

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

200535Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, M.D.
Subject	Division Director Summary Review
NDA/BLA #	200-534
Supplement #	200-535
Applicant Name	Lehigh Valley Technologies Inc.
Date of Submission	December 22, 2009
PDUFA Goal Date	October 22, 2010
Proprietary Name / Established (USAN) Name	Oxycodone Hydrochloride Capsule Oxycodone Hydrochloride Oral Solution
Dosage Forms / Strength	Capsule, 5 mg Oral solution, (b) (4) 100 mg per 5 mL (20 mg/mL)
Proposed Indication(s)	Relief of moderate-to-severe pain in opioid tolerant patients
Action/Recommended Action for NME:	Approval: Capsule, 5 mg and Oral solution 100 mg per 5 mL (20 mg/mL) (b) (4)

Material Reviewed/Consulted	
OND Action Package, including:	
CMC	Eugenia Nashed, Ph.D.,
ONDQA Biopharmaceutics	Minerva Hughes, Ph.D., Angelica Dorantes, Ph.D.
Microbiology	Robert J. Mello, Ph.D.
Pharmacology/Toxicology	Carlic Huynh, Ph.D., Dan Mellon, Ph.D.
Clinical Pharmacology	Wei Qiu, Ph.D., Suresh Doddapaneni, Ph.D.
DDMAC	Twyla Thompson, Mathilda Fienkeng
OSE/DMEPA	Kristina A. Toliver, Pharm.D
OSE/DRISK	Robin Duer, MBA, BSN, RN, Shawna Hutchins, MPH, BSN, RN; Melissa Hulett, MSBA, BSN, RN
CSS	Alicja Lerner, M.D., Lori Love, M.D., Ph.D., Michael Klein, 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 applications are for two products that have been marketed, although previously unapproved, oxycodone hydrochloride capsules (NDA 200-534) and oxycodone hydrochloride oral solution (NDA 200-535) (b) (4) 100 mg per 5 mL (20 mg/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 these 505(b)(2) applications, the applicant has submitted findings from two clinical pharmacology studies conducted under IND 78,623. 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 subjects of these two NDAs, 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 products referenced in the NDA. In these NDAs there is also a drug-related area of concern based on the presence of (b) (4) impurities with a structural alert for mutagenicity, a finding common to thebaine-based opioids.

CHEMISTRY, MANUFACTURING AND CONTROLS

Capsule

The drug substance for the oxycodone hydrochloride capsules is supplied by (b) (4) DMF (b) (4), found to have adequate status as of Sep 29, 2010. (b) (4)

(b) (4). The final revised drug substance controls and specifications are acceptable.

As noted by Dr. Nashed, there were multiple formulation changes during development of the capsule drug product, including substantial changes in excipients and a change in drug substance used in biobatches in comparison to the to-be-marketed product. The drug product controls were revised several times during the course of NDA review. Additional revisions are needed for the drug product dissolution specifications (method,

method validation and acceptance criteria), and these are specified in an agreement from the Applicant as required by the Biopharmaceutics reviewer, Dr. Hughes.

An agreement was provided by the applicant to revise the dissolution method and specifications in a post-approval supplement. The data support an expiry period of 24 months for the drug product, (b) (4)

(b) (4) Due to the interim specifications and limited data available for the drug product dissolution, any extension of drug product expiry period beyond 24 months may be accomplished only *via* a prior-approval supplement with adequate supporting data.

The overall EER status for this NDA is acceptable (AC) as of Jan 7, 2010.

I concur with the conclusions reached by the chemistry and biopharmaceutics reviewers regarding the acceptability of the manufacturing of the drug product and drug substance and the manufacturing site inspections. The applicant for the capsule can be approved with the interim acceptance criteria provided and an agreement to develop and validate a new dissolution method based on unit sampling that is sufficiently discriminating to assure product quality control. A full dissolution method development and validation report, in accordance with applicable ICH, FDA and USP guidelines will need to be submitted within 1 year of receipt of the action letter for review.

Oral Solution (b) (4) 100 mg per 5 mL

The oxycodone hydrochloride drug substance for the oral solution formulations is manufactured by (b) (4) and supported by DMF (b) (4), which has an acceptable status. The manufacturing process was (b) (4)

Revision of drug substance controls has resulted in acceptable controls for identification, assay, individual and total impurities, water content, and residual solvents.

(b) (4)

The 100 mg per 5 mL drug product is a yellow, berry-flavored liquid, packaged in 30 mL white HDPE bottles with a window stripe, CR closures and heat-induction innerseal supplied in an individual carton. A separately overwrapped, 1 mL calibrated oral syringe has been added to the configuration. The oral syringe replaces a (b) (4) closure to provide more reliable dose measurements and its use is supported by a short bridging dose accuracy study. The oral syringe is made from (b) (4) that comply with (b) (4). The oral syringe will not be part of the container closure system, in contrast to the (b) (4), and is acceptable.

The oral solution is manufactured and released by Lehigh Valley Technologies, Inc. Drug product controls were also revised during the course of NDA review. Additional revisions in the microbial limit controls, i.e., development of the method, method validation and acceptance criteria for the content/absence of *Burkholderia cepacia* are required, but can be performed under a proposed post-approval agreement.

The applicant completed a five-way, single-dose, crossover study to establish bioequivalence of the 100 mg per 5 mL oral solution products to the referenced drug product and to establish bioavailability relative to the referenced drug product. (b) (4)



I concur with the conclusions reached by the chemistry and biopharmaceutics reviewers regarding the acceptability of the manufacturing of the drug product and drug substance for the 100 mg per 5 mL formulation which can be approved in conjunction with an agreement to develop and perform an assay for *Burkholderia cepacia*. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months.



MICROBIOLOGY

A microbiology review of the oral solution formulations initially found several deficiencies including a lack of a release specification for microbial limits. The applicant was asked to provide microbial limit specifications at release which include acceptance criteria and associated test methodology (see USP<61>, <62> and <1111>), and microbial limits testing conducted within the stability program. The Applicant has amended the release specifications to include microbial limits testing, and this was found to be acceptable. In addition, the Applicant committed to include microbial limits testing (with the above listed acceptance criteria) within the stability program (b) (4). The applicant has also committed to developing and

validating an analytical method to demonstrate the absence of *Burkholderia cepacia*. Since this will require time to develop and validate, it was agreed that the method and data would be completed and submitted to the NDA as a prior approval supplement by March 31, 2011.

NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

Capsule

As noted by Dr. Huynh, all excipients can be found in the Inactive Ingredient Guide (IIG), are normally used in capsules, and are under the maximum potency limits per capsule. Using 200 mg as the maximum theoretical daily dose (MTDD) of oxycodone from 5 mg strength oxycodone capsules, the exposure of excipients to patients taking the 5 mg strength oxycodone oral is acceptable based on the IIG, status as GRAS, and other products previously approved by FDA containing comparable amounts. From a nonclinical pharmacology toxicology perspective, Dr. Huynh concludes there are no safety concerns.

Oral Solution (b) (4) 100 mg per 5 mL

As with the capsule, the excipients are listed in the IIG at with the exception of the berry flavor, and all are present in amounts within the maximum described in the IIG except sodium benzoate, saccharin sodium, and sorbitol (b) (4). Dr. Huynh notes that, while above the maximum in the IIG, sodium benzoate is within the limit set by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). The amount of exposure to saccharin and sorbitol, based on large theoretical maximum daily doses, do not result in a safety concern as noted by Dr. Huynh. The berry flavor, Natural and Artificial Berry flavor (b) (4), is novel, and the DMF for this product was reviewed and found acceptable.

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 application.

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

Capsule

A five-way, single-dose, crossover study (Study UPN-1189) was conducted to establish bioequivalence of the proposed immediate-release capsule to Roxicodone, the referenced drug. A single oral dose of the 15 mg oxycodone capsules (3 x 5 mg) was found to be bioequivalent to a 15 mg Roxicodone tablet (1 x 15 mg) under fasting conditions. The effect of food was evaluated following a standard high fat breakfast, and demonstrated a decrease in oxycodone C_{max} by 14% and increase in oxycodone AUC_{0-t} and AUC_{inf} by

21 and 23%, respectively. These changes are not expected to have clinical importance with regard to safety or efficacy.

(b) (4)

Oral Solution 100 mg per 5 mL

In Study UPN-1189, the five-way, single-dose, crossover study, a 15 mg dose of the 100 mg per 5 mL oral solution was found to be bioequivalent to a 15 mg Roxycodone tablet and the oxycodone 5 mg capsule, under fasting conditions.

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval of the 5 mg oral capsule and the 100 mg per 5 mL oral solution, (b) (4)

CLINICAL EFFICACY AND SAFETY

No new efficacy or safety studies were conducted or submitted in support of this application. Reliance on the Agency's previous finding of efficacy and safety for Roxycodone tablets is adequately supported by the relative bioavailability study (Study UPN-1189) that evaluated the capsule and the 100 mg per 5 mL oral solution. No additional efficacy or safety studies are needed.

(b) (4)

CONTROLLED SUBSTANCES STAFF

The Controlled Substances Staff recommended routine pharmacovigilance for this drug and reporting of all cases of potential abuse, and misuse or overdose (intentional or unintentional and leading to death) broken down by formulations.

PEDIATRICS

The applicant has agreed to a pediatric plan that will evaluate the pharmacokinetics and safety of immediate-release oxycodone in ages 0 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 is required.

OTHER REGULATORY ISSUES

A medication guide-only REMS has been established for this NDA 200-535, oxycodone hydrochloride oral solution. The primary safety concern is the risk of medication errors. Although no NDA existed for oxycodone oral solutions prior to this NDA, there are many years of experience from marketing of the unapproved products. 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 (b) (4) 1 mL of the 100 mg per 5 mL concentration. It is important for the prescription be written clearly describing the dose in mg and the number of mL to be measured.

Patients and their caregivers will have the medication guide to inform them of these important safety considerations. Physicians will be informed through the addition of a boxed warning added to the package insert. Prescribers will also be alerted to the importance of prescribing (b) (4) 100 mg per 5 mL oral solution (b) (4)

and specifying that it is for relief of moderate to severe acute and chronic pain in opioid-tolerant patients, (b) (4)

The REMS, medication guide and patient instructions for use were reviewed, comments were conveyed to the applicant and the recommended changes were accepted.

It is also necessary to ensure selection of the proper product by the dispensing pharmacist. This will be addressed by clearly distinguishing the cartons for the different concentrations.

The applicant's certification of financial interests and arrangements of clinical investigators, (Form 3454) was reviewed. The sponsor certified that they have not entered into any financial arrangements requiring disclosure.

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 for NDA 200-535.

Agreement has been reached on the language for the package insert and the carton and container labels have also been reviewed and agreed upon.

RECOMMENDATIONS/RISK-BENEFIT ASSESSMENT

- Recommended regulatory action
 - Approval of the capsule 5 mg (NDA 200-534) and the 100 mg per 5 mL oral solution (NDA 200-535).



- Risk Benefit Assessment – The overall benefits associated with immediate-release oxycodone hydrochloride outweigh the overall risk associated with this opioid analgesic.
- Recommendation for Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
 - A Medication Guide-Only REMS will be put into place.
 - Agreements
 1. As a Phase 4 agreement, you are required to develop a new dissolution method for the capsule based on unit sampling that is sufficiently discriminating to assure product quality control. A full dissolution method development and validation report, in accordance with applicable ICH, FDA and USP guidelines should be submitted within 1 year of receipt of the action letter for review. Note that the development of an in-process disintegration test does not preclude the requirement for an acceptable dissolution method for product release. Proposed dissolution tolerances must be based on data and sufficiently justified. The dissolution method is a two part process comprised of the dissolution step and the determinative step. The HPLC method for assaying dissolution samples must be appropriately validated. Validation data (specificity, accuracy, linearity, range, method repeatability, intermediate precision, etc.) should be clearly presented in the dissolution method development report.

2. Submit the method (or methods) that will be used for the demonstration of the absence of *Burkholderia cepacia* in Oxycodone Hydrochloride Oral Solution drug product(s). Provide sufficient data to validate the ability of the assay to detect *Burkholderia cepacia* if present, as well as document the limit(s) of detection. The USP General Chapters <1227> VALIDATION OF MICROBIAL RECOVERY FROM PHARMACOPEIAL ARTICLES and <1223> VALIDATION OF ALTERNATIVE MICROBIOLOGICAL METHODS may provide useful guidance.

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/s/

SHARON H HERTZ
10/20/2010