearance, identification, specific rotation, water content, residue on ignition, chloride, assay, impurities, organic volatile impurities, assay, related substances (specified and unspecified), residual solvents, particle size, and X-ray, diffraction. Oxycodone HCl is packaged in (b) (4). The retest date is (b) (4) months from the manufacturing date.

Chemical name, structure, molecular weight and molecular formula are provided below.

Chemical Name: Morphinan-6-one, 4,5-epoxy-14-hydroxy-3-methoxy-17-methylhydrochloride, (5□)

Figure 3.2.S.1.2-1 Structural Formula Oxycodone Hydrochloride USP



Molecular Formula
 $C_{18}H_{21}NO_4 \cdot HCl$

Molecular Weight
351.82

Conclusion: The drug substance is satisfactory.

Drug Product:

Tradename (oxycodone HCl) Tablets, are round white, convex tablets that are manufactured in 5 mg and 7.5 mg strengths. The two tablets are distinguished with the strengths being debossed on the tablets. The application references New Drug Application (NDA) 021011 for Roxicodone® (Oxycodone Hydrochloride Tablets USP), and establishes safety and efficacy based on bioequivalence with Roxicodone® Tablets, the reference listed drug (RLD).

The functional excipients used in the preparation of the, oxycodone tablets include

(b) (4)
All are well established, and all but one (b) (4) are currently recognized food additives or Generally Recognized as Safe substances. The functional excipients are intended to introduce limits or impediments to two common methods of opioid analgesic product abuse: (1) intravenous injection of oxycodone extracted from dissolved tablets, and (2) nasal snorting of crushed tablets.

(b) (4)
non-dependent recreational opioid users. These potential abuse deterrent (Aversion Technology) properties have been evaluated by Controlled Substance Staff (CSS).

The drug product is packaged in HDPE bottles with child resistant closures. The recommended storage temperature is 25° C (77° F) with excursions permitted from 15° to 30°C (59°-86°F) and an expiry of 24 months.

The manufacturing process of the drug product uses a (b) (4)
(b) (4)
The product is manufactured by King Pharmaceuticals, Cary, NC. Commercial batches of tablets are about (b) (4) Tablets.

NDA 202080
Oxecta

Division Director's Review and Summary Basis for Approval
June 17, 2011

The proposed specifications for the drug product are description, identity, assay, content uniformity, dissolution, impurities, (b) (4), and friability.

The stability data provided in the application support a shelf life of 24 months for the drug product.

CMC issues that are still pending: An update to drug product specifications is being sent by the applicant to reflect the agreed upon dissolution and (b) (4) impurity acceptance criteria.

Conclusion: The drug product is satisfactory.

Overall Conclusion:

From a CMC perspective, the application is recommended for approval.

The request for the drug product specifications update was sent to the sponsor on May 24th and the updated specifications and stability data were provided to us on May 31st. The limits for (b) (4) were revised to NMT (b) (4) and the dissolution acceptance criterion was revised to Q= (b) (4) in 15 minutes as requested. As documented in Dr. Prasad's review addendum of June 14th, the proposed limits meet the Agency's expectations and the issue is now considered resolved.

I concur with the review team that there are no outstanding CMC concerns that would preclude approval of this application.

4. Nonclinical Pharmacology/Toxicology

The following summary of the non-clinical data has been reproduced from pages 28 through 30 of Dr. Chang's review:

Per agreement with the sponsor through a PreNDA meeting held on 9/27/2010 (Meeting minutes dated 11/5/2010) and subsequent correspondences, no new nonclinical toxicology studies were required with this NDA submission. However, the applicant was required to provide a safety assessment to justify the level of cospovidone in TRADENAME® (oxycodone HCl, USP) Tablets based on a total daily intake of 16 tablets. Note that a safety assessment based on 16 TRADENAME® (oxycodone HCl, USP) Tablets was determined by the Division based in part on prescribing data from a Drug Utilization Summary presented by the Agency at the 2010 Joint Meeting of the Anesthetic and Life Support and Drug Safety and Risk Management Advisory Committees to discuss Acurox with Niacin (NDA 22-451). Cospovidone is present in numerous approved and marketed oral drugs in the US and is listed with a maximum potency of 792.0 mg according to the FDA Inactive Ingredient Guide (IIG). The TDI of cospovidone from 16 TRADENAME® (oxycodone HCl, USP) Tablets is (b) (4) than the maximum listed level found in the IIG. Note that no new or additional toxicology studies were conducted by the applicant to qualify this excipient. Rather, the applicant submitted a written justification that cited literature from the public domain that included a safety evaluation from the FAO/WHO (Food and Agriculture Organization of the United Nations/World Health Organization) Joint Expert Committee on Food Additives (JEFCA). The JEFCA report summarized the committee's review of nonclinical studies that addressed the repeat-dose toxicity,

NDA 202080

Oxecta

Division Director's Review and Summary Basis for Approval

June 17, 2011

5

reproductive toxicity, and genetic toxicity of this excipient. In brief, no adverse toxicological findings were noted in a 90-day repeat-dose oral toxicity study in rat and a 6-month repeat-dose oral toxicity study in dog. The highest doses tested were associated with human equivalent doses (HEDs) that provide adequate margins of safety relative to the potential TDI of crosopvidone in TRADENAME® (oxycodone HCl, USP) Tablets. Moreover, crosopvidone tested negative for mutagenicity in a standard battery of genetic toxicity studies, did not have teratogenic effects, and was found to be poorly absorbed by the gastrointestinal tract in humans following oral ingestion. Based on this information, JEFCA determined that an acceptable daily intake (ADI) designation was “not specified” since oral intake of crosopvidone was not considered a toxicological risk to humans based on a weight of scientific evidence. Additionally, this reviewer identified an approved drug (Amitril®; ANDA 83-939) with a TDI of crosopvidone that exceeds the amount in 16 TRADENAME® (oxycodone HCl, USP) Tablets (b) (4) when taken as recommended. Taken together, the information above provides adequate qualification for the level of crosopvidone in TRADENAME® (oxycodone HCl, USP) Tablets based on a total daily intake of 16 tablets.

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

In summary, the applicant has adequately addressed all outstanding nonclinical safety concerns. No additional nonclinical concerns arose during the current review cycle of the NDA. Therefore, from the pharmacology toxicology perspective this NDA may be approved.

I concur with the review team that there are no outstanding pharmacology or toxicology concerns that preclude approval of this application.

5. Clinical Pharmacology/Biopharmaceutics

The following summary of the clinical pharmacology data submitted in this application has been reproduced from pages 15 and 16 of Dr. Pucino’s review:

The following two pharmacokinetic studies were submitted with this NDA:

1. **AP-ADD-100:** This study served as the pivotal bioequivalence pharmacokinetic study with the referenced drug (Roxicodone) in healthy volunteers (see **Error! Reference source not found.** below). This three-period, three-treatment crossover study design compared the PK of Tradename (2 x 7.5 mg) with Roxicodone Tablets (15 mg) and of Tradename (2 x 7.5 mg) with Acurox tablets (oxycodone/niacin, 2 x 7.5 mg/30 mg) (N22451).

This study demonstrated bioequivalence between Tradename and Roxicodone tablets (Figure 1), with the ratios of geometric means and the 90% confidence intervals for C_{max} and systemic exposure (AUC_{last} and AUC_{inf}) within the accepted 80% to 125% limits.

NDA 202080

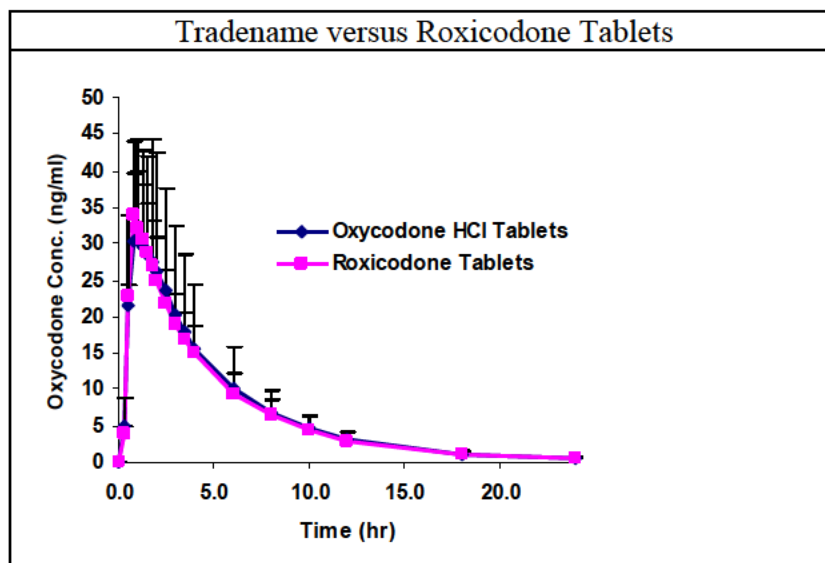
Oxecta

Division Director’s Review and Summary Basis for Approval

June 17, 2011

6

Figure 1: Mean oxycodone concentration-time profiles after administration of Tradename and Roxicodone Tablets



Source: Modified from Dr. Suresh Naraharisetti's Clinical Pharmacology Review, Figure 2.5.1a, p.11 of 56.

2. **K234-10-1001:** This study assessed the dose-proportionality and food-effect of Tradename in healthy volunteers (see **Error! Reference source not found.** below). The study design included a 5-period, 5-way crossover design that evaluated dose-proportionality between 5, 10 and 15 mg Tradename; the food effect on Tradename; and the food effect comparison between Tradename and Roxicodone tablets under fed conditions.

Administration of Tradename with a high-fat meal increased the AUC by 21%, decreased the C_{max} by 14% and delayed the T_{max} from 1.25 hours to 3.0 hours. A similar food effect was also observed with Acurox, and previously reported with oxycodone solution. Compared to Roxicodone, Tradename resulted in similar AUCs, a 17% decrease in C_{max} and a delayed T_{max} (3 hours versus 1.3 hours) under fed conditions. The Clinical Pharmacology review team felt that the observed food effect for Tradename does not warrant any dosing adjustments.

The Clinical Pharmacology review team felt that NDA 202080 is acceptable....

In addition, the following are the recommendations noted on page 12 of Dr. Mahayni's Biopharmaceutics review:

The proposed dissolution method as listed below is acceptable.

The dissolution parameters are as follows:

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

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

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

NDA 202080
Oxecta

Division Director's Review and Summary Basis for Approval
June 17, 2011

I concur with the review team that there are no outstanding clinical pharmacology or biopharmaceutics concerns that would preclude approval of this application. The Division of Scientific Investigations (DSI) audited the analytical and clinical portions of the pivotal bioequivalence study (AP-ADD-100). Based upon these inspections, DSI recommended that the analytical and clinical data from that study can be accepted for Agency review.

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

7. Clinical/Statistical-Efficacy

No clinical efficacy studies were submitted in this application

8. Safety

No new safety studies were submitted in this application. The following summary comments regarding the safety findings in the clinical pharmacology and abuse liability studies have been reproduced from pages 20, 21 and 22 of Dr. Pucino's review:

The extent of exposure to at least one dose of Tradename consists of 114 of 115 enrolled subjects, including 75 healthy volunteers enrolled in the two biopharmaceutics studies (AP-ADD-100 and K234-10-1001) and 40 recreational adult opioid users recruited for the abuse liability study (K234-10-1002). In the biopharmaceutics studies, subjects received three to five separate single doses of 5 to 15 mg of oxycodone HCl while naltrexone blocked, and for the abuse liability study, subjects received 15 mg of oxycodone HCl by insufflation on three separate occasions.

Since subjects were administered single oxycodone HCl doses (up to 15 mg on separate occasions) while naltrexone blocked in the pharmacokinetic studies, the data from these studies is not informative about the safety of oxycodone. There were no novel or unexpected adverse events in the abuse liability studies that enrolled opioid experienced subjects.

A total of ten (8.7%) of 115 subjects enrolled in the Phase 1 Clinical Development program discontinued for any reason from study (Table 1), with vomiting (n=5) and protocol non-compliance (n=2) as the most common reason for withdrawal.

Table 1: Disposition of Subjects in Phase 1 Studies

Study	Enrolled	Discontinued	Reasons
AP-ADD-100	40	3	Viral syndrome (n=1) Vomiting (n=1) Positive urine drug screen (n=1)
K234-10-1001	35	7	Vomiting (n=4) Protocol non-compliance (n=2) Withdrew consent (n=1)
K234-10-1002 (Treatment Phase)	40	0	Not applicable

Source: 2.7.4 Summary of Clinical Safety, Table 3, p.22 of 59.

The Applicant submitted a Phase 1 Abuse Liability study (K234-10-1002) to assess the relative abuse potential of crushed and intranasally administered Tradename (2 x 7.5 mg) compared with crushed and intranasally administered Roxicodone tablets (3 x 5 mg) in non-dependent recreational opioid users (see **Error! Reference source not found.**). As anticipated (b) (4), treatment-emergent adverse events related to nasal irritation (nasal congestion, dryness, and/or discomfort, rhinorrhoea, throat irritation and lacrimation) were more common with Tradename than with Roxicodone... Since subjects had only one exposure to the Applicant's product, possible long-term complications (e.g., ulceration or septal perforation) could not be assessed related to this off-label use.

The Oxecta formulation contains the excipient polyethylene oxide, which has been associated with reports of choking, gagging, regurgitation, tablets stuck in the throat and difficulty swallowing the tablet when used in other products. (b) (4)

Oxecta should not be crushed, dissolved and administered via nasogastric, gastric or other feeding tubes as it may cause obstruction of feeding tubes. Experience with abuse-resistant formulations that gel on contact with water, such as Oxecta, is limited. With one currently approved product, postmarketing reports described a problem with patients having some degree of difficulty swallowing the tablet, reporting that tablets got "stuck" in the esophagus resulting in writhing or vomiting in some patients. Serious adverse events were reported in a very small number of cases in which patients with prior gastrointestinal surgery or injury and resultant gastrointestinal narrowing developed obstruction. The labeling of those products was amended to ensure that patients swallowed the tablets with plenty of water, and this instruction on proper use has been included in the labeling for Oxecta.

I agree with the review team that there are no novel or unusually excessive adverse events that would preclude approval of this application.

9. Advisory Committee Meeting

As this was a reformulation of an approved opioid and as the Agency has already received sufficient advice from our advisory committee on the development of abuse-deterrent opioid formulations, this application was not taken to the advisory committee.

NDA 202080
Oxecta

Division Director's Review and Summary Basis for Approval
June 17, 2011

10. Pediatrics

No pediatric data were required for or submitted with this application because the application does not provide for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration and, therefore, does not trigger PREA.

11. Other Relevant Regulatory Issues

Oxecta's formulation was developed with the intent of reducing the abusability of immediate-release oxycodone by including excipients that made it less extractable for intravenous use, less desirable for nasal insufflation, and less syringable due to the fact that the tablets become a viscous mixture (b) (4)

The following summary of the abuse liability data and the CSS statistical analyses has been reproduced from pages 25 through 27 of Dr. Pucino's review:

Study K234-10-1002 was a randomized, double-blind, active-controlled, single-dose, 2-way crossover study assessing the relative abuse potential of crushed and intranasally administered Tradename (see **Error! Reference source not found.**). In this study, intranasal administration of crushed Tradename (2 x 7.5 mg) was compared with crushed immediate-release oxycodone HCl (Roxicodone) tablets (3 x 5 mg) in non-dependent recreational opioid users (n=40). Eligible subjects were required to be able to distinguish crushed Roxicodone tablets (positive control) from crushed placebo. The primary endpoint for this study was drug liking, measured up to eight hours post dosing using a visual analogue scale (VAS) during the study sessions ("at the moment" Drug Liking VAS) and at the end of the sessions (Overall Drug Liking VAS). Overall Drug Liking and Take Drug Again were secondary outcomes measured at eight hours post-dose (E_{8h}). Least square mean differences were estimated from a linear mixed-effect ANOVA with treatment sequence, period, and treatment as fixed effects, and subject within treatment sequence as a random effect.

The Applicant reported that nasal administration of crushed Tradename resulted in lower drug liking (Table 2; Figure 2) and greater nasal irritation (see **Error! Reference source not found.**) compared with crushed oxycodone HCl tablets, with considerable individual variability observed (ranging from 4% and 100%). The clinical significance of the degree of reduction in drug liking in this study has not been established.

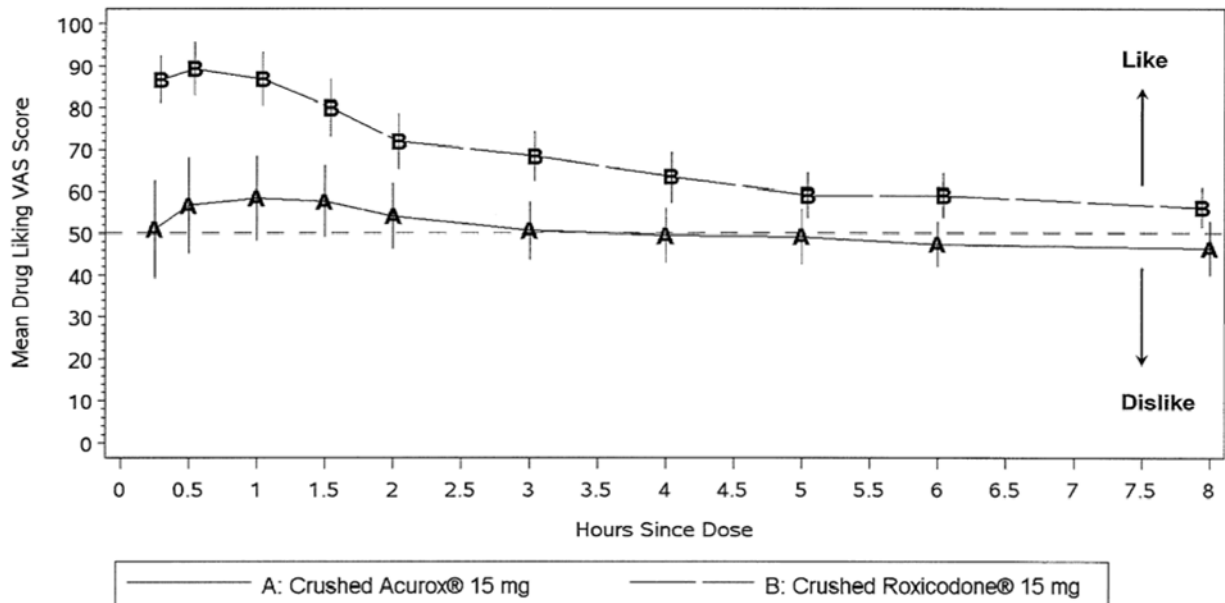
Table 2: Summary of Primary Analyses: Tradename Compared with Roxicodone Tablets

	Least Square Mean Difference ^a (SE)	95% CI	P-value
Drug Liking VAS E_{max}	-22.6 (4.67)	-32.0, -13.3	<0.0001
Overall Drug Liking VAS E_{8h}	-39.5 (6.25)	-52.0, -27.1	<0.0001 ^b
Take Drug Again VAS E_{8h}	-45.4 (7.28)	-59.9, -30.9	<0.0001 ^b

Source: Clinical Overview, Table 1, p.10 of 31.

Abbreviations: E_{8h} , effect at 8 hours; E_{max} , maximum peak effect; SE, standard error; VAS, visual analogue scale.

Figure 2: Mean (\pm 95% CI) Drug Liking VAS Scores Over Time



Source: Clinical Overview, Figure 2, p.9 of 31.

Dr. Ling Chen, the mathematical statistician for the Controlled Substance Staff (CSS), was consulted to evaluate Study K234-10-1002. Please refer to her review for a detailed description of the statistical concerns related to the design and conduct of this study. Overall, the study design of this Abuse Liability Study was considered inadequate. The primary deficiency in the study design was the potential for unblinding due to a greater than three-fold mg weight difference between crushed Tradename and crushed Roxicodone. Within the allotted five minutes of scheduled time, 21 subjects (53%) were unable to completely insufflate Tradename. However, the average percent of the Tradename dose insufflated was similar, regardless of sequence, whether it was administered before (84.7%) or after (82.6%) Roxicodone administration ($p=NS$). The most common reason for incomplete insufflation of Tradename was nasal passages blocked with material from the crushed tablet (reported by 18 subjects). Four subjects had low insufflation percentages for crushed Tradename, but had drug liking VAS scores higher than 90 mm. All patients were able to completely insufflate the entire dose of crushed Roxicodone tablets. Further, a sequence effect was observed in which 17 out of 20 subjects (85%) reported a Drug Liking VAS E_{max} score >60 mm versus 10 out of 20 subjects when Tradename were administered before and after Roxicodone, respectively. Mean differences in Drug Liking VAS E_{max} scores between Tradename and Roxicodone tablets were approximately -15 mm and -30 mm when Tradename was administered first versus second, respectively (All $p<0.05$). Since adjustments for the sequence effects were not possible, only first treatment comparisons were considered acceptable. Based on these data, no statistically significant differences (Wilcoxon-Mann-Witney test) in median responses between treatment groups were observed for the primary ($p=0.2261$) and secondary outcomes ($p>0.0609$).

Dr. Chen concluded that the study did not demonstrate that Tradename had a lower abuse potential than Roxicodone tablets when crushed and administered intranasally to non-dependent recreational opioid users...

However, while drug liking scores did not separate statistically, the difficulty snorting the crushed Tradename relative to Roxicodone, and the increased reports of nasal blocking and irritation

NDA 202080

Oxecta

Division Director's Review and Summary Basis for Approval

June 17, 2011

suggest that the Tradename formulation is less attractive for a nasal route of abuse than conventional formulations.

The following summary of the CSS conclusions and recommendations regarding the abuse liability studies has been reproduced from pages 4 through 6 of Dr. Randall-Thompson's review:

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 (b) (4) and mixing techniques (i.e., (b) (4)). 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.

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,^{1,2} 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 Roxycodone 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.

¹ 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.

² 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.

NDA 202080

12

Oxecta

Division Director's Review and Summary Basis for Approval

June 17, 2011

- 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.

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 [REDACTED] (b) (4)
[REDACTED]
Temperatures, extraction times and multi-step extraction procedures for tested solvents should be explored.
- 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 sponsor submitted the following table to summarize the abuse liability study findings:

Endpoint	OXECTA First in Sequence (n=20)		OXECTA Second in Sequence (n=20)	
	OXECTA	IR Oxycodone	OXECTA	IR Oxycodone
At the Moment Drug Liking (peak) ^a				
Mean (SD)	80.9 (25.2)	96.8 (6.9)	60.8 (28.3)	90.2 (14.4)
Median (Range)	92.5 (4-100)	100 (78-100)	59.5 (0-100)	97.5 (51-100)
Overall Drug Liking ^a				
Mean (SD)	62.8 (36.8)	95.2 (8.9)	32.9 (32.2)	79.6 (24.0)
Median (Range)	78.5 (0-100)	100 (72-100)	26.5 (0-84)	83 (0-100)
Take Drug Again ^b				
Mean (SD)	61.3 (42.1)	96.8 (7.5)	30.4 (40.8)	85.8 (25.1)
Median (Range)	77 (0-100)	100 (70-100)	1 (0-100)	100 (0-100)
Psychiatric disorders^c				
Euphoric Mood	12 (60%)	15 (75%)	9 (45%)	16 (80%)
Respiratory, thoracic and mediastinal disorders^c				
Nasal Congestion	17 (85%)	4 (20%)	15 (75%)	7 (35%)
Rhinorrhea	18 (90%)	1 (5%)	14 (70%)	4 (20%)
Nasal Discomfort	15 (75%)	6 (30%)	14 (70%)	6 (30%)
Throat Irritation	9 (45%)	1 (5%)	10 (50%)	2 (10%)
Eye disorders^c				
Lacrimation Increased	6 (30%)	0	8 (40%)	2 (10%)

^a Drug liking was assessed using a bipolar scale where 0 is strong disliking, 50 is neutral, and 100 is strong liking.

^b Willingness to Take Drug Again was assessed using a bipolar scale where 0 is Definitely Not, 50 is neutral, and 100 is Definitely So.

^c Data presented as number (percent).

While these studies may not have been designed and conducted in an ideal manner, they did meet the basic standards for abuse liability studies in assessing the key features of the formulation that may confer some tamper-resistance and potential for reduced abusability to the product. While the concerns raised regarding the statistical analyses and results of those analyses may bring into question the validity of those inferential statistical examinations, I would note that the descriptive statistical presentations appear to demonstrate a numerical

NDA 202080

Oxecta

Division Director's Review and Summary Basis for Approval

June 17, 2011

15

trend for decreased liking and decreased willingness to “take drug again” for Oxecta when compared to Roxicodone. The blinding may well have been inadequate, but nevertheless, more subjects appeared to “like” snorting Roxicodone compared to Oxecta. And the high dropout rates in the Oxecta arm are certainly what we would like to see with an abuse-deterrent formulation. Whether this was due to the larger quantity of Oxecta, local irritation due to excipients in the formulation (which they had been warned about as part of the informed consent), or a sequence effect, the important outcome is that less people liked or would re-abuse Oxecta compared to Roxicodone. In addition, there were clearly more adverse events related to the nasal irritation with the Oxecta, and there was also less euphoria seen with Oxecta than seen with Roxicodone. Whether this all ultimately translates into an actual impact on lowering abuse in the community will have to be explored post-marketing. The product labeling has been carefully crafted not to overstate the value of these findings.

Although Oxecta is less likely to be abused by the intravenous route (b) (4) the oxycodone can be extracted with the right solvents and under the right conditions. I do not think that the fact that this product is not likely to have a great impact on abuse by the intravenous route should preclude acknowledging the value of potentially reducing abuse by snorting which, as noted in the CSS review, is much more common than IV abuse for immediate-release oxycodone. I also do not agree that it is essential to know the specific mechanisms by which the excipients are causing decreased use, or which specific excipients are responsible for the decreased liking or willingness to re-abuse the product. The fact is, the formulation appears to be providing an incremental impact on abuse, at least in small studies, that may in the long run have some measurable effect on abuse in the community. As such, I do not think that additional abuse liability studies are essential to the approval of this application. However, the sponsor will be required to perform a post-marketing epidemiological study (or studies) to evaluate the impact of their novel formulation on actual abuse in the community.

On June 17th, after discussion between CSS and the division, Dr. Calderon filed an addendum to their earlier review. The following has been reproduced from pages 6 through 8 of that addendum:

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)

(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)

Thus, the main unresolved labeling issue is related to CSS's recommendation to (b) (4)

NDA 202080
Oxecta

Division Director's Review and Summary Basis for Approval
June 17, 2011

16

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.³ 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) 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 oropharyngeal 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 that (b) (4) and because it 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

³ Millovan, D. *et al.*, 2009, CPDD 71st Annual Meeting,
<http://www.cpdd.vcu.edu/Pages/Meetings/CPDD09AbstractBook.pdf>

that OXECTA has a reduced abuse liability compared to immediate-release oxycodone.

As such, the division and CSS are now aligned on the language for the label describing the results of the abuse liability studies. The need for any additional studies to better understand the abuse-deterrent qualities of the Oxecta formulation will be further evaluated and, if it is determined that additional studies might provide useful data, they can be requested as part of the post-marketing evaluation of the product.

12. Labeling

The Agency and the Applicant have reached agreement on the product labeling. The only section of the package insert that required extensive discussion between the Agency and the Applicant was the language describing the abuse liability studies. See Section 11 for a discussion of our review of these studies and the resultant labeling language.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

Considering the well known chemical and pharmacologic characteristics of oxycodone HCl and the established efficacy and safety of the referenced drug, Roxicodone, we have determined that the benefits of Oxecta outweigh the risks for the proposed indication, “for the management of acute and chronic moderate to severe pain where the use of an opioid analgesic is appropriate.” The applicant has also provided sufficient data to demonstrate that the Oxecta formulation appears to provide an incremental decrease in the willingness of subjects to abuse the drug product by the nasal route a second time, compared to Roxicodone. In addition, these subjects experienced an increase in upper respiratory adverse events and less euphoria when snorting Oxecta compared to snorting Roxicodone. While the applicant has not established that these features will result in an actual reduction in the abuse of Oxecta compared to other immediate-release oxycodone products, it is in the best interests of the public health to provide these data to prescribers and patients in the product labeling. Further evaluation of the actual impact of this new formulation on the abuse of immediate-release oxycodone, after a reasonable period to allow for market penetration, will be required as a PMR study, as described below.

- Postmarketing Risk Evaluation and Management Strategies

As an immediate-release opioid product, the applicant was not required to include a REMS as part of the Oxecta application.

- Postmarketing Study Requirements

A postmarketing epidemiology study will be required to address whether this formulation of oxycodone HCl results in an overall decrease in misuse and abuse of immediate-release oxycodone, and the consequences of that abuse, overdose, death and addiction. Depending on the results of this study, additional postmarketing investigations may be required to evaluate the effect of the formulation on misuse and abuse, and their consequences.

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/s/

BOB A RAPPAPORT
06/17/2011