

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201194Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information	
NDA 201194, Resubmission (Complete Response to CR action letter issued Mar. 3, 2011)	
Proprietary Name: Oxycodone Hydrochloride Oral Solution, USP, 5mg/5mL Established/Proper Name: Oxycodone Hydrochloride Dosage Form: oral solution Strengths: 5mg/5mL	
Applicant: VistaPharm, Inc.	
Date of Receipt: July 14, 2011	
PDUFA Goal Date: January 14, 2012	Action Goal Date (if different): January 12, 2012
Proposed Indication(s): Management of moderate to severe pain where the 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)
Roxicodone (oxycodone hydrochloride tablets USP), NDA 021011	Pharmacokinetic data, sections of labeling

*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)

Bioequivalence (BE) studies

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 (oxycodone hydrochloride tablets USP)	NDA 021011	Y

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 (NDA 021011)

- b) Approved by the DESI process?

YES ☐ NO ☒

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

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

- c) Described in a monograph?

YES ☐ NO ☒

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

Name of drug(s) described in a monograph: N/A

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 dosage form, from tablet to oral solution.

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 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): NDA 200535 (Oxycodone Hydrochloride, oral solution, Lehigh Valley); NDA 022272 (Oxycontin XR, oral tablets, Purdue), NDA 200534 (Oxycodone Hydrochloride, oral capsules, Lehigh Valley); NDA 202080 (Oxecta, oral tablets, King Pharmaceuticals), and numerous generic oxycodone hydrochloride tablets.

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): There are no unexpired patents for Roxicodone (NDA 021011).

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/

DOMINIC CHIAPPERINO
01/12/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: December 6, 2011

Reviewer(s): Jamie Wilkins Parker, Pharm.D.
Division of Medication Error Prevention and Analysis

Team Leader Carlos Mena-Grillasca, RPh
Division of Medication Error Prevention and Analysis

Division Director Carol A. Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name(s): Oxycodone Hydrochloride Oral Solution
5 mg per 5 mL (1 mg/mL)

Application Type/Number: NDA 201194

Applicant/sponsor: VistaPharm

OSE RCM #: 2011-2566

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised carton and package insert labeling, and container labels for VistaPharm's Oxycodone Hydrochloride Oral Solution for their potential to contribute to medication errors.

1.1 BACKGROUND OR REGULATORY HISTORY

VistaPharm's Oxycodone Hydrochloride Oral Solution is a marketed, unapproved product. The NDA for this formulation was originally submitted May 4, 2010, and received a Complete Response from the Agency on March 3, 2011. These labels and labeling were initially reviewed by DMEPA in February, 2011 (RCM 2010-1378). The application was re-submitted to the Agency on July 14, 2011. There is no proposed proprietary name for this product at this time.

1.2 PRODUCT INFORMATION

Oxycodone HCl is an opioid analgesic indicated for the management of moderate to severe pain when the use of an opioid analgesic is appropriate. The usual recommended dose of Oxycodone HCl is 5 to 15 mg by mouth every 4 to 6 hours as needed for pain. This product is an oral solution that will be supplied in 5 mg/5 mL unit dose cups and 5 mg/5 mL 500 mL bottles with child resistant closures. The product should be stored from 20-25°C (68-77°F). There is also an approved, currently marketed, concentrated (20 mg/mL) Oxycodone HCl Solution (NDA 200535). It is available in a 30 mL bottle, and the carton labeling and container labels are well-differentiated from those of the 5 mg/5 mL (1 mg/mL) strength via blue coloring.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹ and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted June 9, 2011
- Carton Labeling submitted June 9, 2011
- Insert Labeling submitted June 9, 2011

Additionally, since Oxycodone is currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Oxycodone. The November 28, 2011 AERS search used the following search terms: active ingredients "Oxycodone", verbatim terms "Oxycod%". The reaction terms used were the MedDRA High Level Group Terms (HLGT) "Medication Errors" and "Product Quality Issues". The time frame of the search was limited to July 1, 2007 through the present, secondary to an AERS search completed in a post-marketing review

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

for Oxycodone Immediate Release products (including this liquid concentration). (RCM 2010-1694).

We performed an electronic search of the narratives of the retrieved reports for terms that may indicate that a medication error had occurred. The search terms used were ‘medication error’, ‘wrong’, ‘incorrect’, and ‘accidental’.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review. Reports excluded from the case series include those that did not describe a medication error that did not involve Oxycodone liquid, where Oxycodone was not the primary suspected product, and intentional overdoses.

Following exclusions we evaluated a total of one case relevant to this review.

3 RESULTS AND DISCUSSION

3.1 AERS CASES

A total of 454 reports were retrieved from our AERS search, however, after excluding cases as described in section 2, only one case was relevant to this review. The case is described below:

- Wrong Strength, Wrong Dose (Overdose) (n=1). There are duplicate reports regarding an 18 year old patient who was to receive a dose of Oxycodone 5 mg oral solution for throat pain in 2008 (the intended concentration of the solution was not specified in the narratives). The patient received the Oxycodone 20 mg/mL solution, and therefore, with a 5 mL dose of the incorrect concentration the patient received a 20 fold overdose of 100 mg. The patient required mechanical ventilation and was subsequently confined to a wheelchair.

The root cause of this error is unknown. In one report’s narrative it is speculated that there could have been confusion between mg and mL during interpretation of the prescription, however it is unknown whether or not the solution concentration was specified on the prescription. Alternatively, this error could have been caused by product selection error. Therefore, ensuring that the strength and concentration is prominent on the labels and labeling will assist in the prevention of future medication errors.

4 DISCUSSION OF DEFICIENCIES IDENTIFIED

The Applicant has addressed all the labeling recommendations provided in DMEPA’s initial review. However, there remains areas that introduce vulnerability that can lead to medication errors.

4.1 CARTON LABELING (INCLUDING OVERWRAP, BLISTERS, POUCH, ETC)

The carton labeling does not contain a concentration statement, contains statements that would be better suited for the side panel of the labeling (i.e. storage conditions), unnecessary graphics that crowd the label (i.e. measuring cup), and an imbalance of prominence between the strength and net quantity statements. The blister cup label also requires the relocation of the NDC number to the top 1/3rd of the label.

4.2 CONTAINER LABEL

The container label contains the same deficiencies, with the exception of the prominence of the net quantity statement, as the carton labeling stated above, as they are modeled after one another.

4.3 INSERT LABELING

The insert labeling currently only refers to the concentration per 5 mL of this product, and not the mg/mL concentration. We recommend in section 5 to add the concentration statement following all strength statements in the insert labeling. There is also a reference to the (b) (4) in the Patient Counseling section, which should be changed to address the fact that this medication is dispensed with a dosing cup.

5 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling introduce vulnerability that can lead to medication errors because of decreased prominence of important information, unnecessary coloring and graphics, as well as statements referring to a (b) (4), when this medication is supplied with a measuring cup. We recommend the following:

A. Carton Labeling

- i. Increase the prominence of the strength statement, as the net quantity statement is currently of equal prominence on the principal display panel.
- ii. Add the concentration of the solution in close proximity to the strength statement on the principal display panel, in lesser prominence than the strength statement. The strength and concentration should be presented as follows:
5 mg per 5mL
(1 mg/mL)
- iii. Decrease the prominence of the net quantity statement, as it is currently more prominent than the strength statement.
- iv. Increase the prominence of the medication guide statement by bolding the complete sentence.

- v. Relocate the storage statements to the side panel, to reduce clutter and increase readability of the remaining statements on the principal display panel.
- vi. (b) (4)
- vii. Increase the statement for the pharmacist to dispense with the calibrated measuring cup.
- viii. Remove the (b) (4) from the lower portion of the principal display panel and back panel, as it decreases the readability of the information, and places undue prominence on this area of the carton labeling.

B. Container Label

- i. Increase the prominence of the strength statement, as the net quantity statement is currently of equal prominence on the principal display panel.
- ii. Add the concentration of the solution in close proximity to the strength statement on the principal display panel, in lesser prominence than the strength statement. The strength and concentration should be presented as follows:
5 mg per 5mL
(1 mg/mL)
- iii. Increase the prominence of the medication guide statement by bolding the complete sentence.
- iv. Remove the (b) (4) on the lower portion of the principal display panel, as it decreases the readability of the information, and provides undue prominence to this section of the container label.

C. Insert Labeling

- a. Revise the fifth bullet point in Section 17 (Patient Counseling Information) to refer to the calibrated measuring cup, as it currently refers to an (b) (4) for administration of the drug.

If you have further questions or need clarifications, please contact Danyal Chaudhry, project manager, at 301-796-3813.

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/s/

JAMIE C WILKINS PARKER
12/06/2011

CARLOS M MENA-GRILLASCA
12/08/2011

CAROL A HOLQUIST
12/08/2011



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: December 5, 2011

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

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

From: Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: **NDA 201-194 Oxycodone HCl Oral Solution 5 mg/ 5 mL**
Indication: Relief of moderate to moderately severe pain where an opioid analgesic is appropriate.
Dosages: Oral solution 5 mL to 15 mL every 4 to 6 h as needed
Company: VistaPharm, Inc.

Materials reviewed: NDA 201-194 resubmission is located in EDR (received July 14, 2011)
Previous PIND 105,754

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I. Summary

A. Background

This memorandum responds to the DAAAP consult regarding abuse potential of Oxycodone HCl Oral Solution 5 mg/5 mL by VistaPharm, Inc. The sponsor submitted NDA 201-194 for the currently marketed, but unapproved, oxycodone HCl product to bring it into regulatory compliance. This NDA is submitted as a 505(b)(2) application. The Reference Listed Drug is Roxicodone immediate-release oxycodone tablet 15 mg marketed by (b) (4) NDA 21-011, approved March 17, 2008, of Boehringer Ingelheim Roxane Laboratories, Inc.

FDA issued Complete Response on March 3, 2011, due to deficiencies identified in the methods used at the analytical site (b) (4) for the BA/BE study R09-0988.

The sponsor performed a new BA/BE study R11-0285 which was an open-label, single-dose, randomized, two-period, two-treatment crossover study under fasted conditions in 28 healthy adult subjects (male and female). Each subject received either a single oral dose of Oxycodone Hydrochloride 5 mg/5 mL Oral Solution, or a single oral dose of Roxycodone 15 mg.

The study was found by the Office of Clinical Pharmacology to be acceptable.

B. Conclusions:

1. Oxycodone HCl is listed as a Schedule II narcotic in the Controlled Substances Act.

C. Recommendations:

1. REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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/s/

ALICJA LERNER
12/05/2011

MICHAEL KLEIN
12/05/2011

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Direct-to-Consumer Promotion

******Pre-decisional Agency Information******

Memorandum

Date: October 28, 2011

To: Dominic Chiapperino, Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: L. Shenee' Toombs, Regulatory Review Officer
Division of Direct-to-Consumer Promotion (DDTCP)
Office of Prescription Drug Promotion (OPDP)

CC: Mathilda Fienkeng, Regulatory Review Officer, Division of Professional
Promotion (DPP)
Shefali Doshi, Group Leader, DDTCP, OPDP
Lisa Hubbard, Group Leader, DPP, OPDP

Subject: NDA 201194
DDTCP labeling comments for Oxycodone Hydrochloride Oral Solution

OPDP's Division of Direct-to-Consumer Promotion (DDTCP) has reviewed the proposed Medication Guide (MG) for NDA 201194 for Oxycodone Hydrochloride Oral Solution submitted for consult on September 29, 2011. This review replaces OPDP's October 13, 2011 consult review. DDTCP's comments are based on the proposed draft marked-up labeling titled "\\Fdsfs01\ode2\DAAAP\NDA and sNDA\NDA 201194 (Oxycodone Oral Solution VistaPharm)\Labeling\NDA 201194 USPI-MedGuide submitted 9-7-11.doc" that was sent via email from DAAAP to OPDP on October 5, 2011.

Please note that comments on the proposed product labeling (PI) and Carton and Container labeling were provided under separate cover on October 12, 2011.

DDTCP's comments on the MG are provided directly in the marked-up document attached (see below).

Thank you for the opportunity to comment on the proposed PPI.

If you have any questions regarding the PPI, please contact Shenee' Toombs at 301-796-4174 or LaToya.Toombs@fda.hhs.gov.

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/s/

LATOYA S TOOMBS
10/28/2011

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Direct-to-Consumer Promotion

******Pre-decisional Agency Information******

Memorandum

Date: October 13, 2011

To: Dominic Chiapperino, Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: L. Shenee' Toombs, Regulatory Review Officer
Division of Direct-to-Consumer Promotion (DDTCP)
Office of Prescription Drug Promotion (OPDP)

CC: Mathilda Fienkeng, Regulatory Review Officer, Division of Professional
Promotion (DPP)
Shefali Doshi, Group Leader, DDTCP, OPDP
Lisa Hubbard, Group Leader, DPP, OPDP

Subject: NDA 201194
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/s/

LATOYA S TOOMBS
10/13/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Promotion/Division of Direct-to-Consumer Promotion**

******Pre-decisional Agency Information******

MEMORANDUM

Date: October 12, 2011

To: Dominic Chiapperino – Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: Mathilda Fienkeng – Regulatory Review Officer
Division of Professional Promotion (DPP)

CC: Lisa Hubbard – Professional Group Leader (DPP)
Sheneé Toombs – DTC Reviewer
Shefali Doshi – DTC Group Leader
Division of Direct-to-Consumer Promotion (DTCP)

Subject: **DPP draft labeling comments**
NDA 201194 Oxycodone Hydrochloride Oral solution CII

OPDP has reviewed the proposed product labeling (PI), Medication Guide, and Carton and Container labeling for Oxycodone Hydrochloride Oral Solution CII submitted for OPDP review on September 29, 2011. The following comments are provided using the substantially complete version of the labeling sent via email on October 5, 2011, by Dominic Chiapperino.

DPP's comments are provided directly in the attached marked-up copy of the PI. DTCP's comments on the proposed Medication Guide will be provided under separate cover. If you have any questions about DPP's comments, please do not hesitate to contact Mathilda Fienkeng at 301-796-3692 or at Mathilda.fienkeng@fda.hhs.gov.

Carton and Container Label

DPP has reviewed the sponsor submitted proposed carton and container labeling of June 09, 2011, and has no comment.

22 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MATHILDA K FIENKENG
10/12/2011

MEMORANDUM

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

DATE: September 20, 2011

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

FROM: Arindam Dasgupta, Ph.D. and
Xikui Chen, Ph.D.
Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Chief, Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

SUBJECT: Review of EIR Covering NDA 201-194, Oxycodone Oral
Solution, 5 mg/5 mL, Sponsored by VistaPharm, Inc.

At the request of DAAAP, Division of Bioequivalence and GLP
Compliance audited the analytical portion of the following study:

Study Number: R11-0285

Study Title: A Relative Bioavailability Study of Oxycodone 5
mg/5 mL Oral Solution versus Roxycodone 15 mg
Tablets under Fasted Conditions

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

The inspection was conducted to verify [REDACTED] (b) (4) corrective
actions [REDACTED] (b) (4)

[REDACTED] OSI had concerns about reliability of
BE/BA data generated by [REDACTED] (b) (4) facility between [REDACTED] (b) (4)
[REDACTED] for the following reasons:

[REDACTED] (b) (4)

(b) (4)

Following the audit of the analytical records of study R11-0285
(study conducted after (b) (4)

(b) (4) no Form FDA-483 was
issued and there were no significant adverse findings.

Conclusions:

Following the above inspection, the Division of Bioequivalence
and GLP Compliance concludes that sufficient corrective actions
to the concerns (b) (4)
(b) (4) and recommends
that the analytical data of study R11-0285 be accepted for
Agency review.

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

Arindam Dasgupta, Ph.D.

Xikui Chen, Ph.D.

Sam H. Haidar, Ph.D., R.Ph.

Final Classification:

Cetero Research, Houston, TX - NAI (Analytical)

CC:

CDER DSI PM TRACK

OC/Ball/Moreno

OC/OSI/DBGK/Salewski/Haidar/Dasgupta/Chen/Skelly/Dejernet

ORA/DAL-DO/Gatica

ORAORO/DDFI/NES/McClure

OND/ODEII/DAAAP/Dominic Chiapperino

OTS/OC/DCPII/Yun Xu/Sheetal Agarwal

Draft: XC 9/19/2011

Edit: MFS 9/19/2011; SHH 9/19/2011

OSI: 6254; 0:\BE\EIRC0VER\201194vis.oxy11.doc

FACTS (b) (4)

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/s/

XIKUI CHEN
09/20/2011

ARINDAM DASGUPTA
09/20/2011

SAM H HAIDAR
09/27/2011

MEMORANDUM

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

DATE: August 17, 2011

TO: Director, Investigations Branch
Dallas District Office (DAL-DO)
4040 N. Central Expressway, Suite 300
Dallas, TX 75204

From: Sam Haidar, Ph.D., R.Ph. _____
Chief, Bioequivalence Investigations Branch
Division of Bioequivalence and GLP Compliance (DBGC)
Office of Scientific Investigations (OSI)

SUBJECT: FY 2011, **High Priority PDUFA NDA Pre-Approval Data
Validation Inspection**, Bioresearch Monitoring, Human
Drugs, CP 7348.001

RE: NDA 201194
DRUG: Oxycodone HCl oral solution, USP, 5 mg/5 mL
SPONSOR: VistaPharm, Inc

This memo requests an inspection of the analytical portion of the following bioequivalence study. A scientist from DBGC, OSI (formerly DSI) with specialized knowledge may participate in the inspection of the analytical site to provide scientific and technical expertise. Please contact DBGC upon receipt of this assignment to arrange scheduling of the inspection. However, **we prefer that this study be audited during the inspection planned for the week of** (b) (4)

Study Number: R11-0285

Study Title: A Relative Bioavailability Study of Oxycodone 5 mg/5 mL Oral Solution versus Roxycodone 15 mg Tablets under Fasted Conditions

Analytical Site:

(b) (4)

**Analytical
investigator:**

(b) (4)

Analytical Method: LC/MS/MS

Please note that the sponsor conducted a new bioequivalence study (R11-0285, which is the subject of this assignment) in response to the Agency's Complete Response. The previous inspection at (b) (4) identified deficiencies in the analytical portion of the previous bioequivalence study, R09-0988. In light of the inspectional history at (b) (4) please confirm the following items:

1. (b) (4)

2. (b) (4)

(b) (4)

Following identification of the investigator, background material will be forwarded directly.

Headquarters Contact Person: Seongeun Julia Cho, Ph.D.
(301) 796-5032

CC:

CDER DSI PM TRACK

OSI/DBGC/Salewski/Haidar/Yau/Cho/Chen/DasGupta/Dejernett
/Matthews/CF

HFR-SW150/ Susan Turcovski (DIB)

HFR-SW1540/Joel Martinez (BIMO)

HFR-SW1515/Alanna L. Bias (BIMO)

DAAAP/ Dominic Chiapperino

Draft: SC 8/17/2011

Edit: MFS 8/17/2011

DSI: 6253; O:\BE\assigns\bio201194.doc

FACTS: (b) (4)

APPEARS THIS WAY ON ORIGINAL

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/s/

SEONGEUN CHO

08/19/2011

MICHAEL F SKELLY

08/19/2011

Skelly signing on behalf of Dr. Haidar

DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: August 12, 2011

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

FROM: Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

SUBJECT: Request for Biopharmaceutical Inspections
NDA 201194
Oxycodone HCl oral solution, USP, 5 mg/5 mL
VistaPharm, Inc
7265 Ulmerton Road
Largo, FL 33771, USA
Phone: (707) 530-1633
Email: jlay@vistapharm.com

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) 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)
R11-0285	Alan K. Copa, Pharm.D, Cetero Research Phone: (701) 239-4750 Fax: (701) 239-4955 Email: alan.copa@cetero.com 4801 Amber Valley Parkway Fargo, ND 58104, USA (Whether this clinical site needs to be re-inspected in this 2nd cycle was discussed with Dr. Sam Haidar from DSI. Given DSI busy workload, and recent, uneventful inspection of this site in 1st review cycle, DAAAP and DCP2 consider this site optional for 2nd cycle inspections.)	(b) (4) 

NDA 201194

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: N/A

N/A There is a lack of domestic data that solely supports approval;

N/A Other (please explain):

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **November 20, 2011**. We intend to issue an action letter on this application by **Jan. 13, 2012**.

Should you require any additional information, please contact Dominic Chiapperino, Ph.D., Senior Regulatory Project Manager, DAAAP.

Concurrence:

Sheetal Agarwal, Ph.D., Clinical Pharmacology Reviewer, DCP2

Yun Xu, Ph.D., Clinical Pharmacology Team Leader, DCP2

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/s/

DOMINIC CHIAPPERINO
08/12/2011

SHEETAL S AGARWAL
08/12/2011

YUN XU
08/12/2011

MEMORANDUM

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

DATE: March 16, 2011

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

FROM: Xikui Chen, Ph.D.
Chemist
Division of Scientific Investigations (HFD-48)

THROUGH: Sam H. Haidar, Ph.D., R.Ph. *Sam H. Haidar*
Chief, GLP and Bioequivalence Branch
Division of Scientific Investigations (DSI)

Martin K. Yau, Ph.D. *Martin K. Yau*
Acting Team Leader (Bioequivalence)
Division of Scientific Investigations

SUBJECT: Addendum to the Review of EIRs Covering NDA 201-194, Oxycodone Oral Solution, 5 mg/5 ml, Sponsored by VistaPharm, Inc.

At the request of DAAP, the Division of Scientific Investigations conducted an audit of the clinical and analytical portions of the following bioequivalence study supporting NDA 201-194:

Study Number: R09-0988

Study Title: "A Relative Bioavailability Study of 5mg/5ml Oxycodone Oral Solution Versus 15 mg Roxicodone® Tablets Under Fasting Conditions"

DSI inspection summary memo for the above study was sent to DAAP on February 3, 2011. DSI recommended that the study not be accepted for review at that time due to the lack of information to confirm that (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

On [REDACTED] (b) (4)
[REDACTED] submitted additional response to the Form FDA 483
via an e-mail (Attachment 2). Our evaluation of [REDACTED] (b) (4)
[REDACTED] written response is summarized below:

1

(b) (4)

2.

(b) (4)

(b) (4)

Conclusion:

DSI's recommendation provided in the previous EIR cover memo (dated February 3, 2011) remains unchanged.

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



Xikui Chen, Ph.D.
Chemist

Final Classification:

Cetero Research, (b) (4)
Cetero Research, Fargo, ND - NAI

cc: DARRTS
DSI/Ball/Haidar/Yau/Viswanathan/Chen/DeJernett/CF
HFD-170/Dominic Chiapperino/Ellen Fields (DAAP)
HFR-SW1540/Joel Martinez (BIMO)
HFR-SW150/Susan Turcovski (DIB)
HFR-CE8590/Constance Richard-Math (BIMO)
HFR-CE850/Cheryl A. Bigham (DIB)
HFR-CE300/Darren Holaday
HFR-SW1580/Albert Peacock
Draft: XC 3/11/11, 3/16/11
Edit: MKY 3/14/11
Edit: SHH 3/15/11
DSI: 6118; O:\BE\EIRCover\201194vis.oxy.add. doc
FACTS (b) (4)

cc: email
CDER DSI PM TRACK

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/s/

XIKUI CHEN
03/16/2011

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: February 10, 2011

To: Dominic Chiapperino – Senior Regulatory Health Project Manager
Division of Anesthesia and Analgesia Products (DAAP)

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

Subject: **DDMAC Draft Medication Guide Comments**
NDA 201194 Oxycodone Hydrochloride Oral Solution CII

DDMAC has reviewed the proposed Medication Guide for Oxycodone Hydrochloride Oral Solution, submitted for DDMAC review on January 4, 2011.

The following comments are provided using the updated Medication Guide sent via email on February 3, 2011 by Dominic Chiapperino. If you have any questions about DDMAC's comments, please do not hesitate to contact us.

Comments on the proposed product labeling (PI) were provided in a separate memo on February 9, 2011 by Mathilda Fienkeng.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

TWYLA N THOMPSON
02/10/2011

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

PATIENT LABELING REVIEW

Date: February 10, 2011

To: Bob Rappaport, MD, Director
Division of Analgesics and Anesthetics Products (DAAP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)

Barbara Fuller, RN, MSN, CWOCN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management

From: Latonia M. Ford, RN, BSN, MBA
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name(s): Oxycodone Hydrochloride Oral Solution (5mg/5mL)

Application Type/Number: NDA 201-194

Applicant/sponsor: VistaPharm, Inc.

OSE RCM #: 2010-1379

1 INTRODUCTION

This review is written in response to a request by the Division of Analgesics and Anesthetics Products (DAAP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for Oxycodone Hydrochloride Oral Solution.

VistaPharm, Inc. submitted a New Drug Application (NDA) on May 4, 2010 (received May 5, 2010) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Oxycodone Oral Solution. Oxycodone Hydrochloride Oral Solution is an immediate-release oral formulation indicated for the management of moderate to severe pain where the use of an opioid analgesic is appropriate.

VistaPharm also submitted a Risk Evaluation and Mitigation Strategy (REMS) to inform patients about the serious risks associated with the use of Oxycodone Hydrochloride Oral Solution. DRISK submitted the review of the proposed REMS to DAAP on January 20, 2011, under separate cover.

DRISK conferred with DMEPA and DMEPA deferred to DRISK to provide review comments on patient labeling.

2 MATERIAL REVIEWED

- Draft Oxycodone Hydrochloride Oral Solution Medication Guide (MG) received on May 5, 2010, revised by Review Division throughout the current review cycle and received by DRISK on January 27, 2011.
- Draft Oxycodone Hydrochloride Oral Solution Prescribing Information (PI) received on May 5, 2010, revised by Review Division throughout the current review cycle and received by DRISK on January 27, 2011.

3 RESULTS OF REVIEW

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG, document using the Verdana font, size 11.

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

- ensured that the MG is consistent with the Morphine Sulfate Oral Solution MG approved December 2009 comparator label where applicable

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

LATONIA M FORD

02/10/2011

LASHAWN M GRIFFITHS

02/10/2011

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: February 9, 2011

To: Dominic Chiapperino – Senior Regulatory Health 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 201194 Oxycodone Hydrochloride Oral solution CII

DDMAC has reviewed the proposed product labeling (PI), Medication Guide, and Carton and Container labeling for Oxycodone Hydrochloride Oral Solution submitted for DDMAC review on January 4, 2011. DDMAC's comments on the proposed Medication Guide will be provided under separate cover.

The following comments are provided using the updated proposed PI sent via email on February 03, 2011, by Dominic Chiapperino. If you have any questions about DDMAC's comments, please do not hesitate to contact us.

Carton and Container Labeling

DDMAC has reviewed the carton and container labeling and has no comment.

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MATHILDA K FIENKENG
02/09/2011

MEMORANDUM

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

DATE: February 3, 2011

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

FROM: Xikui Chen, Ph.D.
Chemist
Division of Scientific Investigations (HFD-48)

THROUGH: Sam H. Haidar, Ph.D., R.Ph. Sam H. Haidar
Chief, GLP and Bioequivalence Branch
Division of Scientific Investigations (DSI)

Martin K. Yau, Ph.D. Martin K. Yau 2/3/2011
Acting Team Leader (Bioequivalence)
Division of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 201-194, Oxycodone Oral Solution, 5 mg/5 ml, Sponsored by VistaPharm, Inc.

At the request of DAAP, the Division of Scientific Investigations conducted an audit of the clinical and analytical portions of the following bioequivalence study supporting NDA 201-194:

Study Number: R09-0988

Study Title: "A Relative Bioavailability Study of 5mg/5ml Oxycodone Oral Solution Versus 15 mg Roxicodone® Tablets Under Fasting Conditions"

The clinical portion of Study R09-0988 was conducted at Cetero Research, Fargo, ND. Following inspection of the clinical site (November 29 - December 1, 2010), no Form FDA 483 was issued.

The analytical portion was conducted at [REDACTED] (b)(4)
[REDACTED] Following inspection of the analytical site
[REDACTED] (b)(4) Form FDA 483 was issued

(Attachment 1). In addition to the studies mentioned above, the inspection at the analytical site also included a follow-up investigation of a complaint received by the Agency in (b)(4), in which an (b)(4) - (b)(4) in a number of bioanalytical studies. The response to the Form FDA-483 from (b)(4) (b)(4) was received on (b)(4) electronically via an e-mail (Attachment 2). The 483 observations, (b)(4) written response, and our evaluations follow:

(b)(4)

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(b) (4)



Conclusion:

Following DSI's evaluation of the inspectional findings,
DSI recommends the following:

(b) (4)



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



Xikui Chen, Ph.D.
Chemist

Final Classification:

 (b) (4)
Cetero Research, Fargo, ND - NAI

cc: DARRTS
DSI/Ball/Haidar/Yau/Viswanathan/Chen/DeJernett/CF
HFD-170/Dominic Chiapperino/Ellen Fields (DAAP)
HFR-SW1540/Joel Martinez (BIMO)
HFR-SW150/Susan Turcovski (DIB)
HFR-CE8590/Constance Richard-Math (BIMO)
HFR-CE850/Cheryl A. Bigham (DIB)
HFR-CE300/Darren Holaday
HFR-SW1580/Albert Peacock
Draft: XC 1/21/11; 1/28/11; 2/3/11
Edit: MKY 1/28/11
Edit: SHH 1/30/11
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/s/

XIKUI CHEN
02/03/2011

**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: February 2, 2011

Application Type/Numbers: NDA 201-194

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

Through: Irene Z. Chan, PharmD, BCPS, Acting Team Leader
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: L. Shenee' Toombs, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Oxycodone Hydrochloride Oral Solution 5 mg/5 mL

Applicant/sponsor: VistaPharm

OSE RCM #: 2010-1378

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1.1	INTRODUCTION	3
1.2	REGULATORY HISTORY	3
1.3	PRODUCT INFORMATION	3
2	METHODS AND MATERIALS.....	3
2.1	LABELS AND LABELING RISK ASSESSMENT	3
2.2	ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE	4
3	RESULTS	4
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1 BACKGROUND

1.1 INTRODUCTION

This review evaluates the container labels and package insert labeling for VistaPharm's Oxycodone Hydrochloride for their potential to contribute to medication errors.

1.2 REGULATORY HISTORY

VistaPharm's Oxycodone Hydrochloride Oral Solution is a marketed, unapproved product. The NDA for this formulation was submitted on May 4, 2010. There is no proposed proprietary name for this product at this time.

Fourteen postmarketing medication error cases associated with unapproved, marketed oxycodone products were reviewed in OSE 2010-1694. These cases involved wrong drug, wrong dose, wrong strength, and wrong patient errors. Of the 14 cases, one is relevant to this review.

LeHigh Valley Technologies' Oxycodone Hydrochloride capsules (5 mg) and oral solution (100 mg/5 mL) are the only approved immediate-release oxycodone hydrochloride products. These products were recently approved under NDA 200534 and NDA 200535 on October 20, 2010.

1.3 PRODUCT INFORMATION

Oxycodone hydrochloride is an opioid agonist indicated for the relief of moderate to severe acute and chronic pain where the use of an opioid analgesic is appropriate. The usual dose is 5 mg to 15 mg every 4 to 6 hours as needed. The product will be supplied in 5 mL unit dose cups and 500 mL bottles of the 5 mg/5 mL solution.

2 METHODS AND MATERIALS

2.1 LABELS AND LABELING RISK ASSESSMENT

We use Failure Mode and Effects Analysis (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling; thereafter, we provide recommendations that aim at reducing the risk of medication errors.

The Applicant submitted container labels on May 4, 2010 (see Appendix A and B) and insert labeling on May 24, 2010:

- Container Label: 5 mL unit dose cups (5 mg per 5 mL)
- Container Label: 500 mL bottle (5 mg per 5 mL)
- Insert labeling (no image)

2.2 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

We used the findings of the AERS search conducted in OSE 2010-1649, to identify post-marketing cases involving single ingredient oxycodone immediate-release products.

3 RESULTS AND DISCUSSION

3.1 LABELS AND LABELING

It was determined that the labels and labeling need improvement in the following areas: appropriate presentation of the established name, decreased prominence of the Applicant's name, elimination of negative statements, inclusion of lot number and expiration date, modification of background colors and text to increase readability, and inclusion of a medication guide statement. Our recommendations are further explained in Section 4.

3.2 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

The search conducted in OSE 2010-1694 identified one medication error case that is pertinent to the review of the container labels and carton labeling for VistaPharm's oxycodone oral solution. The one case involved a 21-month old patient who received a prescription for Oxycodone 1 mg/mL, but was dispensed 20 mg/mL. This type of medication error demonstrates the need for the differing product strengths to be readily distinguishable for the proposed product and other approved oxycodone products. See our recommendations in Section 4 with regard to this issue.

4 RECOMMENDATIONS

Our evaluation of the proposed container labels noted areas of needed improvement in order to minimize the potential of medication errors. We provide recommendations on the insert labeling in Section 4.1, Comments to the Division. Section 4.2, Comments to the Applicant, contains our recommendations for the container labels. We request the recommendations in Section 4.2 be communicated to the Applicant prior to approval (See Appendices A and B for the container labels). Additionally, DMEPA is aware that the Applicant may be submitting a dosing device with this application. We request to be consulted for assessment of the dosing device once submitted.

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, please contact the OSE Regulatory Project Manager, Bola Adeolu, at 301-796-4264.

4.1 COMMENTS TO THE DIVISION

DMEPA notes the Division is currently revising the submitted insert labeling to maintain consistency with the approved labeling for LeHigh Valley Technologies' oxycodone hydrochloride (NDA 200535). Therefore we have only one additional comment at this time. In the Dosage and Administration section of the insert labeling, there are instructions t (b) (4)

However the Applicant is submitting a different dosing device and the language should be modified to reflect the approved dosing device.

4.2 COMMENTS TO THE APPLICANT

A. All Labels (500 mL bottle, 5 mL unit dose cups)

1. A placeholder for the lot number and expiration date are not indicated on the labels, include the lot number and expiration date on the labels.
2. Relocate the company name, 'VistaPharm' from the (b) (4) of the principal display panel. Minimize the font to ensure that the company name does not compete with the prominence of the established name and the strength presentation.

B. Container Labels for 500 mL bottle

1. Due to the recommended dosage and administration of oxycodone, it is feasible that the bottle may be dispensed as a unit-of-use container. This is concerning because children may inadvertently access these bottles. Ensure the bottle utilizes a child-resistant closure to prevent accidental exposure.
2. We note that although the 500 mL bottle may be a unit-of-use container, it may also be used for more than one patient. Ensure a sufficient number of medication guides are provided.
3. The active ingredient is 'Oxycodone Hydrochloride'. As currently presented 'Oxycodone' has a greater prominence due to the font size and the use of uppercase. Modify the presentation of the active ingredient so that "Oxycodone" and "hydrochloride" have equal prominence. Additionally, consider revising the active ingredient to appear in title case (i.e. Oxycodone Hydrochloride). Words set in upper and lower case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all-upper case.
4. Include a medication guide statement to remind pharmacist to dispense a medication guide to each patient. In addition, the statement should include how the medication guide is provided. For example, the statement could read, "Pharmacist: Dispense with attached Medication Guide to each patient".
5. The black text color over the green shaded background is difficult to read. Change the color hue of the shaded background to increase the contrast with the black text.
6. Delete the negative statement, (b) (4) Negative statements can be misinterpreted as the opposite intended meaning.
7. Revise the statement, "Each 5 mL contains: Oxycodone-----5 mg" to read, "Each 5 mL Contains: Oxycodone Hydrochloride_____5 mg"

8. Decrease the prominence of the Manufacture's statement, "VistaPharm, Inc., Largo...". As currently presented, it is more prominent than more important information presented above.

C. Container Labels for 5 mL Unit Dose Cups

1. Remove the established name and dosage form (Oxycodone Hydrochloride Oral Solution) out of the (b) (4). Use the (b) (4) the strength statement (5 mg per 5 mL) only.
2. As currently displayed the barcode is prominently located, relocate the barcode to the bottom of the label, away from the more pertinent information on the label.
3. Modify the statement, (b) (4) to read "5 mL". As currently presented the use of the word (b) (4) is supplied in the unit dose cup.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

LATOYA S TOOMBS
02/02/2011

IRENE Z CHAN
02/02/2011

CAROL A HOLQUIST
02/03/2011

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information	
NDA # 201194	
Proprietary Name: Oxycodone HCl, Oral Solution, USP, 5mg/mL Established/Proper Name: oxycodone HCl Dosage Form: oral solution Strengths: 5mg/5mL	
Applicant: VistaPharm, Inc. Agent for Applicant (if applicable): n/a (not applicable)	
Date of Application: May 4, 2010 Date of Receipt: May 5, 2010 Date clock started after UN: n/a	
PDUFA Goal Date: March 5, 2011	Action Goal Date (if different): n/a
Filing Date: July 4, 2010	Date of Filing Meeting: June 23, 2010
Chemical Classification: (1,2,3 etc.) (original NDAs only) 7 (marketed, unapproved drug product)	
Proposed indication: Management of moderate to severe pain where the use of an opioid analgesic is appropriate.	
Type of Original NDA: AND (if applicable) Type of NDA Supplement: <i>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.</i>	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification:	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐ <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ 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): n/a				
List referenced IND Number(s): 105754 (only for Pre-IND interaction)				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, 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.</i>	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	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.			X	
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?		X		Copy of waiver letter from FDA provided
<u>User Fee Status</u> <i>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 UN letter and contact user fee staff.</i>	Payment for this application: ☐ Paid ☐ Exempt (orphan, government) ☒ Waived (e.g., small business, public health) ☐ Not required			
<i>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.</i>	Payment of other user fees: ☒ Not in arrears ☐ In arrears			
Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).				

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 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))?		X		
<i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>				
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		X		
If yes, please list below:				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<i>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.</i>				
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 [21 CFR 316.3(b)(13)]?				
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only)	X			
If yes, # years requested: 3 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		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)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	☐ 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 guidance¹? If not, explain (e.g., waiver granted).	X			Some sections do not appear in correct eCTD section. Sponsor will be asked to correct this with an amendment.
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) If no, explain.	X			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? <i>If yes, date consult sent to the Controlled Substance Staff: JUN-21-2010</i>	X			

BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				

Forms and Certifications				
<i>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.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>				
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?			X	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?	X			Not included with original submission, but was requested and submitted in an amendment.
<i>Forms must be signed by the APPLICANT, not an Agent.</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)	X			
<i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i>				
<i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(l) 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...”</i>				

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? <i>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)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>				

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)</i> <i>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.</i>	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		Full waiver requested, but not granted.
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? <i>If no, request in 74-day letter</i>	X			Full waiver requested, but will not be granted. We will work with sponsor to obtain a pediatric plan that addresses PREA requirements.
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) <i>If no, request in 74-day letter</i>	X			
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i>		X		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>		X		It was already discussed that their intention to market using only established name is acceptable.
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? <i>If no, request in 74-day letter.</i>	X			Not in original submission, but was requested and received before filing letter.
Is the PI submitted in PLR format?	X			Not in original submission, but was requested and received before filing letter.
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? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			X	
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			
REMS consulted to OSE/DRISK?	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	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?				
<i>If no, request in 74-day letter.</i>				

Are annotated specifications submitted for all stock keeping units (SKUs)?				
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)				
<i>If yes, specify consult(s) and date(s) sent:</i>				

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):		X		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s):		X		A Pre-IND meeting was held, which discussed issues more appropriate as Pre-NDA. These minutes were distributed.
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):		X		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 23, 2010

BLA/NDA/Supp #: NDA 201194

PROPRIETARY NAME: none requested

ESTABLISHED/PROPER NAME: Oxycodone Oral Solution, USP

DOSAGE FORM/STRENGTH: 5 mg/5 mL oral solution

APPLICANT: VistaPharm, Inc.

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

BACKGROUND: This application is for a marketed unapproved product. It is a (b)(2) application consisting of bioequivalence studies, comparing to RLD, Roxicodone (oxycodone HCl) IR tablets.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Dominic Chiapperino	Y
	CPMS/TL:	Parinda Jani	
Cross-Discipline Team Leader (CDTL)	Rob Shibuya		Y
Clinical	Reviewer:	n/a	
	TL:	Rob Shibuya	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	n/a	
	TL:	n/a	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	n/a	
	TL:	n/a	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	n/a	
	TL:	n/a	

Clinical Pharmacology	Reviewer:	Sheetal Agarwal	Y
	TL:	Suresh Doddapaneni	Y
Biostatistics	Reviewer:	n/a	
	TL:	Dionne Price	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Beth Bolan	Y
	TL:	Dan Mellon	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	n/a	
	TL:	n/a	
Product Quality (CMC)	Reviewer:	Julia Pinto	Y
	TL:	Danae Christodoulou	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	n/a	
	TL:	n/a	
CMC Labeling Review (<i>for BLAs/BLA supplements</i>)	Reviewer:	n/a	
	TL:	n/a	
Facility Review/Inspection	Reviewer:	Not yet assigned at time of filing meeting	
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	n/a	
	TL:		
OSE/DRISK (REMS)	Reviewer:	Not yet assigned at time of filing meeting	
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Not yet assigned at time of filing meeting	
	TL:		

Other reviewers		
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: The application was received with some problems with organization and completeness, but it can be filed and the issues addressed.	☐ Not Applicable
CLINICAL	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE
Comments:	☐ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain:	☐ YES ☐ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an original NME or BLA application, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>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</i>	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

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: No efficacy studies for this (b)(2) application.	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ 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

<u>Environmental Assessment</u> • 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
<u>Quality Microbiology (for sterile products)</u> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments:	☐ Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? Comments:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review (BLAs/BLA supplements only)</u> Comments:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Bob A. Rappaport 21st Century Review Milestones (see attached) (optional): Primary and secondary reviews: by Jan. 5, 2011 CDTL review and package to Signatory: by Feb. 12, 2011 PDUFA/Action date: on Mar. 5, 2011 Comments: No other comments.	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☒	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	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

☒	Other... (1) Work with sponsor about PREA requirements and pediatric plan. (2) Work with sponsor to fix placement of documents within eCTD format. (3) Follow up on information requests.
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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/

DOMINIC CHIAPPERINO
01/14/2011



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

Date: January 3, 2011

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

Through: Michael Klein, Ph.D., Director
Lori A. Love, M.D., Ph.D., Lead Medical Officer
Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: **NDA 201-194** Oxycodone HCl oral solution 5 mg/ 5 mL
Indication: relief of moderate to moderately severe pain where an opioid analgesic is appropriate.
Dosages: oral solution 5 mL to 15 mL every 4 to 6 h as needed
Company: VistaPharm, Inc.

Materials reviewed: NDA 201-194 is located in EDR (received May 5, 2010)
Previous PIND 105,754

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A. Background:

This memorandum responds to the DAAP consult regarding abuse potential of oxycodone HCl oral solution 5 mg/5 mL by VistaPharm, Inc. The sponsor submitted NDA 201-194 for the currently marketed, but unapproved, oxycodone HCl product to bring it into regulatory compliance. This NDA is submitted as a 505(b)(2) application. The Reference Listed Drug is Roxicodone (oxycodone HCl) Tablets 15 mg, NDA 21-011, (approved March 17, 2008) of Boehringer Ingelheim Roxane Laboratories, Inc.

The present submission includes a CMC section and description of two bioavailability studies in healthy adult subjects: study R09-0988 (under fasted condition after a single dose of oxycodone oral solution 15 ml vs 1 tablet 15 mg of Roxicodone) and study R09-098 (under fed conditions after a single dose of oxycodone oral solution 15ml vs 1 tablet 15 mg of Roxicodone).

The final drug product is supplied with 5 mL unit dose container and 500 mL multi use bottle and cap. This product has the same indication, dosage, and route and duration of administration as the previously marketed, but unapproved drug product.

The sponsor has no questions specific for CSS, but DAAP requests input from CSS regarding this NDA.

B. Conclusion

The sponsor states that Oxycodone HCl oral solution 5 mg per 5 mL (VistaPharm, Inc.) and Roxicodone® Tablets 15 mg (b) (6) are bioequivalent after a single oral dose of 15 mg in fasted healthy subjects but not in fed subjects.

Oxycodone HCl is listed as a Schedule II narcotic in the Controlled Substances Act.

C. Recommendation (to be relayed to the Sponsor)

1. Conduct routine pharmacovigilance of this drug and report all cases of potential abuse, misuse or overdose (intentional or unintentional including cases leading to death).
2. 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.

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/s/

ALICJA LERNER
03/02/2011

LORI A LOVE
03/02/2011

LORI A LOVE on behalf of MICHAEL KLEIN
03/02/2011

DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: September 20, 2010

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

THROUGH: (Required for international inspections)
Bob A. Rapport, MD, Director, Division of Anesthesia and Analgesia Products (DAAP),
HFD-170

FROM: Dominic Chiapperino, PhD, Regulatory Project Manager, DAAP, HFD-170

SUBJECT: Request for Biopharmaceutical Inspections
NDA 201194
Oxycodone oral solution, 5mg/ 5mL
VistaPharm Inc.

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) 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)
R09-0988 A RELATIVE BIOAVAILABILITY STUDY OF 5 MG/5 ML OXYCODONE ORAL SOLUTION VERSUS 15 MG ROXICODONE® TABLETS UNDER FASTING CONDITIONS	Clinical Research Facility and Principal Investigator: Alan K. Copa, Pharm.D. Cetero Research 4801 Amber Valley Parkway Fargo, ND 58104, USA Phone(701) 239-4750 Clinical Laboratory Facility: Cetero Research – Fargo Clinical Laboratory 4801 Amber Valley Parkway Fargo, ND 58104, USA	Bioanalytical Facility: (b) (4) Pharmacokinetic and Statistical Analyses: Cetero Research 4801 Amber Valley Parkway Fargo, ND 58104, USA

	Sponsor Representative: John Lay VistaPharm Inc. 7265 Ulmerton Road Largo, FL 33771, USA Phone: (707) 530-1633 Email: jlay@vistapharm.com	Report Author:  (b) (4)
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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 INSPECTION SUMMARY GOAL DATE. We intend to issue an action letter on this application by **March 5, 2011.**

Should you require any additional information, please contact Dominic Chiapperino, PhD, Regulatory Project Manager, at 301-796-1183.

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/s/

DOMINIC CHIAPPERINO
09/20/2010