CLINICAL PHARMACOLOGY REVIEW

NDA or BLA Number	212854 505(b)(2) Resubmission
Link to EDR	\\cdsesub1\evsprod\NDA212854\0037 \\cdsesub1\evsprod\NDA212854\0043 \\cdsesub1\evsprod\NDA212854\0045
Submission Date	September 27, 2019, February 25, 2020, and May 15, 2020
Submission Type	Standard
Brand Name	ZIMHI
Generic Name	Naloxone HCl Injection Single-use Prefilled Syringe for Intramuscular (IM) or Subcutaneous (SC) Use 5 mg/0.5 mL
Dosage Form and Strength	Inject on: 5 mg/0.5 mL naloxone HCl solution in a pre-filled syringe
Route of Administration	IM or SC injection
Proposed Indication	• Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression in adults and pediatric patients. • Immediate administration as emergency therapy in settings where opioids may be present. • It is not a substitute for emergency medical care.
Applicant	Adamis Pharmaceuticals Corporation
Associated IND	IND 136148
Clinical Pharmacology Reviewer	Wei Qiu, PhD.
Clinical Pharmacology Team Leader	Yun Xu, MD, PhD.

Table of Contents

1 Executive Summary....2
1.1 Recommendation....2
1.2 Summary of Clinical Pharmacology Findings....2
2 Bioanalytical Method....6
3 Labeling Recommendations....7
4 Appendix....11
4.1 Filing Memo....11
4.2 Study APC 6000-03 Synopsis....20

1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Neuropsychiatric Pharmacology (OCP/DNP) has reviewed the NDA 212854 resubmission dated May 15, 2020 and finds it acceptable from clinical pharmacology perspective.

1.2 Summary of Clinical Pharmacology Findings

Key Clinical Pharmacology Findings:

In the comparative bioavailability study APC 6000-03, a single dose of 5 mg naloxone IM injection for the proposed product, ZIMHI (Naloxone HCl injection single-use prefilled syringe for IM or SC use 5 mg/0.5 mL), exhibited the same median Tmax (15 min), greater naloxone concentrations at all time points including earlier time points (e.g., 2.5, 5 min post-dose), 2.6-fold greater AUC0-2.5min, 4.1-fold greater AUC0-5min, 4.9-fold greater Cmax, 2.8-fold greater AUClast, and 2.7-fold greater AUC0-inf values, than a single dose of 2 mg naloxone IM injection for the reference product, naloxone HCl injectable (1 mg/1 mL, International Medical Systems, ANDA 072076). The comparator dose of 2 mg naloxone IM injection is within the approved initial dose range (i.e., 0.4 to 2 mg) for the listed drug product Narcan Injectable (NDA 016636). Note the original product Narcan Injectable (NDA 016636) was discontinued not because of safety or effectiveness reasons, so its generic product ANDA 072076 was used as the comparator in the comparative bioavailability study APC 6000-03.

Summary

The original NDA 212854 submitted on 12/31/2018 received a complete response letter due to several deficiencies from different disciplines on 11/22/2019. In addition, the comparative bioavailability study APC 6000-03 using International Medication System's ANDA 072076 product (Naloxone injectable 1 mg/mL) as the comparator was submitted

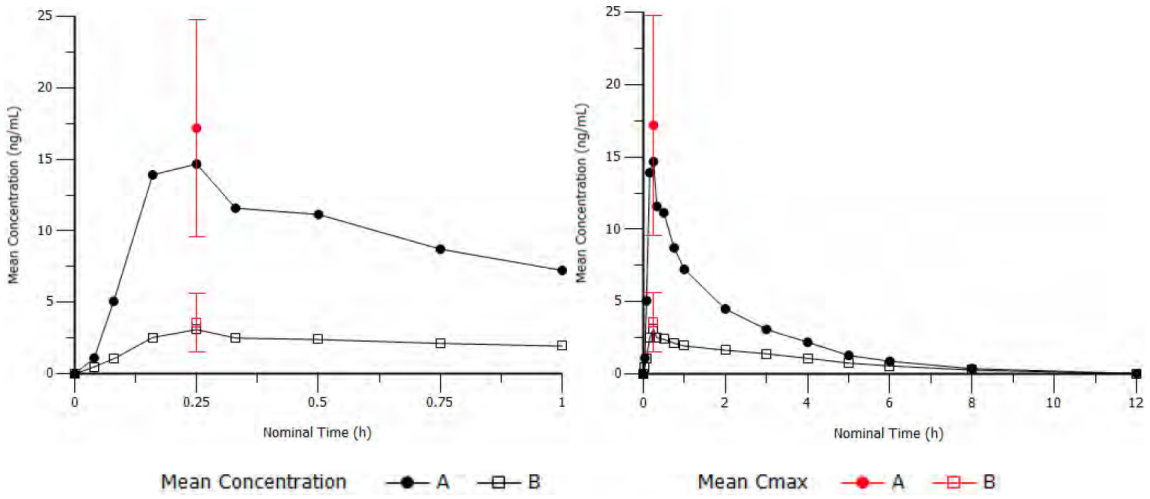
too late in the review cycle to allow for a substantive review. Therefore, it could not be determined whether the sponsor had established an acceptable scientific bridge between their proposed product and the listed drug product Narcan injectable (NDA 016636) in the original review cycle.

This resubmission consists of one comparative bioavailability study (Study APC 6000-03). In Study APC 6000-03, a single dose of 5 mg naloxone IM injection for the proposed naloxone HCl injection single-use prefilled syringe 5 mg/0.5 mL product was compared with a single dose of 2 mg naloxone IM injection of naloxone HCl injectable (1 mg/1 mL, International Medical Systems). The final to-be-marketed product of naloxone HCl injection single-use prefilled syringe 5 mg/0.5 mL was used in Study APC 6000-03. Because Narcan injectable (NDA 016636) is discontinued but not because of safety or efficacy reasons and ANDA 072076 is the generic to NDA 016636 and listed as reference standard in the orange book, this approach of using ANDA 072076 product to Narcan injectable NDA 016636 as the comparator in the comparative bioavailability study to establish PK bridging is acceptable. Narcan injectable may be administered via IV, IM or SC routes. Because the approved initial dose of Narcan injectable is from 0.4 mg to 2 mg in adults and rapid onset of action is critical for reversal of opioid overdose, the sponsor conducted the comparative bioavailability study to demonstrate that Naloxone HCl injection single-use prefilled syringe 5 mg/0.5 mL would provide comparable or higher naloxone exposure (e.g., Cmax, AUClast, and AUC0-inf), and comparable or higher exposure during the early absorption phase (e.g., naloxone concentrations at 2 to 5 min post-dose) in comparison to the reference product at the tested dose of 2 mg via IM injection. Therefore, efficacy for the proposed naloxone HCl injection product is demonstrated since it demonstrated higher systemic exposure than NDA 016636. Refer to the clinical review regarding the systemic safety associated with the higher naloxone exposure.

Comparative Bioavailability of 5 mg Naloxone IM Injection (ZIMHI Naloxone HCl Injection Single-use Prefilled Syringe 5 mg/0.5 mL) in Comparison to 2 mg Naloxone IM Injection (Naloxone HCl Injection 1 mg/1 mL, International Medical Systems):

Study APC 6000-03 was an open-label, randomized, single-dose, 2-period, 2-treatment crossover bioavailability study comparing a single dose of 5 mg naloxone IM injection for the proposed product, naloxone HCl injection single-use prefilled syringe 5 mg/0.5 mL (test), with 2 mg naloxone IM injection (1 mg/1 mL, International Medical Systems, reference) in 14 healthy subjects. The injection site was the anterolateral aspect of the thigh. There was a 48-hour washout period between treatments. Blood samples for PK determination were collected from each subject at pre-dose, and 2.5, 5, 10, 15, 20, 30 and 45 minutes; 1, 2, 3, 4, 5, 6, 8, and 12 hours post-dose.

A single dose of 5 mg naloxone IM injection of the proposed product, naloxone HCl injection single-use prefilled syringe 5 mg/0.5 mL, exhibited the same median Tmax values (0.25 h), greater naloxone concentrations at all time points including earlier time points (e.g., 2.5, 5, 10 min), 2.6-fold greater AUC0-2.5 min, 4.1-fold greater AUC0-5 min, 4.9-fold greater Cmax, 2.8-fold greater AUClast, and 2.7-fold greater AUC0-inf values, than a single dose of 2 mg naloxone IM injection of naloxone HCl injection (1 mg/1 mL, International Medical Systems). The point estimates (90% CI) of the geometric mean ratio (naloxone HCl injection 5 mg (test)/naloxone HCl injection 2 mg (reference)) for naloxone AUC0-2.5 min, AUC0-5 min, Cmax, AUClast and AUC0-inf were 260.73% (151.68%, 448.18%), 406.26% (288.61%, 571.89%), 487.10% (432.44%, 548.66%), 279.67% (257.32%, 303.96%), and 267.63% (249.14%, 287.49%), respectively (see **Figure 1**, **Tables 1, 2, and 3**).



Source: Study Report APC 6000-03 Figures 1 and 2

Figure 1 Mean Naloxone Plasma Concentration Profiles (Left, 0-1 h; Right, 0-12 h) and Mean Cmax (± SD) of Naloxone for Treatment A (5 mg Naloxone IM Injection of Naloxone HCl Injection Single-use Prefilled Syringe 5 mg/0.5 mL, Test) and Treatment B (2 mg Naloxone IM Injection of Naloxone HCl Injectable 1 mg/mL, Reference) (Study APC 6000-03)

Table 1 Mean (SD) (min, max) Naloxone Plasma Concentrations at Early Time Points for Treatment A (5 mg Naloxone IM Injection of Naloxone HCl Injection Single-use Prefilled Syringe 5 mg/0.5 mL, Test) and Treatment B (2 mg Naloxone IM Injection of Naloxone HCl Injectable 1 mg/mL, Reference) (Study APC 6000-03)

Time (min)	**Naloxone Mean (SD) (min, max) Plasma Concentration (ng/mL)**	
	Treatment A: 5 mg Naloxone IM Injection of Naloxone HCl Injection Single-use Prefilled Syringe 5 mg/0.5 mL (Test)	Treatment B: 2 mg Naloxone IM Injection of Naloxone HCL Injectable 1 mg/mL (Reference)
2.5	1.12 (2.35) (0.00, 9.02)	0.51 (0.92) (0.00, 3.45)
5	5.08 (4.78) (0.178, 15.3)	1.07 (1.18) (0.108, 4.48)
10	13.9 (7.47) (3.09, 27.6)	2.56 (2.47) (0.64, 10.2)
15	14.7 (7.60) (5.31, 32.5)	3.11 (1.71) (1.15, 8.05)

Source: recreated from Table 14.4.1 in Study Report APC 6000-03

Table 2 Mean (SD) (%CV) naloxone PK Parameters for 5 mg Naloxone IM Injection for Naloxone HCl Injection Single-use Prefilled Syringe 5 mg/0.5 mL (Test) and 2 mg Naloxone IM Injection for Naloxone HCl Injectable 1 mg/mL (Reference) (Study APC 6000-03)

PK Parameter	5 mg Naloxone IM injection (Naloxone HCl Injection Single-use Prefilled Syringe 5 mg/0.5 mL, Test) (n = 14)	2 mg Naloxone IM Injection (Naloxone HCl Injectable 1 mg/mL, Reference) (n = 14)
Cmax (ng/mL)	17.2 (7.57) (44.0%)	3.58 (2.08) (58.1%)
Tmax[1] (h)	0.25 (0.17, 0.52)	0.25 (0.05, 3.00)

AUC0-2.5min (ng.h/mL)	0.0225 (0.0469) (208%)	0.00921 (0.0151) (164%)
AUC0-5min (ng.h/mL)	0.147 (0.171) (117%)	0.0410 (0.0525) (128%)
AUClast (ng.h/mL)	26.2 (5.63) (21.5%)	9.43 (2.24) (23.8%)
AUC0-inf (ng.h/mL)	26.6 (5.64) (21.2%)	9.97 (2.26) (22.6%)
T1/2 (h)	1.50 (0.23) (15.2%)	1.86 (0.54) (28.9%)

[1]Tmax reported as median (min, max)

Source: Study Report APC 6000-03 Tables 6 and 7

Table 3 Summary of Statistical Analyses for the Naloxone PK for Treatment A (5 mg Naloxone IM injection for Naloxone HCl Injection Single-use Prefilled Syringe 5 mg/0.5 mL, Test) and Treatment B (2 mg Naloxone IM Injection for Naloxone HCl Injectable 1 mg/mL, Reference) (Study APC 6000-03)

PK Parameter	**Geometric Mean**		**Geometric Mean Ratio (%)**	**90% CI**	
	Test	**Reference**		**Lower**	**Upper**
Cmax (ng/mL)	15.8	3.24	487.10	432.44	548.66
AUClast (ng.h/mL)	25.7	9.18	279.67	257.32	303.96
AUC0-inf (ng.h/mL)	26.0	9.72	267.63	249.14	287.49
AUC0-2.5min (ng.h/mL)	0.0129	0.00496	260.73	151.68	448.18
AUC0-5min (ng.h/mL)	0.0782	0.0192	406.26	288.61	571.89

Source: Study Report APC 6000-03 Table 8

2 Bioanalytical Method

The bioanalytical LC/MS/MS method for the determination of naloxone in human plasma was adequately validated. The assay precision and accuracy of the analytical method for Study APC 6000-03 are summarized in **Table 4**.

Table 4 Naloxone Assay Precision and Accuracy

	Study APC 6000-03
Nominal range for the calibration curve	0.0500 – 50.0 ng/mL
LLOQ	0.05 ng/mL
QC	0.150, 2.50, 10.0, and 40.0 ng/mL
Precision (%CV)	5.0% – 7.2%

Accuracy (% difference from theoretical)	-3.5% – -1.3%

Source: APC 6000-03 Bioanalytical Study Report Table 3

OSIS declined to conduct an on-site inspection on both the clinical site at Worldwide Clinical Trials Early Phase Services and analytical site at (b) (4) for the comparative bioavailability study APC 6000-03 because an inspection is not warranted. OSIS inspected the clinical site in October 2018, which falls within the surveillance interval, and recommended that all study data were reliable to support a regulatory decision. OSIS inspected the analytical site in (b) (4), which falls within the surveillance interval, and the final classification for the inspection was No Action Indicated (more details in OSIS memos in DARRTS dated 6/23/2020 and 7/7/2020).

3 Labeling Recommendations

(b) (4)

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