CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200535Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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:	October 12, 2010
To:	Robert Rappaport, MD, Director **Division of Analgesics and Anesthetics Products (DAAP)**
Through:	Claudia Karwoski PharmD, Director **Division of Risk Management (DRISK)** Melissa Hulett, MSBA, BSN, RN Patient Labeling Reviewer **Division of Risk Management (DRISK)**
From:	Robin Duer, MBA, BSN, RN Senior Patient Labeling Reviewer (MG, PIFU) **Division of Risk Management (DRISK)** Shawna Hutchins, MPH, BSN RN Patient Labeling Reviewer (REMS) **Division of Risk Management (DRISK)**
Subject:	DRISK Review of Patient Labeling (Medication Guide, Patient Instructions for Use) and Proposed Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	Oxycodone Hydrochloride Oral Solution (20 mg/mL)
Application Type/Number:	NDA 200535
Applicant/sponsor:	Lehigh Valley Technologies, Inc.
OSE RCM #:	2010-1488

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), Patient Instructions for Use (PIFU), Proposed Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document for Oxycodone Hydrochloride Oral Solution (20 mg/mL). Please let us know if DAAP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

The DRISK review of the methodology and survey instruments to be submitted by the Applicant to evaluate the REMS will be provided under separate cover.

2. BACKGROUND

Lehigh Valley Technologies, (LVT) Inc., submitted a New Drug Application (NDA) dated and received December 22, 2009, under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Oxycodone Hydrochloride Oral Solution ((b) (4) 20 mg/mL

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks. In accordance with section 505-1 of the FDCA, the FDA determined that a REMS is necessary for Oxycodone Hydrochloride Oral Solution ((b) (4) 20 mg/mL) to ensure that the benefits of the drug outweigh the risk of medication errors, which may result in overdose. On May 25, 2010, a teleconference was held between DAAP and LVT, Inc. during which DAAP indicated that LVT must submit a Risk Evaluation and Mitigation Strategy (REMS) that includes a Medication Guide and a Timetable for Submission of Assessments.

DAAP (b) (4) does plan to approve the 20mg/5mL dose. (b) (4) (b) (4) DAAP requested that the Applicant submit an amendment which provided for an oral syringe medicine delivery device identical to that used for the approved for Morphine Sulfate Oral Solution. An amendment providing for the use of the syringe (b) (4) was received by the Agency on September 21, 2010. Amended labeling has not been submitted by the Applicant as of this date.

During the team labeling meeting on September 29, 2010, DAAP requested that DRISK:

- Propose a Patient Instructions for Use (PIFU) using the oral syringe identical to the Morphine Sulfate Oral Solution PIFU approved on January 25, 2010.
- Refer to the (b) (4) only in the patient labeling (20 mg/mL)
- Refer to the approved Morphine Sulfate Oral Solution MG dated January 25, 2010 as a comparator for the review of the Oxycodone Hydrochloride Oral Solution MG.

DRISK conferred with DMEPA and DMEPA deferred to DRISK to provide PIFU review comments.

3. MATERIAL REVIEWED

- Draft Oxycodone Hydrochloride Oral Solution ([(b) (4)] 20 mg/mL) Prescribing Information (PI) submitted December 22, 2009, revised by the Review Division throughout the current review cycle and received by DRISK on September 29, 2010.
- Draft Oxycodone Hydrochloride Oral Solution [(b) (4)] 20 mg/mL) Medication Guide (MG) submitted on June 9, 2010 and received by DRISK on September 29, 2010.
- Approved Morphine Sulfate Oral Solution Medication Guide (MG) and Patient Instructions for Use (PIFU) dated January 25, 2010.
- Oxycodone Hydrochloride Oral Solution ([(b) (4)] 20 mg/mL) REMS Notification Letter, submitted May 26, 2010.
- Proposed Oxycodone Hydrochloride Oral Solution ([(b) (4)] 20 mg/mL) Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document, submitted on June 09, 2010.

4. RESULTS OF REVIEW

In our review of the MG and PIFU, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and PIFU 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 and PIFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and PIFU are consistent with the approved comparator labeling where applicable.

In our review of the proposed REMS and REMS Supporting Document, we have:

- Ensured it includes the elements outlined in the REMS Notification Letter.
- Ensured it meets the statutory requirements under the Food and Drug Administration Amendments Act (FDAAA) of 2007.

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

5. CONCLUSIONS AND RECOMMENDATIONS

DRISK concurs with the elements of the REMS as proposed by the Applicant.

Please note, the timetable for submission of the assessment is required to be approved as part of the REMS, but not the Applicant's proposed information about the details of the REMS evaluation (methodology/instruments). The methodology and instruments do not need to be reviewed or approved prior to approval of the REMS.

We have the following comments and recommendations for the DAAP and Applicant with regard to the MG, PIFU and the proposed REMS.

Comments to the Division of Analgesics and Anesthetics Products (DAAP):

Our annotated MG and PIFU are appended to this memo (Appendix A Marked Copy, Appendix B Clean Copy). Any additional revisions to the PI should be reflected in the MG and PIFU.

(b) (4)

Comments to Lehigh Valley Technologies, Inc.:

See the appended Oxycodone Hydrochloride Oral Solution ((b) (4) 20 mg/mL) REMS proposal (Appendix C of this memo) for track changes corresponding to comments in this review.

a. **GOAL**

Revise your goal as follows:

The goal of this REMS is to inform patients of the serious risks associated with the use of Oxycodone Hydrochloride Oral Solution ((b) (4) 20 mg/mL).

b. Your Medication Guide distribution plan appears to be acceptable. Your detailed plan for how you plan to distribute the Medication Guide in accordance with 21 CFR 208.24 is more appropriate for the REMS Supporting Document.

- We remind you that under 21 CFR 208.24, you are responsible for ensuring that sufficient numbers of Medication Guides are provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. (b) (4) For the 20 mg/mL dosage you state that one Medication Guide will be included in the individual folding carton for each 30 mL bottle. We find this Medication Guide Distribution plan acceptable.
- We remind you that under 208.24, you are responsible for ensuring that the that you will include a statement on the Oxycodone Hydrochloride Oral Solution ((b) (4) 20 mg/mL) carton or container label stating that the Medication Guide should be dispensed to each patient.
- See our editorial comments on this section of the proposed REMS (see Appendix C).

c. Your proposed timetable for submission of assessments (18 months, 3 years, and 7 years) is acceptable.

We have some editorial comments in this section of the proposed REMS.

d. Regarding your REMS Assessment Plan

Your REMS Assessment Plan does not contain enough information to determine if it is acceptable.

1. Submit for review the detailed plan you propose to use to evaluate patients' understanding about the safe use of Oxycodone Hydrochloride Oral Solution ((b) (4) 20mg/mL). You may submit the proposed plan after approval of the REMS, however submit it at least 90 days before you conduct the evaluation. Code the submission "REMS Correspondence." If the plan is to conduct the required assessment using a survey, make sure the submission includes all methodology and instruments used to evaluate the knowledge about the risks associated with and safe use of Oxycodone Hydrochloride Oral Solution ((b) (4) 20mg/mL).
2. Recruit respondents using a multi-modal approach. For example, you might recruit respondents through physicians' offices, pharmacies, managed care providers, consumer panels, or on-line.

   Explain how often you perform non-respondent follow-up or reminders.

   If you use an incentive or honorarium, provide details on what is offered and the estimated dollar value.

   Explain how you select recruitment sites.

   Submit for review any recruitment advertisements.
3. Describe the rationale for your sample size. Report the 95% confidence interval around the expected level(s) of patient knowledge for each key risk(s).
4. Define the expected number of people to be contacted to obtain the proposed sample size, and how the sample is determined (selection criteria).
5. Ensure the sample is demographically representative of the population who use the drug (patients).
6. When possible and appropriate, ensure the sample is diverse in terms of age, race, ethnicity, sex, socio-economic status, education level, and geographically.
7. List the inclusion criteria. For example, eligible patient respondents must be:
   - Age 18 or older
   - Currently taking Oxycodone Hydrochloride Oral Solution ((b) (4) 20mg/mL) or have taken the drug in the past 3 months
   - Not currently participating in a clinical trial involving Oxycodone Hydrochloride Oral Solution ((b) (4) 20mg/mL)
   - Not a healthcare provider

   Submit any screener instruments, and describe any quotas of sub-populations used.
8. Explain how you administer surveys and the intended frequency.

Offer respondents multiple options for completing the survey. Be sure to include an option for the lower literacy population. For example, respondents might complete surveys online or through email, in writing or by mail, over the phone, and in person.

Explain how you train surveyors.

9. Explain how you control for limitations or bias associated with the methodology and survey instrument(s).

10. Submit for review the introductory text used to inform respondents about the purpose of the survey.

    Tell potential respondents that their answers will not affect their ability to receive or take (patients) the drug, and that their answers and personal information will be kept confidential and anonymous.

11. Clarify in your methodology that respondents are eligible for one wave of the survey only.

12. The assessment evaluates the effectiveness of the REMS in achieving the goal by evaluating patients' knowledge of the serious risks associated with use of the drug. The assessment does not evaluate consumer comprehension of the Medication Guide.

    According to regulation (21 CFR 208.24), patients receive the Medication Guide at the time the prescription is filled/dispensed. Do not offer respondents an opportunity to read or see the Medication Guide, Package Insert, or any other related educational materials again prior to taking the survey.

13. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in the Medication Guide.

14. Ensure the patient knowledge survey includes questions that ask about the specific risks or safety information conveyed in the Medication Guide to determine if the patient understands the information and knows what to do if they experience an adverse event.

    Derive the risk-specific questions from information located in the "What is the Most Important Information I should know about Oxycodone Hydrochloride Oral Solution?" section of the Medication Guide.

    Ensure the risk-specific questions are not biased or leading, and that multiple choice questions include an instruction to "select all that apply." Ensure that each question has an "I don't know" answer option.

    Randomize the order of the multiple choice responses on each survey.

15. Order questions so the risk-specific questions are asked first, followed by questions about receipt of the Medication Guide. Collect demographic questions last or as part of any screener questions.

Do not allow respondents the opportunity or ability to go back to previous questions in the survey.

Explain if and when any education will be offered for incorrect responses.

16. Include questions about receipt of the Medication Guide in the patient survey as a way to fulfill the obligation to report on the distribution of the Medication Guide.

17. Prior to the questions about receipt of the Medication Guide, include text that describes a Medication Guide. For example,

    Now we are going to ask you some questions about the Medication Guide you may have received with Oxycodone Hydrochloride Oral Solution ([redacted] 20mg/mL). The Medication Guide is a paper handout that contains important information about the risks associated with use of Oxycodone Hydrochloride Oral Solution ([redacted] 20mg/mL) and how to use Oxycodone Hydrochloride Oral Solution ([redacted] 20mg/mL) safely. Medication Guides always include the title "Medication Guide" followed by the word Oxycodone Hydrochloride Oral Solution and its pronunciation. The Medication Guide usually has sections titled "What is the most important information I should know about Oxycodone Hydrochloride Oral Solution," "What is Oxycodone Hydrochloride Oral Solution, " and "Who should not take Oxycodone Hydrochloride Oral Solution."

18. Use the following (or similar) questions to assess receipt and use of the Medication Guide.

    - Who gave you the Medication Guide for Oxycodone Hydrochloride Oral Solution ([redacted] 20mg/mL)? (Select all that apply)
        a) My doctor or someone in my doctor's office
        b) My pharmacist or someone at the pharmacy
        c) Someone else - please explain: _____
        d) I did not get a Medication Guide for Oxycodone Hydrochloride Oral Solution ([redacted] 20mg/mL)
    - Did you read the Medication Guide?
        a) All,
        b) Most,
        c) Some,
        d) None
    - Did you understand what you read in the Medication Guide?
        a) All,
        b) Most,
        c) Some,

d) None

- Did someone offer to explain to you the information in the Medication Guide?
    a) Yes, my doctor or someone in my doctor's office
    b) Yes, my pharmacist or someone at the pharmacy
    c) Yes, someone else – please explain: _____
    d) No
- Did you accept the offer? Yes or No
- Did you understand the explanation that was given to you?
    a) All,
    b) Most,
    c) Some,
    d) None
- Did or do you have any questions about the Medication Guide? Yes or No (If Yes, list your question(s) below) Note: Group/code this open text field prior to submitting to FDA

19. Analyze results on an item-by-item or variable-by-variable basis. You may present the date using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables). You may stratify the data by any relevant demographic variable, and presented in aggregate. Submit with your assessments all methodology and instruments utilized.

Please let us know if you have any questions.

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/s/

ROBIN E DUER
10/12/2010

CLAUDIA B KARWOSKI
10/13/2010
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FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA AND ANALGESIA PRODUCTS

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

DATE:	May 10, 2010
NDA #:	NDA 200535
PRODUCT:	Oxycodone hydrochloride Oral Solution, (b) (4), 20mg/mL
APPLICANT:	Lehigh Valley Technologies, Inc.
FROM:	Sharon Hertz, M.D. Deputy Director, DAAP

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary to ensure that the benefits of Oxycodone HCL Oral Solution, when available in multiple formulations including (b) (4) 20mg/mL, outweigh its risks of: 1) medication errors, such as administering a 20-ml dose instead of the prescribed 20mg dose. Such errors have been reported with a similar product used for the same indication, morphine sulfate oral solution, and have resulted in life-threatening overdoses. A 20-ml dose would result in a 100mg or 400mg dose, depending upon which concentration was available; and 2) Use of the 20mg/ml concentration in non-opioid tolerant individuals.

In reaching this determination we considered the following:

A. It is difficult to estimate the size of the population likely to use Oxycodone HCL Oral Solution, but somewhere (b) (4) .

B. (b) (4) Oxycodone HCL oral solution is used for pain (b) (4) in patients who are unable to swallow solid dosage forms. This is considered serious, as patients with inadequately treated pain are at risk for suicide. This formulation of Oxycodone HCL is also used in the setting of hospice care in terminal patients with pain, also a serious condition.

C. (b) (4)

D. The expected duration of treatment is from days to months depending on the underlying disorder causing the pain.

E. The most serious likely adverse event with these formulations of Oxycodone HCL is medication errors. Oxycodone HCL is available in (b) (4) 20mg/mL (unapproved formulations proposed for this NDA). There have been reports for a similar product, morphine sulfate oral solution, where prescriptions for a 20mg dose were administered as a 20mL dose. A 20ml dose would result in a 100mg or 400mg dose depending on which concentration was available. Such errors have resulted in life threatening overdoses. Patients and caregivers must have information to alert them to this possible error so that they can dispense the correct dose. There are no data to determine a background incidence for this. In addition to the reports of medication errors, immediate release oxycodone has been associated with various other adverse effects including death, respiratory depression, CNS depression, severe hypotension, gastrointestinal tract reactions such as nausea, vomiting and diminutive effects on the propulsive peristaltic waves, hypersensitivity reactions, and the known potential to elevate intracranial pressure and biliary tract pressure.

F. Oxycodone HCL Oral Solution is not a new molecular entity.

In accordance with section 505-1 of the FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Oxycodone HCL Oral Solution. FDA has determined that Oxycodone HCL Oral Solution when available in multiple formulations, including 20mg/mL (b) (4) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Oxycodone HCL Oral Solution, when available in multiple formulations, including 20mg/mL (b) (4). FDA has determined that Oxycodone HCL Oral Solution is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or continue to use Oxycodone HCL Oral Solution.

The elements of the REMS will be a Medication Guide and a timetable for submission of assessments of the REMS.

_____
Sharon Hertz, M.D.
Deputy Director, Division of Anesthesia and Analgesia Products

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200535	ORIG-1	Lehigh Valley Technologies, 514 North 12th Street, Allentown PA	OXYCODONE ORAL SOLUTION (b) (4) 20mg/mL

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/s/

TANYA D CLAYTON
05/25/2010

SHARON H HERTZ
05/25/2010