Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Division Director Summary Review for Regulatory Action

Date	July 21, 2021
From	Rigoberto Roca, MD
NDA Numbers / Supplement numbers	201194 / S-009 200534 / S-010 200535 / S-017
Applicant Name	VistaPharm (NDA 201194) Genus Lifesciences Inc. (Genus), formerly Lehigh Valley Technologies, Inc. (NDAs 200534 and 200535)
Date of Original Submission	January 3, 2020 (NDA 201194) January 17, 2020 (NDA 200534 and NDA 200535) Complete Response letter issued December 29, 2020
Date of First Complete Response Submission	January 21, 2021 (NDA 201194) January 29, 2021 (NDAs 200534 and 200535)
PDUFA Goal Date	July 21, 2021
Established (USAN) Name	Oxycodone HCl oral solution 5 mg/5 mL (NDA 201194) Oxycodone HCl capsules for oral use 5 mg (NDA 200534) Oxycodone HCl oral solution 100 mg/5 mL and 5 mg/5 mL (NDA 200535)
Dosage Forms / Strength	Oxycodone HCl oral solution 5 mg/5 mL (NDA 201194) Oxycodone HCl capsules for oral use 5 mg (NDA 200534) Oxycodone HCl oral solution 100 mg/5 mL and 5 mg/5 mL (NDA 200535)
	(b) (4)
Action	Approval

Material Reviewed/Consulted OND Action Package, including reviews by:	
Medical Officer	Robert Levin, MD; Ning Hu, MD (First cycle reviews)
Pharmacology Toxicology	Elizabeth Bolan, PhD; Dan Mellon, PhD (First cycle reviews)
OCP / DCP II	Wei Qiu, PhD; Yun Xu, PhD
Project Management Staff	Jaimin Patel, PharmD; Swati Patwardhan
DPMH	Heather Buck; Elizabeth Dermowicz, MD; Mona Khurana, MD (First cycle reviews)
OSIS / DGDSI	Monica Javidnia, PhD; Seongeun Cho, PhD
OPDP / DMPP	L. Shenee Toombs, PharmD; Sam Skariah, PharmD, RAC

DCP II = Division of Clinical Pharmacology II
DGDSI = Division of Generic Drug Study Integrity
DMPP = Division of Medical Policy Programs
DPMH = Division of Pediatrics and Maternal Health
OCP = Office of Clinical Pharmacology
OPDP = Office of Prescription Drug Promotion
OSIS = Office of Study Integrity and Surveillance

1. Benefit-Risk Assessment

I concur with the benefit-risk assessment for the product as described in the review by Dr. Levin and Dr. Hu from their review during the first cycle.

The following is reproduced from their review.

> The benefits of using Oral Oxycodone Solution in treating pain severe enough to require an opioid analgesic when alternative treatments are inadequate, have been established in the adult population. The Division believes efficacy can be extrapolated from adults to pediatric patients two years of age and older for opioid analgesics when there is a demonstration of comparable exposures between the two populations (Berde 2012). The submitted data established that comparable exposures were achieved between pediatric patients two years of age and older and adults with the starting doses, allowing extrapolation of efficacy to pediatric patients. Based on single-dose PK comparison, a dose of 0.07 mg/kg for patients aged 13 to <17 years, 0.08 mg/kg for patients aged 7 to 12 years, and 0.10 mg/kg for patients aged 2 to 6 years and for patients aged 6 months and <2 years will provide similar oxycodone exposure to that of a 5 mg single-dose in adults. We expect the same titration-to-effect treatment strategy used in adults will be effective in pediatric patients considering the comparable exposure between the starting doses in both populations.
>
> Known risks associated with the use of an opioid such as Oxycodone Hydrochloride Oral Solution in adults are described in the product labeling. Some of the serious risks associated with the use of an opioid include life-threatening respiratory depression, severe hypotension, addiction, abuse, and misuse. In the study conducted by the Applicants, there were no serious or unexpected adverse events, or deaths. Safety findings were generally consistent with post-operative experiences and with the known safety profile of opioid analgesics. However, the study had several limitations in assessing safety, including open-label study design without a control group, single-dose administration of only the starting dose, and small sample size. There were no data to support that the administered doses were efficacious except for PK extrapolation of the starting dose. Because risks associated with use of a drug are often dose-dependent, to adequately assess safety, multiple-doses and doses that are efficacious should be studied. Specifically, the risk of opioid-related respiratory depression is known to be dose-dependent and therefore cannot be fully evaluated by the limited safety data obtained from the study. The Applicants submitted literature in addition to their study results to help support the safety of multiple-dosing with oxycodone. However, the references which included 3 multiple dose studies of 104 subjects and additional single-dose studies did not provide sufficient safety data to support the safety of multiple-doses.

Respiratory depression is a known risk of an opioid analgesic and has been included in the boxed warning in the product labeling. It is important to note that several patients had oxygen desaturation with a decrease of up to 10% in Study 2012O004. Although it is difficult to determine the cause of oxygen desaturation in postoperative patients, it is impossible to exclude oxycodone as the cause or a contributing factor in some of the patients. This raises the serious safety concern of whether higher doses and/or multiple-doses of Oxycodone Hydrochloride Oral Solution, could result in more frequent and severe respiratory depression.

A total of 16 patients had a decrease in pulse oximetry of 4% or greater from pre-dose baseline. Excluding the six patients that received hydromorphone at the same time as oxycodone, leaves 10 patients with the following pulse oximetry changes in decreasing order: 1 patient 10% decrease at 60 minutes, 1 patient 7% at 2 hours, 1 patient 6% at 30 min and again at 2 hours, 2 patients 5% (1 at 4 hours and 1 at 60 minutes) and 5 patients 4% (1 at 10 minutes, 2 at 8 hours, 1 each at 30 minutes and 60 minutes). Although it is impossible to determine from this open-label study in post-operative patients the cause of the oxygen desaturation, Oxycodone Oral Solution cannot be excluded as a contributing factor or cause in some patients.

From the safety information submitted, it is impossible to predict what effect multiple-therapeutic doses of oxycodone would have on safety in general and specifically on respiratory depression. (b) (4)

However, if the studies were appropriately conducted, then the Division believes that the Applicant has fulfilled their PMR because the requirement for assessing safety with clinically-relevant doses was not included in the previous communications. With respect to the single dose study conducted, the Division said that if the Applicant believes that adequate safety information exists in the literature on multiple doses, they could submit the final study report and the literature. The Applicant decided to choose this approach, but the Division after reviewing the literature concluded that it was not adequate to support the safety evaluation. It should be noted that even if the Applicant had conducted a multiple-dose study but did not provide evidence that the doses were clinically effective, the safety data would still not have been adequate to support the safety evaluation.

2. Background

The background information regarding these supplements is well described in the reviews by Dr. Levin and Dr. Hu from the first review cycle. The following is reproduced from that review.

VistaPharm's Oxycodone Hydrochloride Oral Solution 5 mg/5 mL, Genus' Oxycodone Oral Capsule 5 mg and Oxycodone Oral Solutions 100 mg/5 mL and 5 mg/5 mL are approved for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Both Oxycodone Hydrochloride Oral Solution and Oxycodone Hydrochloride Capsules were previously marketed unapproved products. Oxycodone Hydrochloride Oral Solution 5 mg/5 mL was approved under NDA 201194 (VistaPharm) on January 12, 2012 and under NDA 200535 (Lehigh Valley Technologies [now Genus Life Sciences]) on August 22, 2013. Oxycodone Hydrochloride Capsules 5 mg and Oxycodone Hydrochloride Oral Solution 100 mg/5 mL were approved under NDA 200534 and NDA 200535, respectively on October 20, 2010. At the time of approval, a post-marketing requirement (PMR) under the Pediatric Research Equity Act (PREA) was issued for these NDAs to study the pharmacokinetics (PK) and safety of oxycodone oral solution in the pediatric population 2 to <17 years of age, and a separate PMR was issued for a safety, efficacy and pharmacokinetic study in subjects 0 to <2 years. VistaPharm and Genus are working in collaboration to fulfill their PMRs. The purpose of this supplement is to fulfill the PMR for the 2 to <17 year old population. The Applicants conducted one pediatric PK and safety study (2012O004) to fulfill this requirement. Efficacy data were not required or collected because FDA allows extrapolation of efficacy from adults to pediatric patients two years of age and older for opioid analgesics when there is comparable exposure between the two populations.

(b) (4)

As was noted in that review, the supplements received a Complete Response letter due to the need to complete an inspection. The following is the deficiency identified in the letter dated December 29, 2020.

BIOPHARMACEUTICAL INSPECTIONS
There is an inability to ensure the reliability of the clinical study data of the Phase IV Study to Evaluate the Pharmacokinetics and Safety of Oxycodone Oral Solution in Pediatric and Adolescent Subjects. The Office of Study Integrity and Surveillance (OSIS) is unable to complete an inspection or remote record review of the Cincinnati Children's Hospital Medical Center clinical study site. Specifically, the Clinical Investigator for the study was unavailable, and the person identified as the replacement was not authorized to speak or make decisions on behalf of the study.

Information needed to resolve Deficiency:
Satisfactory results from an inspection or a remote record review is required before this supplemental application can be approved. Notify us in writing when this facility is ready for an inspection or remote record review.

3. Product Quality

There were no product quality issues identified in the original submissions and the overall recommendation from the OPQ review team was for approval of the supplements.

Outstanding or Unresolved Issues

I concur with the conclusions reached by the product quality reviewers that there are no product quality issues that will preclude approval of these supplemental applications.

4. Nonclinical Pharmacology/Toxicology

There were no pharmacology/toxicology issues identified in the original submissions that would have precluded approval and the overall recommendation from the review team was for approval of the supplements. No new pharmacology/toxicology data were submitted with this resubmission.

Outstanding or Unresolved Issues

I concur with the conclusions reached by the pharmacology/toxicology review team that there are no product quality issues that will preclude approval of these supplemental applications.

5. Clinical Pharmacology/Biopharmaceutics

As noted above, the reason for the Complete Response action in December 2020 was the inability to conduct an inspection of the clinical sites. Dr. Qiu and Dr. Xu noted in their review that there was no new clinical pharmacology information submitted with this re-submission. The following was their recommendation for this review cycle:

> The Office of Clinical Pharmacology/Division of Neuropsychiatric Pharmacology (OCP/DNP) has reviewed the resubmissions for NDA 201194/S-009, NDA 200534/S-010 and NDA 200535/S-017 submitted on January 21, 2021 and January 29, 2021, respectively, and finds them acceptable.
>
> No new clinical pharmacology information was submitted in this re-submission. The original sNDA submissions were acceptable from a clinical pharmacology perspective pending satisfactory OSIS inspection on the clinical sites including Cincinnati Children's Hospital Medical Center and Children's Medical Center Dallas for Study 2012O004 (see clinical pharmacology review dated October 10, 2020 in DARRTS for more details). Complete Response letters were issued on December 29, 2020 because OSIS was unable to complete an inspection or remote record review of the Cincinnati Children's Hospital Medical center clinical study site so there was an inability to ensure the reliability of the clinical study date of the Phase IV Study to Evaluate the Pharmacokinetics and Safety of Oxycodone Oral Solution in Pediatric and Adolescent Subjects. The applicants submitted the resubmissions for NDA 201194/S-009, NDA 200534/S-010 and NDA 200535/S-017 on January 21, 2021 and January 29, 2021, respectively. OSIS conducted an inspection on clinical sites including Cincinnati Children's Hospital Medical Center and Children's Medical Center Dallas and concluded the data from the audited study 2012O004 are reliable (see OSIS review dated May 14, 2021 in DARRTS for details). Therefore, from a clinical pharmacology perspective, these resubmissions are acceptable and PMR 1863-1, PMR 1698-2, and PMR 1695-2 for NDA 201194, NDA 200534, and NDA 200535, respectively, are considered fulfilled.

Outstanding or Unresolved Issues
I concur with the review team that there are no clinical pharmacology issues that would preclude approval of these supplements.

6. Clinical Microbiology

The proposed product is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for these supplemental applications.

7. Clinical/Statistical – Efficacy

There were no new efficacy data submitted with this re-submission. For additional details, please refer to Dr. Levin's and Dr. Hu's review of December 24, 2020.

Outstanding or Unresolved Issues
I concur with the review team that there are no efficacy issues that would preclude approval of these supplements.

8. Safety

There were no new safety data submitted with this re-submission. For additional details, please refer to Dr. Levin's and Dr. Hu's review of December 24, 2020.

Outstanding or Unresolved Issues
I concur with the review team that there are no safety issues that would preclude approval of these supplements.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for these applications as there were no issues in these applications that required presentation or discussion at an advisory committee meeting.

10. Pediatrics

The Applicant submitted these supplements to address the requirements under the Pediatric Research Equity Act (PREA).

The Division of Pediatrics and Maternal Health was consulted to assist with evaluation of the proposed labeling and determination whether the submitted study fulfilled the outstanding PREA requirements. The application was discussed with the Pediatric Review Committee (PeRC) on October 6, 2020. DPMH and PeRC agreed that that the PREA PMRs for these products for pediatric patients 2 years of age and older should be considered fulfilled.

11. Other Relevant Regulatory Issues

There were no other relevant regulatory issues in these submissions.

12. Labeling

Consultations were obtained from the Office of Prescription Drug Promotion (OPDP), and DPMH.

As noted in the review by Dr. Levin and Dr. Hu during the first review cycle, information on (b) (4)

The following language is to be included in Section 8.4: Pediatric Use:

> The safety and effectiveness of Oxycodone Hydrochloride Oral Solution have not been established in pediatric patients. The safety and pharmacokinetics of a single-dose of Oxycodone Hydrochloride Oral Solution were evaluated in an open-label clinical trial in 89 pediatric patients 2 years to less than 17 years of age with postoperative pain. However, definitive conclusions were not possible because of insufficient information.

13. Post-Marketing

There are no post-marketing requirements, commitments, or risk management activities.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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07/21/2021 10:51:32 AM

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