

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201194Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, M.D.
Subject	Division Director Summary Review
NDA/BLA #	201-194/000 Second Review Cycle
Applicant Name	VistaPharm, Inc.
Date of Submission	July 14, 2011
PDUFA Goal Date	January 14, 2012
Proprietary Name / Established (USAN) Name	Oxycodone Hydrochloride Oral Solution
Dosage Forms / Strength	Oral solution, 5 mg per 5 mL
Proposed Indication(s)	For the relief of moderate to moderately severe pain where the use of an opioid analgesic is appropriate
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted	
OND Action Package, including:	
CMC	Julia Pinto, Ph.D., Prasad Peri, Ph.D.
Pharmacology/Toxicology	Elizabeth Bolan, Ph.D., Dan Mellon, Ph.D.
Clinical Pharmacology	Sheetal Agarwal, Ph.D., Yun Xu, M.D., Ph.D.
OPDP/DDDTCP	Twyla Thompson, Mathilda Fienkeng
OSE/DMEPA	Jamie Wilkins Parker, Pharm.D., L. Shenee Toombs, Pharm.D, Irene Chan, Pharm.D. BCPS
OSE/DRISK	Steve Morin, RN, BSN, Latonia Ford, RN, BSN, MBA, LaShawn Griffiths, RN, MSN, CWOCN,
CSS	Alicja Lerner, M.D., Lori Love, M.D., Ph.D., Michael Klein, Ph.D.
OSI	Arindam Dasgupta, Ph.D., Xikui Chen, Ph.D.

OND=Office of New Drugs
 DDDTCP=Division of Direct-to-Consumer Promotion
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication ErrorsPrevention
 CSS=Controlled Substance Staff

INTRODUCTION

Numerous unapproved narcotic analgesics are currently marketed, many under the mistaken belief that as very old products, it was not necessary for applications to be submitted for review under the Drug Efficacy Study Implementation program in support of the continued marketing of these products. The current application is for a product that has been marketed, although in unapproved regulatory status, oxycodone hydrochloride solution 5 mg per 5 mL.

The application received a complete response action on March 3, 2011 due to problems identified during the inspection of the analytic site for the clinical pharmacology studies. The current submission represents a complete response to the deficiency noted. The applicant conducted and submitted the results from a new bioequivalence (BE) study.

BACKGROUND

Opiate receptors were first identified in the early 1970's followed by the discovery of the first endogenous opiate-like substance, enkephalin. The existence of mu, delta and kappa sub-types of opiate receptors was also confirmed in the 1970's. Oxycodone, along with most of the clinically used opioids, is relatively selective for the mu receptor and it is through the mu receptor that it exerts its clinical effects.

In support of this 505(b)(2) application, the applicant has submitted findings from a clinical pharmacology study. No IND was opened for this product. No new clinical efficacy or safety studies and no new nonclinical studies were performed in support of this application. The applicant cites the pharmacokinetic data, published, peer-reviewed literature, and the Agency's previous findings of efficacy and safety for oxycodone hydrochloride for one referenced product:

- Roxycodone, oxycodone hydrochloride tablet, NDA 21-011, approved in 2000.

For immediate-release oxycodone hydrochloride products, such as the subject of this NDA, there is clear evidence of efficacy and safety based on the Agency's prior findings from other products. Therefore, the focus of this type of 505(b)(2) application is the chemistry, manufacturing and controls information, and the individual products' pharmacokinetic characteristics and how these relate to the listed product referenced in the NDA. In addition, there is a drug-related area of concern based on the presence of (b)(4) impurities with a structural alert for mutagenicity associated with (b)(4) opioids.

CHEMISTRY, MANUFACTURING AND CONTROLS

No new CMC data was submitted with this application. There were no CMC deficiencies noted from the original review cycle for this NDA. A review of the dosing cup was completed and found adequate.

The applicant has agreed to a postmarketing commitment to conduct a microbial challenge test to understand if the preservative matrix would eliminate the *Burkholderia cepacia*. The applicant will provide the test method(s) for *Burkholderia cepacia* and the relevant method validations. The test method(s) validation will address multiple strains of the species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested. The applicant will provide to the Agency no later than March 1, 2012, the results of the testing, and the Agency, upon evaluation of the data, will recommend appropriate specifications for *Burkholderia cepacia*.

As noted in my original memo, I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance and the manufacturing site inspections. Stability testing supports an expiry of 24 months.

MICROBIOLOGY

NA

NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

No new nonclinical information was submitted with this application.

As noted in my original memo, I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS

The following is from my original memo:

Two clinical pharmacology studies were conducted in support of this application. Both were single-dose, two-period, crossover studies in naltrexone blocked healthy volunteers, one in fasted subjects (Study R09-0988) and one in fed subjects (Study R09-0989.) Oxycodone oral solution was found to be bioequivalent to Roxicodone tablet in the fasted state, but not in the fed state. In the fed state, AUC was similar, but C_{max} was approximately 17% lower for the oxycodone oral solution. This difference is not great enough to expect any difference in efficacy or safety based on whether the patient is fasted or fed, nor does it require dosing instructions to take fed state into consideration.

The proposed dosing instructions of 5 to 15 mg every 4 to 6 hours as needed are acceptable. The absolute bioavailability of an oral dose of oxycodone is 60% to 87%. Oxycodone hydrochloride is extensively metabolized by CYP3A4 to noroxycodone and to a lesser extent by CYP2D6 oxymorphone. Oxycodone and its metabolites are excreted primarily via the kidney as both conjugated and unconjugated metabolites. Plasma protein binding of oxycodone is about 45%. Oxycodone has been found in breast milk. Apparent elimination half-life of oxycodone is 3.5 to 4 hours.

As described below, substantial deficiencies were identified at the analytic site for the bioequivalence studies. I concur with the conclusions reached by the clinical pharmacology reviewer that the deficiencies at the analytical site regarding analytical methodology preclude approval of the 5 mg per 5 mL oral solution. To address these deficiencies, the applicant will need to reanalyze the samples if feasible, alternatively, a new fasting bioequivalence study will need to be performed, as described below.

Dr. Agarwal has reviewed the new clinical pharmacology study. The following is from her review:

Study R11-0285 was an open-label single-dose, randomized, two-period, two-treatment crossover study under fasted conditions comparing exposure of oxycodone from 15 mL of the Oxycodone Oral Solution 5 mg/5 mL (test product) to that of a single oral dose of Roxicodone 15 mg tablets following an overnight fast of at least 10 hours. A total of 28 healthy adult subjects (male and female) were enrolled in the study, and 25 subjects completed the study. Subjects were dosed sequentially, in groups of 3 in each of the two dosing periods for a total of two doses per subject. Subjects were administered naltrexone (1 x 50 mg tablet) with oxycodone administration.

Dr. Agarwal concludes that a single oral dose of the 15 mg oxycodone oral solution (15 mL of 5 mg/5 mL) is bioequivalent to a 15 mg Roxicodone tablet under fasting conditions as shown in Table 1 from her review (p. 4). The median (min-max) Tmax was 1.0 h (0.5 – 2.0) for the test formulation and 1.0 h (0.75 - 3.0) for the reference formulation.

Parameter	Test	Reference	% Ratio	90% C.I.
AUC _{0-t} (ng*hr/mL)	150.91	146.22	103.21	(97.78, 108.94)
AUC _{0-inf} (ng*hr/mL)	153.33	148.48	103.27	(97.93, 108.90)
C _{max} (ng/mL)	32.53	33.39	97.43	(90.40, 105.00)

The analytical assay (AP LC/MS/MS 382.100) for determining oxycodone concentrations in plasma samples for Study R11-0285 was conducted at (b)(4). A DSI inspection was conducted for the analytical portion of the new BE study, R11-0285, which was conducted (b)(4). This was the same analytical site that was found to be unacceptable upon DSI inspection. The clinical portion of the repeat BA/BE study R11-0285 was the same as for the prior study and the inspection team had not identified any issues with this site previously.

The analytical site was found acceptable on inspection and no Form FDA-483 was issued for this study.

CLINICAL EFFICACY AND SAFETY

No new clinical efficacy or safety studies were submitted in support of this application. The clinical pharmacology studies were conducted in naltrexone-blocked healthy volunteers. As a result, safety information was not available for review. Reliance on the Agency's previous finding of efficacy and safety for Roxicodone tablets is adequately supported by the relative bioavailability study (Study R09-0988). No additional efficacy or safety studies are needed.

CONTROLLED SUBSTANCES STAFF

The Controlled Substances Staff had two recommendations. First, that the applicant conduct routine pharmacovigilance of this drug and report all cases of potential abuse, misuse or overdose (intentional or unintentional including cases leading to death). Second, the applicant should submit a summary of analysis in two years of all available data (including DAWN and AERS) and relevant information on drug diversion from the US market for the product, oxycodone HCl oral solution.

PEDIATRICS

The applicant has agreed to a pediatric plan that will evaluate the pharmacokinetics and safety of immediate-release oxycodone in ages ^(b)₍₄₎ to 17 years, and to evaluate the efficacy of immediate-release oxycodone in ages 0 to 2 years. Based on what is known about the site of action of oxycodone and what is known about the developmental maturity of the mu opioid receptor, efficacy can be extrapolated from adults for most age groups. However, it is not as clear that efficacy can be extrapolated below the age of 2 years and for this reason, efficacy studies for ages 0 to 2 years are required.

OTHER REGULATORY ISSUES

DSI Inspection

During the first review cycle, the DSI inspection found the following:

Substantial problems were identified at the ^(b)₍₄₎ analytic site for BE study R09-0988.

In particular, Dr. Chen noted:



(b) (4)

Dr. Chen recommended that Study R09-0988 not be accepted for review because (b) (4)

From Dr. Dasgupta's current review:

Following the above inspection, the (b) (4) Bioequivalence and GLP Compliance concludes (b) (4) (b) (4) were implemented for the current study (b) (4) and recommends that the analytical data of study R11-0285 be accepted for Agency review.

Exclusivity

The applicant has requested three years of exclusivity as a new delivery dosage, but in the absence of having performed any clinical studies necessary for approval, this application is does not support the applicant's request.

Financial Disclosure

There were no efficacy or safety studies conducted in support of this application.

LABELING

No proprietary names were proposed for this product.

The labeling has been reviewed and comments from DMEPA and OPDP DDTCP, and the review team have been incorporated. A medication guide to alert patients and caregivers about the risk for dosing errors with the oral solutions has been added to the labeling.

The package insert and the carton and container labels have been reviewed and comments sent to the applicant. The container labels have also been reviewed by DMEPA and recommendations for improvement have been forwarded to the applicant. Final agreement on these labeling components has been reached.

RECOMMENDATIONS/RISK-BENEFIT ASSESSMENT

- Recommended regulatory action - Approval
- Risk Benefit Assessment – The overall benefits associated with immediate-release oxycodone hydrochloride outweigh the overall risk associated with this opioid analgesic. The prior deficiency has been adequately addressed with a repeat BE study and an acceptable inspection of the analytic site for the clinical pharmacology study.
- Recommendation for Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps

The applicant has agreed to a postmarketing commitment to conduct a microbial challenge test to understand if the preservative matrix would eliminate the *Burkholderia cepacia*. The applicant will provide the test method(s) for *Burkholderia cepacia* and the relevant method validations. The test method(s) validation will address multiple strains of the species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested. The applicant will provide to the Agency no later than March 1, 2012, the results of the testing, and the Agency, upon evaluation of the data, will recommend appropriate specifications for *Burkholderia cepacia*.

The postmarketing requirement for pediatric studies for this NDA, which have been deferred are as follows:

1863-1 Pharmacokinetic and safety study in subjects >2 years to <17 years of age.

Final Protocol Submission: June 30, 2012
Study/Trial Completion: May 31, 2014
Final Report Submission: January 31, 2015

1863-2 Pharmacokinetic, safety, and efficacy study in subjects from birth to 2 years of age.

Final Protocol Submission: June 30, 2012
Study/Trial Completion: May 31, 2014
Final Report Submission: January 31, 2015

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

/s/

SHARON H HERTZ
01/12/2012