CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200534Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**200534**
SERIAL NUMBER:	**1**
DATE RECEIVED BY CENTER:	**December 22, 2009**
PRODUCT:	**Oxycodone hydrochloride capsules (5 mg)**
INTENDED CLINICAL POPULATION:	**Management of moderate to severe pain where the use of an opioid analgesic is appropriate**
SPONSOR:	**Lehigh Valley Technologies, Inc.**
DOCUMENTS REVIEWED:	**Modules 2 and 4 of electronic submission**
REVIEW DIVISION:	**Division of Anesthesia and Analgesia Products (DAAP; HFD-170)**
PHARM/TOX REVIEWER:	**Carlic K. Huynh, Ph.D.**
PHARM/TOX SUPERVISOR:	**R. Daniel Mellon, Ph.D.**
DIVISION DIRECTOR:	**Bob A. Rappaport, M.D.**
PROJECT MANAGER:	**Tanya Clayton**
Date of review submission to Document Archiving, Reporting & Regulatory Tracking System (DARRTS):	**September 17, 2010**

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

The NDA is recommended for approval.

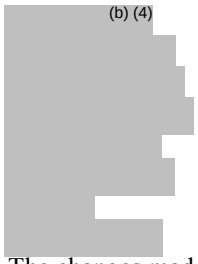
B. Recommendation for nonclinical studies

At this time, there are no recommendations for further nonclinical studies.

C. Recommendations on labeling

The labeling for Lehigh Valley Technology, Inc's oxycodone hydrochloride capsule will be the same as the referenced drug product, ROXICODONE®.

Applicant's proposed labeling	Reviewer's proposed changes	Rationale for changes
(from highlights section) **INDICATIONS AND USAGE** Oxycodone hydrochloride capsule is an opioid (b) (4), indicated for the relief of moderate to severe acute and chronic pain where use of an opioid analgesic is appropriate.	***(from highlights section)*** **INDICATIONS AND USAGE** Oxycodone hydrochloride capsule is an opioid (b) (4) agonist, indicated for the relief of moderate to severe acute and chronic pain where use of an opioid analgesic is appropriate.	This is fine as the Sponsor is using the PLR format.
8 USE IN SPECIFIC POPULATIONS **8.1 Pregnancy** Teratogenic Effects (Pregnancy Category B) (b) (4) Nonteratogenic Effects Neonates whose mothers have taken oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.	**8 USE IN SPECIFIC POPULATIONS** **8.1 Pregnancy** Teratogenic Effects (b) (4) There are no adequate and well-controlled studies of oxycodone use during pregnancy. Based on limited human data in the literature, oxycodone does not appear to increase the risk of congenital malformations. Because animal reproduction studies are not always predictive of human response, oxycodone should be used during	(b) (4) The changes made are identical to the current Roxicodone® label, except that it has been formatted to comply with PLR format. Additional edits were made by the reviewer in order to comply with PLR format.

	pregnancy only if clearly needed. Reproduction studies in Sprague-Dawley rats and New Zealand rabbits revealed that when oxycodone was administered orally at doses up to 16 mg/kg (approximately 2 times the daily oral dose of 90 mg for adults on a mg/m^2 basis) and 25 mg/kg (approximately 5 times the daily oral dose of 90 mg on a mg/m^2 basis), respectively was not teratogenic or embryo-fetal toxic. Nonteratogenic Effects Neonates whose mothers have taken oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.	
13 NONCLINICAL TOXICOLOGY **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** Studies of oxycodone hydrochloride to evaluate its carcinogenic potential have not been conducted. (b) (4) 	**13 NONCLINICAL TOXICOLOGY** **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenesis Studies of oxycodone hydrochloride to evaluate its carcinogenic potential have not been conducted.  (b) (4)	(b) (4)  The changes made are identical to the current Roxicodone® label, except that it has been formatted to comply with PLR format. Additional edits were made by the reviewer in order to comply with PLR format.

(b) (4)	(b) (4) Mutagenesis Oxycodone hydrochloride was genotoxic in an *in vitro* mouse lymphoma assay in the presence of metabolic activation. There was no evidence of genotoxic potential in an *in vitro* bacterial reverse mutation assay *(Salmonella typhimurium* and *Escherichia coli)* and in an assay for chromosomal aberrations (*in vivo* mouse bone marrow micronucleus assay). Impairment of Fertility (b) (4)	

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

The Sponsor did not submit any new nonclinical studies in this NDA. The Sponsor is relying up the Agency's previous findings for safety and efficacy to ROXICODONE®. The levels of the impurities from the drug substance and drug product specifications sent by the Sponsor are deemed adequate. Analysis of the excipients at the maximum theoretical daily dose (MTDD) indicated that the exposures of the exicipients are deemed safe.

B. Pharmacologic activity

Oxycodone is a semi-synthetic opioid. It is a full mu-opioid receptor agonist whose principal therapeutic action is analgesia. Oxycodone is metabolized in part to oxymorphone via the cytochrome p450 isoenzyme CYP2D6, a pathway that may be blocked by a variety of drugs (e.g., certain cardiovascular drugs and antidepressants). The precise mechanism of the analgesic action of oxycodone is unknown but is thought to involve CNS opioid receptors. Oxycodone in therapeutic doses, produces peripheral vasodilatation (arteriolar and venous), decreased peripheral resistance, and inhibits baroreceptor reflexes. It produces respiratory depression by direct action on brain stem respiratory centers. Oxycodone, like other opioid analgesics, produces some degree of nausea and vomiting which is caused by direct stimulation of the chemoreceptor trigger zone (CTZ) located in the medulla.

C. Nonclinical safety issues relevant to clinical use

There are no nonclinical safety issues relevant to clinical use as the Sponsor is relying upon the Agency's previous findings for safety and efficacy to ROXICODONE®.

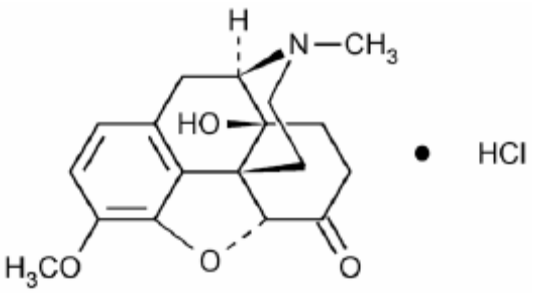
2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number:	200534
Review number:	1
Sequence number/date/type of submission:	SDN 1 / submit and receive date December 22, 2009; SDN 5 / submit and receive date March 30, 2010; SDN 9 / submit date August 19, 2010 and receive date August 20, 2010 / 505(b)(2) type NDA
Information to sponsor:	Yes ( ) No (X)
Sponsor and/or agent:	Lehigh Valley Technologies, Inc. 514 N. 12th Street Allentown, PA 18105
Manufacturer for drug substance:	(b) (4)
Reviewer name:	Carlic K. Huynh, Ph.D.
Supervisor name:	R. Daniel Mellon, Ph.D.
Division name:	Division of Anesthesia and Analgesia Products (DAAP)
HFD #:	170
Review completion date:	September 17, 2010

Drug:

Trade name:
Generic name: oxycodone hydrochloride
Code name:
Chemical name: 4,5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride
CAS registry number: 124-90-3
Molecular formula/molecular weight: $C_{18}H_{21}NO_4 \cdot HCl/351.83$
Structure:



Relevant INDs/NDAs/DMFs:
The development program for this drug product was conducted under IND 78,623 submitted by Glenmark Generics Inc. for the indication of moderate to severe pain and has been active since May 17, 2008.

The referenced drug for this 505(b)(2) NDA is ROXICODONE® (NDA 21-011; Xanodyne Pharmaceuticals, Inc.).

NDA#	Drug Name	Div	Strength (route)	Marketing Status	AP Date	Indication	Company
21-011	Roxicodone (oxycodone hydrochloride tablets)	DAAP	5, 15, 30 mg (oral)	AP	8/31/2000	Moderate to severe pain	Xanodyne
200-535	Oxycodone Oral Solutions	DAAP	1 mg/mL and 20 mg/mL	Pending		Moderate to severe pain	Lehigh Valley

DMF#	Subject of DMF	Holder	Submit Date	Reviewer's Comment
(b) (4)			11/6/2007	Specification for (b) (4) which is acceptable.
			8/14/2007	See CMC review.
			4/2/1974	See CMC review.
			9/4/1975	See CMC review.
			11/8/1978	See CMC review.
			12/23/2003	See CMC review.
			12/10/1980	See CMC review.

Drug class: opioid agonist

Intended clinical population: Management of moderate to severe pain where the use of an opioid analgesic is appropriate.

Clinical formulation:
The composition of the oxycodone HCl capsules (5 mg) is in the following table:

Component	Composition		Function
	mg/capsule	%/capsule	
Oxycodone hydrochloride, USP	(b) (4)		Active (analgesic)
Microcrystalline cellulose, NF			(b) (4)
Lactose anhydrous, NF			
Pre-gelatinized starch, NF			
Sodium starch glycolate, NF			
Colloidal silicon dioxide, NF			
Magnesium stearate, NF			
Sodium lauryl sulfate, NF			
Theoretical weight			
Imprinted size # 4 hard gelatin capsule ((b) (4); imprinted with edible black ink)			
			(b) (4)

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. Although there is no maximum daily dose for opioid drug products due to the development of tolerance, based on existing clinical use data, the Division has concluded that the maximum theoretical daily dose (MTDD) of oxycodone from 5 mg strength oxycodone capsules is 200 mg/day. The exposure of excipients to patients taking the 5 mg strength oxycodone oral capsule at the MTDD is illustrated the following table:

Excipients	Exposure of excipients in 5 mg strength capsule at the MTDD of 200 mg/day (mg)	IIG maximum potency limit (mg)
No. of doses to MTDD	40	
Microcrystalline cellulose, NF	(b) (4)	551.25
Lactose anhydrous, NF		402.50
Pre-gelatinized starch, NF		600.00
Sodium starch glycolate, NF		180.00
Colloidal silicon dioxide, NF		11.66
Magnesium stearate, NF		256.40
Sodium lauryl sulfate, NF		15.00
Imprinted size #4 hard gelatin capsule ((b) (4); imprinted with edible black ink)		N/A (Empty shell)

At the MTDD of 200 mg/day for the 5 mg strength capsule, the exposure levels of most of the excipients exceed the IIG maximum potency limits; however, the exposure levels of sodium starch glycolate, magnesium stearate, and sodium lauryl sulfate do not exceed the IIG maximum potency limits. Microcrystalline cellulose (21 CFR §182.1480 for methylcelluose), pregelatinized starch, and colloidal silicon dioxide are listed as generally recognized as safe (GRAS) with no limitations. Lactose anhydrous is used as a sweetener in foods (21 CFR §168.122) and the Agency has previously approved products containing lactose anhydrous, the daily usage of which exceeds 1500 mg. Therefore, there are no safety concerns with the excipients in this formulation even taking into consideration the MTDD.

The sponsor has proposed the following drug substance specifications:

Impurity	Proposed Specification	ICH Q3A(R2) qualification threshold (MDD ≤ 2 g/day)	Reviewer's Assessment
(b) (4)		0.15% or 1 mg, whichever is lower	Acceptable
		Below ICH, as this contains a structural alert for mutagenicity	Acceptable
		0.15% or 1 mg, whichever is lower	Acceptable
		0.15% or 1 mg, whichever is lower	Acceptable
		NMT 3000 ppm NMT 5000 ppm NMT 5000 ppm	Acceptable, as per ICHQ3C

The sponsor has proposed the following drug product stability specifications:

Impurity	Proposed Specification	ICH Q3B(R2) qualification threshold (MDD >100 mg - 2 g)	Reviewer's Assessment
(b) (4)		0.2% or 3 mg, whichever is lower	Acceptable
		0.2% or 3 mg, whichever is lower	Acceptable

Route of administration: oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 200-534 are owned by Lehigh Valley Technologies, Inc. or are data for which Lehigh Valley Technologies, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 200-534 that Lehigh Valley Technologies, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Lehigh Valley Technologies, Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 200-534.

Studies reviewed within this submission:
The Sponsor did not conduct any new nonclinical studies for this NDA submission.

Studies not reviewed within this submission:
None.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Oxycodone is a semi-synthetic phenanthrene opioid. It is a full mu-opioid receptor agonist whose principal therapeutic action is analgesia. Oxycodone is metabolized in part to oxymorphone via the cytochrome p450 isoenzyme CYP2D6, a pathway that may be blocked by a variety of drugs (e.g., certain cardiovascular drugs and antidepressants). The precise mechanism of the analgesic action of oxycodone is unknown but is thought to involve CNS opioid receptors. Oxycodone in therapeutic doses, produces peripheral vasodilatation (arteriolar and venous), decreased peripheral resistance, and inhibits baroreceptor reflexes. It produces respiratory depression by direct action on brain stem respiratory centers. Oxycodone, like other opioid analgesics, produces some degree of nausea and vomiting which is caused by direct stimulation of the chemoreceptor trigger zone (CTZ) located in the medulla.

(b) (4)

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(b) (4)

2.6.6.2 Single-dose toxicity
There were no single-dose toxicity studies submitted in this NDA.

2.6.6.3 Repeat-dose toxicity
There were no repeat-dose toxicity studies submitted in this NDA.

2.6.6.4 Genetic toxicology
There were no genetic toxicology studies submitted in this NDA.

2.6.6.5 Carcinogenicity
There were no carcinogenicity studies submitted in this NDA.

2.6.6.6 Reproductive and developmental toxicology
There were no reproductive and developmental toxicology studies submitted in this NDA.

2.6.6.7 Local tolerance
There were no local tolerance studies submitted in this NDA.

2.6.6.8 Special toxicology studies
There were no special toxicology studies submitted in this NDA.

2.6.6.9 Discussion and Conclusions
See "overall conclusions and recommendations" below.

2.6.6.10 Tables and Figures
None.

2.6.7 TOXICOLOGY TABULATED SUMMARY
None.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:
The drug product subject in this NDA is oxycodone hydrochloride, 5 mg capsule from Lehigh Valley Technology, Inc. The Sponsor is relying upon the Agency's previous findings for safety and efficacy to ROXICODONE®. From a nonclinical pharmacology toxicology perspective, there are no safety concerns.

Unresolved toxicology issues (if any): None.

Recommendations:
This NDA is recommended for approval.

Suggested labeling:
The sponsor has proposed the same language as the referenced product labeling, ROXICODONE®. Minor edits have been made to the ROXICODONE® label to comply with the PLR format (see "Executive Summary" above). This is acceptable; however, it is noted that the Sponsor has proposed a single label for the capsules as well as the liquid oral solutions (being reviewed under NDA 200-535).

APPENDIX/ATTACHMENTS

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

/s/

CARLIC K HUYNH
09/17/2010

RICHARD D MELLON
09/17/2010
I concur.

PHARMACOLOGY/TOXICOLOGY NDA FILEABILITY CHECKLIST

NDA/BLA Number: 200534 and 200535	**Applicant: Lehigh Valley Technologies, Inc.**	**Stamp Date: December 22, 2009**
Drug Name: Oxycodone HCl oral capsule and solution	**NDA/BLA Type: 505(b)(2)**	**DAARP/OND/CDER/FDA**

On **initial** overview of the NDA application for Refuse to File (RTF): **Fileable**

(b) (4)

	Parameters	Yes	No	Comment
1	On its face, is the pharmacology section of the NDA/BLA organized (in accord with 21 CFR 314 and current guidelines for format and content) in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section of the NDA/BLA indexed and paginated in a manner allowing substantive review to begin?	X		
3	On its face, is the pharmacology/toxicology section of the NDA/BLA legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505(b1) and (b2) including referenced literature) completed and submitted in this NDA (carcinogenicity*, mutagenicity*, teratogenicity*, effects on fertility*, juvenile studies, acute and repeat dose adult animal studies*, maximum tolerated dose determination, dermal irritancy, ocular irritancy, photo co-carcinogenicity, animal pharmacokinetic studies, safety pharmacology, etc)?	X		The Sponsor did not conduct any new nonclinical studies. The submitted 505(b)(2) New Drug Application (NDA) included referenced nonclinical studies. The Sponsor is also proposing to rely upon the literature as well as the Agency's previous finding of safety for Roxicodone® for nonclinical support.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies been conducted with the appropriate formulation?			Not applicable. At the time of the filing review, the Sponsor is proposing to rely upon the published scientific literature as well as the Agency's previous findings of safety for Roxicodone® for toxicology

				studies.
6	Is (are) the excipient(s) appropriately qualified (including interaction between the excipients if applicable)?	X		This NDA contains excipients that are found in the FDA IIG. The amount of excipients in this formulation is below the maximum potency limits.
7	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route?			Not applicable. The Sponsor has not conducted any animal studies in support of this NDA.
8	Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			Not applicable. The Sponsor has not conducted any animal studies in support of this NDA.
9	Has the sponsor submitted all special studies/ data requested by the Division during pre-submission discussions with the sponsor?			Not applicable. The Sponsor did not conduct any new nonclinical studies in support of this NDA.
10	Are the proposed labeling sections relative to pharmacology, reproductive toxicology, and carcinogenicity appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?		X	The referenced labels do not contain exposure margins; therefore, they will be incorporated into the label during this review cycle based on the dosage form. This need not be a filing issue.
11	Has the sponsor submitted any toxicity data to address impurities, new excipients, leachables, etc. issues.	X		The Sponsor has submitted specifications for the drug substance and drug product in module 3. Adequate specifications for the (b) (4) are provided. The specifications for (b) (4) will need to be discussed during review as there is a difference in opinion regarding

				the maximum daily dose for these products.
12	Has the sponsor addressed any abuse potential issues in the submission?	X		The Sponsor provides discussion on the addiction potential of oxycodone HCl.
13	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable. This is a 505(b)(2) New Drug Application (NDA) submitted to support a Rx.
14	From a pharmacology/ toxicology perspective, is the NDA/BLA fileable? If ``no`` please state below why it is not.	X		FILING ISSUES: There are no filing issues at this time.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

Comments to Sponsor:
Please provide the following information:

1. The proposed drug substance impurity specification for 6-α-oxycodol ((b) (4)) exceeds the ICHQ3A(R2) qualification threshold of NMT 0.15%. Either this specification must be tightened to NMT 0.15% or you must provide adequate safety qualification for this impurity. As noted in the preNDA meeting minutes, adequate qualification of an impurity must include:

    a. Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.

    b. Repeat dose toxicology of appropriate duration to support the proposed indication. For a chronic indication, a study of at least 90-days is appropriate.

2. The proposed drug product specification for (b) (4) ((b) (4) in both NDA 200534 and 200535 exceeds the ICHQ3B(R2) qualification threshold of NMT 0.2% for a drug product with a maximum daily dose of >100 mg to 2 g. Unless you can provide adequate clinical use data to document that these products will not be used at a maximum daily dose that exceeds 100 mg/day, either this specification must be tightened to NMT 0.2% or you must provide adequate safety qualification for this impurity. As noted in the preNDA meeting minutes, adequate qualification of an impurity must include:

    a. Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.

b. Repeat dose toxicology of appropriate duration to support the proposed indication. For a chronic indication, a study of at least 90-days is appropriate.

3. NDA 200535 must contain information on potential leachables and extractables from the drug container closure system (HDPE bottle, innerseal cap and (b) (4)). Provide a toxicological evaluation of those substances identified as leachables and extractables to determine the safe level of exposure via the labeled oral route of administration. The approach for toxicological evaluation of the safety of extractables must be based on good scientific principles and take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen (chronic dosing). This should be specifically discussed in module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission.

Reviewing Pharmacologist: _____
Date

Team Leader: _____
Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200534	ORIG-1	Lehigh Valley Technologies, Inc. 514 N. 12th Street, Allentown, PA 18105	OXYCODONE HCL CAPSULES
NDA-200535	ORIG-1	Lehigh Valley Technologies, 514 North 12th Street, Allentown PA	OXYCODONE ORAL SOLUTION (b) (4) 20mg/mL

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

/s/

CARLIC K HUYNH
02/26/2010

RICHARD D MELLON
02/26/2010