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APPLICATION NUMBER:

208411Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Addendum to the Primary Clinical Pharmacology Review Dated October 22, 2015

NDA: 208411	Submission Date(s): July 20, 2015
Proposed Brand Name	NARCAN
Generic Name	Naloxone HCl Nasal Spray
Reviewer	Suresh B Naraharisetti, Ph.D.
Team Leader	Yun Xu, Ph.D.
OCP Division	DCPII
OND division	DAAAP
Sponsor	Adapt Pharma
Relevant IND(s)	IND 114704
Submission Type	Original Submission; 505(b)(2)
Formulation; Strength(s)	Solution for Nasal Spray; 40 mg/ mL
Indication	NARCAN nasal spray is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.

This addendum to Primary Clinical Pharmacology review (documented in DARRTS on 10/22/2015) is to address the recommendations made by Office of Study Integrity and Surveillance (OSIS) on the audited pivotal relative bioavailability study, Naloxone-Ph1a-002. At the time of signing-off the primary Clinical Pharmacology review for NDA 208411, OSIS inspection-report for study Naloxone-Ph1a-002 was pending. Subsequently, OSIS finalized their report on October 30, 2015 (see review by Dr. Dasgupta, Arindam, Ph.D. dated 10/30/2015 for details). Overall, the OSIS inspection-report concluded that there were no objectionable conditions observed related to the study Naloxone-Ph1a-002.

For study Naloxone-Ph1a-002, the clinical site where the study was conducted was at Vince Associates Clinical Research, KS 66212, USA; and the bio-analytical facility where the pharmacokinetic samples were analyzed was at (b) (4) , The OSIS inspection-report covered both the observations of Office of Regulatory Affairs (ORA) investigator's findings for clinical site and also the bioanalytical facility inspection.

The ORA investigator had the following two observations related to study Naloxone-Ph1a-002 identified at the clinical site, where a Form FDA 483 was issued to Vince & Associates Clinical Research. The two observations in the Form 483 were:

a) Late to transfer the collected PK samples to -20 °C freezer within 60 minutes of collection (Observation 1B, OSIS Inspection report)
b) Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation (Observation 2A OSIS Inspection report)

The OSIS investigator requested more data to address the two observations mentioned in the Form 483. After reviewing the additional data, it was concluded in the final OSIS report that these two observations are unlikely to impact integrity or outcome of study Naloxone-Ph1a-002. This addendum review focuses on the details of these two observations, and whether the findings impact the study Naloxone-Ph1a-002 data. The details are as follows.

a) Late to transfer the collected PK samples to -20 °C freezer within 60 minutes of collection (Observation 1B, OSIS Inspection report)

At the clinical site, the collected PK samples were not transferred to the -20 °C freezer within 60 minutes after the collection. To address this issue, the OSIS inspectors during their inspection at the bioanalytical facility requested the (b) (4) to design and conduct a benchtop stability study of Naloxone in human whole blood up to 60 minutes at both room temperature and 4 °C.
The detailed description of this aspect (Observation 1B) and the conclusion of the conducted naloxone bench top stability experiment, copied from the OSIS inspection report are as below.

OSIS Evaluation:
The firm failed to transfer a substantial number of PK samples to the -20°C freezer within 60 minutes of sample collection as specified in the study protocol. Additionally, the source data did not document the storage condition (e.g. on ice or at room temperature) of the collected blood samples before they were centrifuged. Although bench top stability was validated for 26 hours during method validation study for naloxone, this data was generated from frozen plasma samples. Stability in fresh plasma or in whole blood for naloxone was not established during method validation.

To assess the integrity of the "Late to Freezer (LTF)" samples, the analytical site for this study, (b) (4) was requested to design and conduct a benchtop stability study of Naloxone in human whole blood up to 60 minutes at both room temperature and 4°C. The plasma was to be transferred to the -20°C freezer after 30 minutes storage in refrigerator. The storage conditions in this experiment would mimic the sample handling procedure at the clinical site and would represent the worst-case scenario for these "Late to Freezer (LTF)" samples.

The results of this study were made available to the FDA investigators during the inspection and revealed that naloxone was

Reviewer Conclusions on Observation 1B:
Based on the conducted naloxone bench top stability experiment and the obtained results, we agree with OSIS conclusion that, Observation 1B is unlikely to impact the integrity of the naloxone concentration data."

b) Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation (Observation 2A OSIS Inspection report)

At the clinical site, discrepancies were observed between the reported protocol deviations and the source documents. Specifically, the protocol deviations submitted to the Agency do not accurately represent the information from the PK Specimen Processing Log.

The detailed description of Observation 2A copied from the OSIS inspection report is as below.

OSIS Evaluation:
Discrepancies were observed between the reported protocol deviations and the source documents. Specifically, the protocol deviations submitted to the Agency (**Please refer to submission**) do not accurately represent the information from the PK Specimen Processing Log (**Attachment 4**).
We compared the data submitted to the Agency in the ADPC Study dataset to the data obtained from the source documents to verify the accuracy of the reported actual dosing and sampling times in the dataset. After comparing the actual dosing times, we conclude that the dosing times were accurately reported for all subjects. When we compared the sampling times for 2.5, 5, 10, 15, 20, 30 and 60 min post-dose for all treatments, we found discrepancies in the sampling times for three subjects (see table below). We request the OCP reviewer to include the actual sampling times in their pharmacokinetic analysis. This observation is unlikely to impact the outcome of the study because all the data except the examples below were accurately reported in the ADPC Study dataset.

Subject	Actual time reported	Actual time from source Data	Time Point	Dose	Period
NALOXONE-PH1A-002-VACR-02031	9:43AM	9:44AM	5 min	0.4mg	3
NALOXONE-PH1A-002-VACR-02033	9:44AM	9:49AM	5 min	2 mg	3
NALOXONE-PH1A-002-VACR-02045	10:57AM	10:55AM	60 min	2 mg	3

Reviewer Conclusions on Observation 2A:
In study Naloxone-Ph1a-002, at total of 29 subjects completed the study in an open-label, randomized, 5-period, 5-treatment, 5-sequence, crossover design. Each participant received following 5 naloxone treatments during the 5 dosing periods:

- Treatment A: 2 mg IN (one 0.1 mL spray of a 20 mg/mL solution in one nostril)
- Treatment B: 4 mg IN (one 0.1 mL spray of a 20 mg/mL solution in each nostril)

- Treatment C: 4 mg IN (one 0.1 mL spray of a 40 mg/mL solution in one nostril)
- Treatment D: 8 mg IN (one 0.1 mL spray of a 40 mg/mL solution in each nostril) and
- Treatment E: 0.4 mg IM (1 mL of a 0.4 mg/mL commercial formulation, as reference)

In this study, two strengths of naloxone nasal spray, 20 mg/mL and 40 mg/mL were used. However, sponsor plans to market only 40 mg/mL strength (4 mg in 0.1 mL). Hence the clinical pharmacology review for study Naloxone-Ph1a-002 focused only on the 40 mg/mL strength and the reference IM injection treatments (Treatments C, D and E).

As per OSIS review with regards to the deviations in actual sampling times, there is one deviation in one time point for each of the three different subjects, #2031, #2033 and #2045 in period 3.

Out of these three deviations, two deviations, in subject #2033 and subject #2045 were from 20 mg/strength (2 mg dose, Treatment A), which the sponsor is not planning to market. Hence these two deviations need not to be considered.

Subject # 2031 had a one-minute deviation at the 5 minute time point, which is from the reference treatment group of IM injection. A total of 29 subjects completed the study, and 16 samples per subject were taken for each treatment up to 720 minutes post dose. Therefore, this one minute deviation at 5 minute time point in one subject, would not affect the calculated PK parameters and conclusion for the study.

Conclusions:

Overall, the conclusions made in the primary clinical pharmacology review dated October 22, 2015, will remain the same.

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