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RESEARCH**

APPLICATION NUMBER:

201194Orig1s000

MEDICAL REVIEW(S)

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, M.D.
Subject	Division Director Summary Review
NDA/BLA #	201-194/000
Applicant Name	VistaPharm, Inc.
Date of Submission	May 4, 2010
PDUFA Goal Date	March 3, 2011
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:	Complete response

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., Ph.D., Suresh Doddapaneni, Ph.D.
DDMAC	Twyla Thompson, Mathilda Fienkeng
OSE/DMEPA	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.
DSI	Xikui Chen, Ph.D., Martin K. Yau, Ph.D.

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication ErrorsPrevention

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 in support of the continued marketing of these products. The current application is for a product that has

been marketed, although previously unapproved, oxycodone hydrochloride solution 5 mg per 5 mL.

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

The drug substance for the oxycodone hydrochloride oral solution is supplied by (b)(4) initially under DMF (b)(4) and then (b)(4). Under DMF (b)(4), the process to produce the drug substance, also produced an (b)(4). To limit the amount of (b)(4) that forms, (b)(4) modified their process and decreased the amount of (b)(4) to less than (b)(4). Under DMF (b)(4), oxycodone is produced using a new process resulting in a minimal of (b)(4) formation. The drug substance specifications were updated during the course of the review, with the (b)(4) controlled at NMT (b)(4) as requested by the Agency. The final revised drug substance controls and specifications are acceptable.

The drug product is manufactured by Vista Pharm, Inc. Largo, FL, as a 5mg/5ml oral red solution including sodium benzoate (b)(4), red colorant and raspberry flavoring. It is packaged in 5 mL unit dose cups and 500 mL HDPE bottles. The Agency requested that the applicant add a dosing device to be packaged with the 500 mL bottles,

preferably an oral syringe. The applicant submitted a calibrated cup; however, this has not been fully evaluated due to the late arrival of the submission (February 7, 2011.) The drug substance and drug product manufacturing sites were found acceptable on (b) (4) respectively.

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. However, a review of the dosing cup must be completed prior to approval of this oral solution oxycodone to ensure reliable doses are administered.

MICROBIOLOGY

NA

NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

No new nonclinical studies were submitted in support of this application. As noted in the CMC section, (b) (4) opioid analgesics often have impurities (b) (4) with a structural alert for mutagenicity. The initial specification for (b) (4) was too high, and the applicant was able to lower the specification to NMT (b) (4). Updated acceptance specifications were also submitted for several drug substance impurities which were not included the original NDA application. The specifications for all of the substances, including impurity (b) (4) meet thresholds set by ICH Q3A and were all acceptable. One impurity, (b) (4) has been determined not to be an (b) (4) by our CMC group and therefore may be regulated as a typical non-genotoxic impurity. The specification for (b) (4) was set at (b) (4) by the applicant which exceeds ICH Q3A qualification thresholds, (b) (4) 6- α -oxycodol is a well-characterized human metabolite. See Dr. Bolan's review addendum for further discussion of acceptable thresholds for (b) (4).

There are no novel or unique excipients. The container closure system is acceptable in terms of the leachable/extractable safety justification.

From the nonclinical pharmacology/toxicology perspective, the proposed drug products do not present any unique toxicology concerns and no further studies are required to support this NDA.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS

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 Roxycodone tablet in the fasted state, but not in the fed state. In the fed state, AUC was similar, but Cmax 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.

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 Roxycodone 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

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)

(b) (4)

The deficiencies were conveyed to the applicant along with possible remedial actions to address the deficiencies. Options for remedial action include:

1. Provided adequate subject samples from bioequivalence study R09-0988 are still available, reanalyze the samples for oxycodone and submit data establishing bioequivalence of oxycodone hydrochloride oral solution with Roxicodone. Ensure that the inspectional deficiencies identified in Agency's audit of study R09-0988 are properly addressed in the reanalysis of the subject samples.

2. Conduct another pharmacokinetic study to establish bioequivalence of oxycodone hydrochloride oral solution with Roxicodone under fasting conditions using adequately validated analytical methodology.

Exclusivity

The applicant has requested three years of exclusivity as a new delivery dosage. This will be reviewed once the application can be approved.

REMS

A medication guide-only REMS was submitted. The primary safety concern for oral solution opioid analgesics is the risk of medication errors due to confusion between mg and mL and between oral solutions with different concentrations. While this application only includes a 5 mg per 5 mL oral solution, there are oxycodone oral solutions currently on the market with other concentrations. There are many years of experience from marketing of the unapproved products during which medication errors have been reported based on mistakes in understanding how to properly measure the prescribed dose. It is necessary to understand that a 20 mg dose of oxycodone can be represented by 20 mL of a 5 mg per 5 mL concentration or 1 mL of the 100 mg per 5 mL concentration. It is important that the prescription be written clearly describing the dose in mg and the number of mL to be measured and the concentration of the solution to be dispensed.

Patients and their caregivers will have the medication guide to inform them of these important safety considerations. The REMS and the medication guide were reviewed. REMS comments were not conveyed to the applicant, however, a REMS may no longer be required by the time of approval for a product that only has a medication guide and does not have any elements to assure safe use. This will be addressed further upon the submission of a complete response. However, review of the final instructions for use of the proposed dosing cup have not been completed due to the late timing of submission of this information.

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 DDMAC, DMEPA, 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 not yet been reached.

RECOMMENDATIONS/RISK-BENEFIT ASSESSMENT

- Recommended regulatory action - Complete response
- Risk Benefit Assessment – The overall benefits associated with immediate-release oxycodone hydrochloride outweigh the overall risk associated with this opioid analgesic; however, problems identified during the inspection of the analytic site for the clinical pharmacology studies preclude approval until the deficiencies have been resolved by either reanalysis of the data or repeat of the bioequivalence study.
- Recommendation for Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
 - None at this time.

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/s/

SHARON H HERTZ
03/03/2011