November 6, 2019

Sharon Hertz, MD, Director
Division of Anesthesia, Analgesia, and Addictive Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Central Document Room
Food and Drug Administration
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RESPONSE TO PREA NON-COMPLIANCE LETTER

Reference: NDA 201194, Oxycodone Hydrochloride Oral Solution, USP 5 mg/5 mL, CII
eCTD 0069 – Response to PREA Non-Compliance Letter
Electronic Submission Size: 1 MB (Approx.)

Dear Dr. Hertz:

Reference is made to NDA 201194, Oxycodone Hydrochloride Oral Solution USP, 5 mg/5 mL CII, held by VistaPharm, Inc. (VistaPharm), approved on January 12, 2012 and to the July 9, 2019 PREA Non-Compliance Notification ("Notification") that is scheduled to be posted on the FDA website. VistaPharm herein is providing their response to this Notification.

As agreed with the Division of Anesthesia, Analgesia and Addiction Products, the assigned Postmarketing Requirements (PMRs) (b) (4) currently conducted under Study Protocol 2012O004. The study protocol was submitted under IND 105754 (cross referencing this NDA 201194).

Introduction

Since 2013, VistaPharm (b) (4) have worked diligently and continuously with the Division's continued (and appreciated) collaboration to complete the study of Oxycodone Hydrochloride Oral Solution, 5 mg/5 mL CII, in pediatric and neonate patients referenced in the Notification. While we are disappointed that the Notification will be posted on the FDA website given the amount of work we have successfully completed to date, we appreciate the Division allowing us the opportunity to summarize the progress we have made to date in the below letter, and would like this response to the Non-Compliance Notification to reflect our intentions to fully comply with the Pediatric Research Equity Act (PREA).

Overall, we believe the missed PMR deadline and subsequent Division Notification resulted from a misunderstanding (b) (4) Instead, VistaPharm submitted a CSR with integrated data for the 2 - 6 years, 7 -

12 years, and 13 - 17 years age groups, including pharmacokinetic reports, bioanalytical and method reports on September 18, 2019.

(b) (4)

Background Facts

For context and completeness, reference is made to New Drug Application (NDA) 201194 approved in accordance with Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, on January 12, 2012 and to the post marketing requirements, as outlined in the NDA approval letter. As part of the post marketing requirements, VistaPharm was required to conduct a safety, pharmacokinetic, and efficacy study in ages > 2 Years (PMR number 1863-1).

Following multiple communications regarding finalizing a protocol, the study was initiated in May 2013 with a total of ten (10) sites enrolling, and PMR completion dates of May 31, 2014 for trial completion and January 31, 2015 for final report submission. On May 17, 2016 a deferral extension was granted for this PMR with trial completion and final Clinical Study Report (CSR) dates of January 2017 and June 2017, respectively. Further, additional Investigators were added to the study as enrollment had reached a plateau.

As of January 27, 2017, (b) (4) Due to slow enrollment, a deferral was requested, and was subsequently granted, to extend the enrollment to January 2019 and final CSR submission to June 2019, respectively.

Pursuant to the Division's request, VistaPharm issued the final clinical study report (as a part of PMR 1863-1) for the 13-17-year age group upon completion of enrollment in this population. VistaPharm submitted this final study report (Clinical Summary Report, Bioanalytical Report, and Method validation Report) to the IND on July 27, 2018. In addition, VistaPharm contracted with (b) (4) to conduct a full pharmacokinetic modeling with the currently available data from PMR 1863-1. This data encompassed the pharmacokinetic data in patients as young as 2 years of age and was also submitted on July 27, 2018.

In summary, the pharmacokinetic modeling reported:

- (b) (4)
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(b) (4)

[redacted]

On September 10, 2018, (b) (4) [redacted] VistaPharm continued enrollment into the ≤ 12 age group.

On March 15, 2019, VistaPharm submitted a Deferral Request. At the request of the Division, a teleconference was held on April 1, 2019. Dr. Ellen Fields, MD, MP, Associate Director for Analgesics, DAAAP, indicated in the teleconference that the Division would not grant the deferral

request, and that the currently enrolled patients were enough to provide the information required for the 2 – 12 years age group and therefore, further enrollment in the study could be discontinued. During this teleconference, VistaPharm informed the Division that, under the study protocol 2012O004 (PMR 1683-1), (b) (4). The Division also requested that VistaPharm submit the final report for the 2 – 12 years age group as a supplemental report to the previously submitted 13 – 17 years CSR report. As such, VistaPharm and Genus, in collaboration, stopped further enrollment in the 2 – 17 years study and initiated the pharmacokinetic and statistical analysis.

On August 22, 2019, VistaPharm submitted a Deferral Request in response to the July 9, 2019 Non-Compliance Notification to allow for additional time to finalize the CSR. On September 18, 2019, VistaPharm submitted the CSR to the NDA. Subsequent to this submission, as advised by the Division, VistaPharm formally withdrew the August 22nd Deferral Request on September 24, 2019.

There were several clarification communications between the Division and VistaPharm relating to the expectations of the Division with respect to the final CSR. During these communications, the Division clarified that this report would be a supplement to the previously submitted 13-17 year old CSR. VistaPharm mistakenly assumed, and in hindsight should have more definitively confirmed, that the Division was indicating the filing would be a supplemental CSR to the 13-17-year group; VistaPharm did not understand the Division to be requiring a sNDA for the completion of PMR-1683-1.

Notice & Response

In an October 11, 2019 Information Request, VistaPharm was notified by the Division that the final CSR did not satisfy the PMR commitment as VistaPharm was required to submit a sNDA. A teleconference was requested by VistaPharm and held on October 24, 2019. During this call, the PREA Committee Representative indicated that had VistaPharm filed a deferral request prior to the June 30, 2019 due date that a deferral extension would have been issued, as it is "reasonable for a time extension based on formatting the sNDA". VistaPharm reminded the Division and the PREA Committee representatives that VistaPharm had previously filed a deferral request on March 15, 2019 and subsequently withdrew that deferral request on April 5, 2019 under guidance the deferral request would not be approved.

As described above, VistaPharm and the Division have worked cooperatively and cordially throughout the process in good faith to deliver the PREA commitment. VistaPharm acknowledges that there was some misalignment of communication that is now being corrected that should not detract from the common pursuit of full PREA compliance, which has always been the goal of both VistaPharm and the Division. VistaPharm remains committed to that goal (b) (4)

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(b) (4). In closing, we again express our appreciation for the Division's continued cooperation and understanding in that common pursuit.

This submission has been created in eCTD format and its being submitted via Electronic Submission Gateway. An antivirus scan was conducted using Webroot Secured *Anywhere* Endpoint Protection version 9.0.26.61 and the submission is virus-free.

Should you have any questions, or require additional information related to this request, please contact me, at the information provided below.

Sincerely,

Billie J. Wiltison

Digitally signed by Billie J. Wiltison
Date: 2019.11.06 14:49:34 -05'00'

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