CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208969Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	208969
Link to EDR	\\CDSESUB1\evsprod\NDA208969\0049
Submission Date	9/7/2022
Submission Type	*Standard Review*
Brand Name	Naloxone Hydrochloride Nasal Spray
Generic Name	Naloxone Hydrochloride Nasal Spray
Dosage Form and Strength	Nasal Spray, 4 mg naloxone hydrochloride in 0.25 mL
Route of Administration	Intranasal Spray
Proposed Indication	Opioid overdose reversal
Applicant	Amphastar Pharmaceuticals Inc.
Associated IND	*124672*
OCP Division:	*Division of Neuropsychiatric Pharmacology*
OND Division:	*Division of Anesthesiology, Addiction Medicine and Pain Medicine*
Clinical Pharmacology Reviewer	*Srikanth C. Nallani, Ph.D.*
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1. EXECUTIVE SUMMARY

1.1 Recommendations

The submitted PK study is acceptable from a clinical pharmacology perspective.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The PK study API-N002-CL-A3 provided adequate scientific bridge to rely on Agency's previous findings of efficacy and safety for the listed drug, Narcan NDA 016636. Since NDA 016636 is discontinued not because of safety or effectiveness reasons, generic drugs to NDA 016636 were used as reference product in this study. The new product demonstrated higher systemic exposure, including early absorption phase to the lowest approved dose of the listed drug, 0.4 mg IM injection. It also showed lower systemic exposure to the highest approved dose of the listed drug, 2 mg IV injection.
General dosing instructions	The recommended initial dose of Naloxone Hydrochloride Nasal Spray in adults and pediatric patients is the contents of one device delivered by intranasal administration, which delivers 4 mg of naloxone hydrochloride. If the desired response is not obtained after 2 minutes, administer an additional dose of Naloxone Hydrochloride Nasal Spray using a new Naloxone Hydrochloride Nasal Spray device.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The proposed dosing and administration apply to pediatric patients [redacted] (b) (4) and adults.
Labeling	The proposed label describes pharmacokinetics of naloxone following administration of intranasal naloxone compared to reference products.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation was used in the pivotal clinical PK study API-N-002-CL-A3 establishing scientific bridge between nasal spray of 4 mg naloxone (0.25 mL spray) and reference NDA 016636.

1.2 Post-Marketing Requirements and Commitments

None.

2. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

2.1 Overview of the Product and Regulatory Background

Amphastar submitted NDA 208969 relying on Agency's previous findings of efficacy and safety for Narcan (NDA 016636) to the proposed intranasal (IN) delivery of naloxone (N002) by utilizing the 505(b)(2) pathway. NDA 016636 was discontinued not because of safety or effectiveness reasons. The current submission supports the re-submission of the NDA 208969 for Naloxone Hydrochloride (HCl) Nasal Spray, referred as N002 throughout this Section, and to respond the deficiencies given in the Complete Response Letter (CRL) dated February 17, 2017, as well as subsequent correspondence and communication from the Agency. This resubmission includes changes as listed below:

- Naloxone dose is (b) (4) 4 mg;
- The filling volume is (b) (4) 0.25 mL;
- The device is (b) (4) pre-assembled (b) (4) and

New clinical studies (N002-A3, A4 and N002-C) were conducted to address the deficiencies identified in the complete response letter dated 2/17/2017.

2.2 General Pharmacology and Pharmacokinetic Characteristics

Naloxone is a well-known opioid antagonist used commonly in a hospital setting to reverse opioid overdose via IM, SC and IV routes. New intranasal spray products have been approved for use by a family member to treat opioid overdose patients while waiting for first responders. Naloxone has a short half-life (~1.5 hrs) and hence intranasal products as such are not a substitute for emergency medical care for the treatment of opioid overdose.

2.3 Clinical Pharmacology Review Questions

2.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Agency recognizes the life-saving nature of the treatment of opioid overdose indication. The sponsor was advised, in a pre-IND meeting, that the "The standard for approval for all naloxone products intended to be delivered in settings where opioids may be present (e.g., out-of-hospital/community settings) is to demonstrate that the proposed product achieves comparable or higher naloxone concentrations as the reference product at the Tmax of the reference product". The pharmacokinetic standard, described above, is based on the life-saving nature of the therapy in the setting of an opioid overdose in the community, the known efficacy of naloxone by the intramuscular and subcutaneous routes of administration, and the relatively wide safety margin for naloxone. This requirement ensures that there will not be a delay in onset of action after administration of your product compared to the reference product.

2.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The listed drug for this 505(b)(2) application, Narcan injection (NDA 016636), is approved as a solution for intravenous, intramuscular and subcutaneous administration in three concentrations: 0.02 mg, 0.4 mg and 1 mg of naloxone hydrochloride per mL. For adults with known or suspected opioid overdose, an initial dose of 0.4 mg to 2 mg of NARCAN may be administered intravenously. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available. If the desired degree of counteraction and improvement in respiratory functions are not obtained, it may be repeated at two- to three-minute intervals.

The proposed dose for this new product is to administer the contents (0.25 mL) of a single unit of the Nasal Spray intranasally into one nostril with a dose of 4 mg naloxone. If the patient does not respond or responds and then relapses into respiratory depression, additional doses of the Nasal Spray may be given after 2 minutes until emergency medical assistance arrives. The dosing regimen of the proposed product N002 4 mg nasal spray was evaluated as a single spray of 0.25 mL.

The primary purpose for pharmacokinetic study (API-N002-CL-A3) provided in this submission supporting N002 naloxone hydrochloride nasal spray is to provide a scientific bridge from the Agency's previous findings of efficacy and safety for Narcan (NDA 016636) by utilizing the 505(b) (2) pathway. However, original Narcan injection is not currently marketed and therefore, the sponsor utilized two generic products in the clinical study (API-N002-CL-A3): Naloxone administration by 0.4 mg (Hospira, ANDA 070256) through IM, and 2 mg (Amphastar/IMS, ANDA 072076) through IV infusion to investigate the efficacy and safety of the proposed N002.

Study N002-CL-A3 was designed as a randomized, evaluator-blind, single-dose, four-treatment, four-period, cross-over and fasting PK study in healthy adult volunteers (age between 18 and 45 years). Treatments V1, and V2 were delivered by IN in one nostril, at a volume of 0.25mL. Note: The sponsor is not seeking approval of product used in treatment V2. Treatment C3 was delivered by IM injection with a prepared 3-mL syringe. Treatment C4 was administered by IV infusion over 2 minutes.

Study Arms	**V1**	**V2**	**C3**	**C4**
Products				
Drug Formulation Code*	**N002-16-0.25**	**N002-40-0.25**	**Comparator**	**Comparator**
Manufacturer	IMS	IMS	Hospira (ANDA 070256)	IMS (ANDA 072076)
Naloxone Concentration (mg/mL)	16	40	0.4	1
Fill Volume, mL	0.25	0.25	1	2
Delivery				
Delivery Route	IN	IN	IM	IV
# of Nostrils for IN	1	1	-	-
Total volume delivered (mL)	0.25	0.25	1	2
Total Naloxone Dose (mg)	**4**	**10**	**0.4**	**2**

The sponsor defined the primary endpoints as follows:

1) AUC0-t*, (where t*= tmax of Treatment C3), defined as the partial area under the curve (AUC) in the plot of plasma Naloxone concentration versus time from time 0 to the tmax of Naloxone delivered by IM of Treatment C3.
2) *t' (t prime)*, defined as the time at which the plasma naloxone concentration of a given IN treatment first reaches the peak plasma Naloxone concentration (*Cmax*) of the IM treatment. Namely, *t'* satisfies the following equation: $C^{IN}(t') < C^{IM}_{max}$ Where $t' < t^{max}_{IM}$

A total of 32 subjects were enrolled and randomized. The numbers of evaluable subjects were 25, 24, 27 and 26 for treatments V1, V2, C3 and C4, respectively.

The sponsor's strategy appears to be one of achieving plasma naloxone concentrations with the 4 mg intranasal naloxone spray between the lowest approved dose of 0.4 mg IM naloxone injection and highest approved dose of 2 mg IV naloxone injection. The mean (SD) peak plasma concentrations of naloxone with IV naloxone were 15.1 (14.83) noted immediately after the 2-minute infusion (Mean 5 minutes, Range 3-10 minutes). The mean (SD) peak plasma concentrations of naloxone with IM naloxone were 0.81 (0.37) noted at median time of 30 minutes. The intranasal spray of 4 mg N002 produced mean plasma concentrations (4.07 ± 1.81 ng/mL) that were higher than the intramuscular injection of 0.4 mg naloxone and lower than IV injection of 2 mg naloxone (See Table 1).

The peak plasma concentrations noted at 30 minutes (median) with intramuscular injection were achieved after a median of 5.6 minutes (t' or t prime) following intranasal administration of N002 (4 mg dose or Treatment V1) (See Table 1). The mean plasma concentration of naloxone following N002 (Treatment V1) administration were higher than that noted with IM injection over the early timepoints of importance, that is over the first 30 minutes (See Table 2).

Table 1: Descriptive statistics of pharmacokinetics of naloxone following administration of intranasal (Treatments V1 and V2), intramuscular (Treatment C3), and intravenous (Treatment C4) naloxone.

Item	V1	V2	C3	C4
Study Drug	**N002-16-0.25**	**N002-40-0.25**	**Naloxone HCl**	**Naloxone HCl**
Delivery Route	**IN**	**IN**	**IM**	**IV**
Dose, mg	4	10	0.4	2
Number of Subjects (Evaluable Population)	**25**	**24**	**27**	**26**
Primary Endpoints				
AUC_{0-t*}, ng/mL*min, Geometric Mean ± S.D	**27.21 ± 6.32**	**57.78 ± 7.16**	**10.14 ± 2.53**	**120.06 ± 2.75**
Range: Min, Max	**(0.06, 263.63)**	**(0.10, 506.89)**	**(0.58, 30.36)**	**(7.64, 481.68)**
Arithmetic Mean ± S.D	**61.27 ± 63.92**	**137.46 ± 131.46**	**13.39 ± 8.03**	**166.68 ± 109.12**
t', min, Median	**5.6**	**3.8**	**30.0**	
Range: Min, Max	**(1.8, 29.9)**	**(1.1, 17.6)**	**(3.0, 90.0)**	**n/a**
Arithmetic Mean ± S.D	**6.9 ± 5.5**	**4.6 ± 3.2**	**33.2 ± 24.0**	
Secondary Endpoints				
$AUC_{0-\infty}$, ng/mL*hr , Geometric Mean ± S.D	**6.63 ± 1.32**	**13.50 ± 1.33**	**1.60 ± 1.27**	**8.64 ± 1.33**
Range: Min, Max	**(3.86, 11.04)**	**(8.67, 30.43)**	**(1.09, 2.67)**	**(4.33, 13.07)**
Arithmetic Mean ± S.D	**6.87 ± 1.92**	**14.11 ± 4.86**	**1.65 ± 0.40**	**8.96 ± 2.32**
C_{max}, ng/mL, Geometric Mean ± S.D	**3.71 ± 1.55**	**7.12 ± 1.54**	**0.73 ± 1.56**	**11.10 ± 2.15**
Range: Min, Max	**(1.45, 7.90)**	**(2.84, 17.49)**	**(0.30, 1.84)**	**(3.44, 75.74)**
Arithmetic Mean ± S.D	**4.07 ± 1.81**	**7.78 ± 3.49**	**0.81 ± 0.37**	**15.10 ± 14.83**
AUC_{0-6hr}, ng/mL*hr, Geometric Mean ± S.D	**6.41 ± 1.33**	**13.03 ± 1.35**	**1.54 ± 1.27**	**8.44 ± 1.34**
Range: Min, Max	**(3.67, 10.74)**	**(7.89, 29.56)**	**(1.05, 2.63)**	**(4.17, 12.69)**
Arithmetic Mean ± S.D	**6.67 ± 1.91**	**13.68 ± 4.87**	**1.59 ± 0.40**	**8.77± 2.32**
t_{max}, min, Median	**30**	**30**	**30**	**5**
Range: Min, Max	**(15, 90)**	**(10, 120)**	**(3, 90)**	**(3, 10)**
Arithmetic Mean ± S.D	**35.9 ± 17.8**	**36.5 ± 25.7**	**33.2 ± 24.0**	**5.2 ± 1.9**
C^{IN}(t*), ng/mL, Geometric Mean ± S.D	**2.09 ± 2.28**	**4.18 ± 2.57**		
Range: Min, Max	**(0.08, 6.21)**	**(0.17, 14.78)**	**n/a**	**n/a**
Arithmetic Mean ± S.D	**2.55 ± 1.36**	**5.44 ± 3.18**		

(Refer to SAR **Table 5.3.3.1.3-9-2207**)

Table 2: Mean (± SD) Naloxone Plasma Concentration within 30 minutes of administering intranasal (Treatments V1 and V2), intramuscular (Treatment C3), and intravenous (Treatment C4) naloxone.

#	Item	V1	V2	C3	C4
1	Study Drug	N002-16-0.25	N002-40-0.25	Naloxone 0.4 mg	Naloxone 2 mg
2	Active Drug Ingredient	Naloxone HCl	Naloxone HCl	Naloxone HCl	Naloxone HCl
3	Delivery Route	IN	IN	IM	IV
4	Dose, mg	4	10	0.4	2
5	Concentration, mg/mL	16	40	0.4	1
6	Volume, mL	0.25	0.25	1	2
7	# of Nostrils for IN	1	1	n/a	n/a
8	# of subjects, n3trt	25	24	27	26
9	Baseline	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
10	1 min	0.02 ± 0.06	0.02 ± 0.08	0.00 ± 0.01	0.75 ± 3.22
11	2 min	0.08 ± 0.15	0.09 ± 0.13	0.06 ± 0.10	4.70 ± 9.98
12	3 min	0.34 ± 0.39	0.71 ± 1.15	0.20 ± 0.27	10.56 ± 14.72
13	5 min	0.97 ± 1.16	1.79 ± 1.67	0.26 ± 0.20	12.56 ± 8.49
14	10 min	2.15 ± 1.64	4.29 ± 3.05	0.59 ± 0.42	7.06 ± 2.76
15	15 min	2.90 ± 1.90	5.39 ± 3.72	0.63 ± 0.38	5.19 ± 2.12
16	18 min	3.33 ± 1.94	5.84 ± 3.62	0.64 ± 0.35	5.09 ± 2.08
17	21 min	3.23 ± 1.68	6.07 ± 3.52	0.67 ± 0.35	4.96 ± 1.81
18	24 min	3.08 ± 1.47	5.76 ± 2.86	0.61 ± 0.31	4.49 ± 1.82
19	27 min	3.10 ± 1.41	5.89 ± 3.03	0.62 ± 0.27	4.26 ± 1.80
20	30 min	3.12 ± 1.29	6.17 ± 3.15	0.64 ± 0.29	4.09 ± 1.52

Source: Statistical Analysis Report SAR-N002-A3

Table 3: Statistical Evaluation for Partial AUC0-t (t =0-30 min), IN vs. IM

Partial AUC_{0-t}, ng/mL*min	BE Statistical Analysis				IN vs. IM (0.4mg)	
	Ratio* %	LCI** %	UCI** %	LCI > 80%?	*p*-value	*p*-value <0.05?
1. $AUC_{0-2'}$	117.5	66.5	207.5	X	0.1608	X
2. $AUC_{0-3'}$	159.0	88.8	284.7	√	0.1170	X
3. $AUC_{0-5'}$	208.3	136.8	317.2	√	0.0113	√
4. $AUC_{0-10'}$	291.5	213.8	397.5	√	0.0004	√
5. $AUC_{0-15'}$	334.5	254.6	439.6	√	<0.0001	√
6. $AUC_{0-18'}$	363.2	281.7	468.1	√	<0.0001	√
7. $AUC_{0-21'}$	385.4	304.1	488.5	√	<0.0001	√
8. $AUC_{0-24'}$	399.6	319.8	499.4	√	<0.0001	√
9. $AUC_{0-27'}$	411.1	333.2	507.2	√	<0.0001	√
10.$AUC_{0-30'}$	419.8	343.5	513.0	√	<0.0001	√

* Ratio -- Ratio (%) of Geometric Mean for IN vs IM

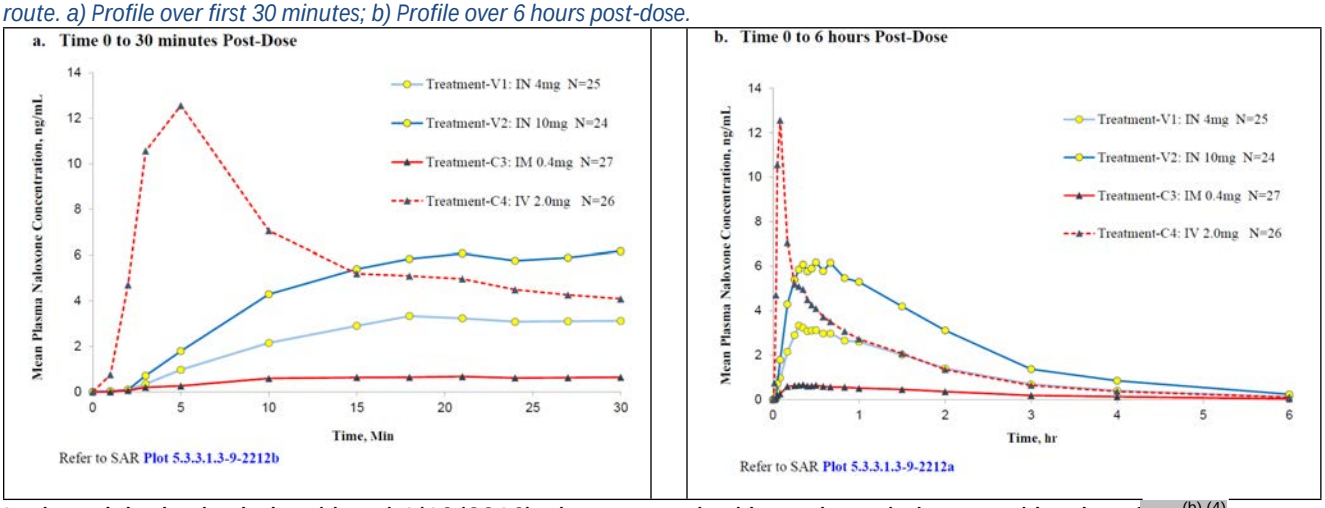
** LCI -- Lower confidence interval of Ratio; UCI -- Upper confidence interval of Ratio

Reference: SAR, Table 5.3.3.1.3-9-2205a

The 90% CIs of geometric mean ratios of IN treatment to IM for the partial AUC0-t (0 – 30 minutes) were calculated and summarized in Table 3. With the exception for AUC0-2min, (for which the ratio of geometric mean is 117.5%, but the lower 90% CI < 80%; the result is likely due to the sample size is not sufficiently large) the lower limits of the 90% CIs (LCIs) were all greater than 80%, highlighted in Table 3. The data demonstrate that the 4 mg N002 IN exceeded the exposure of the 0.4mg dose of IM during the

first five (5) minutes post-dosing. The data provides further evidence that the formulation used by the proposed N002 at 4mg has a higher systemic exposure than the IM comparator during the early absorption phase. Additional PK parameters are documented in the study synopsis in the appendix.

Figure 1: PK profile of naloxone following administration of different treatments via intranasal, intramuscular or intravenous route. a) Profile over first 30 minutes; b) Profile over 6 hours post-dose.



In the original submission (dated 4/19/2016), the sponsor had investigated pharmacokinetics of (b) (4) (See Clinical Pharmacology review dated 1/11/2017). The partial AUC's at 5 minutes and the ratio to IM injection suggest that adequate naloxone is absorbed after intranasal spray irrespective of the two doses evaluated. In the current study which evaluated 0.25 mL of 4 mg dose with a preassembled device, the early partial AUC at 5 minutes also appear higher than intramuscular injection. Taken together, these observations support that the to-be-marketed formulation and device of naloxone nasal spray with 4 mg dose has reasonable expectation of delivering effective levels of naloxone to allow for repeated use every 2-3 minutes until emergency medical services arrive.

(b) (4)

Source: Clinical Pharmacology Review dated 1/17/2017

2.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

In response to the CR letter deficiencies regarding the (b) (4) mL volume of previously developed nasal spray, the device and formulation were revised (b) (4) to 0.25 mL. The recommended initial dose of Naloxone Hydrochloride Nasal Spray in adults and pediatric patients is the contents of one device delivered by intranasal administration, which delivers 4 mg of naloxone hydrochloride. If the desired response is not obtained after 2 minutes, administer an additional dose of Naloxone Hydrochloride Nasal Spray using a new Naloxone Hydrochloride Nasal Spray device.

3. Labeling

The sponsor proposed labeling is presented as regular text and additions or deletions are marked as bold or strikethrough text, respectively.

(b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

4. APPENDICES

[Please note: The appendices listed below are examples only; appendices should be tailored to the review of a particular submission.]

3.1 Summary of Bioanalytical Method Validation and Performance

In this study, naloxone and added internal standard, naloxone-d5, were extracted from human plasma using solid phase extraction (SPE) plates. These extracts are then subjected to ultra-high performance liquid chromatography on Waters ACQUITY BEH C18 2.1 x 50 mm, 1.7 µm column. Naloxone and internal standard are detected by AB Sciex QTRAP 6500+ MS/MS system. Quantification is achieved by monitoring the product ions (m/z 328.1 → 212.1 for naloxone and m/z 333.1 → 212.1 for naloxone-d5). System calibration is accomplished by a weighted (1/x2) linear regression of the peak area ratio (analyte/internal standard) versus the concentration of the analyte. The analytical method, "Determination of Naloxone in Human Plasma by LC-MS/MS" (LTM-O-0030), has been validated per FDA's Guidance for Industry, Bioanalytical Method Validation (2021).

OSIS inspection was requested for the clinical site and analytical site for the pivotal PK study. However, in the inspection memo dated 11/14/22 in Darrts (entered on 11/25/2022), OSIS declined the inspection request and determined that inspections are not needed, considering that the clinical site and analytical site were inspection in (b) (4) and found acceptable. Previously, an OSIS inspection was requested for the studies (b) (4), submitted in the original NDA in 2016. The data from the audited studies were found to be reliable by OSIS reviewers and the data were accepted for further review in 2016.

The sensitivity (LLOQ 10 pg/mL), specificity, inter-day precision and accuracy, linearity (10 to 8000 pg/mL), incurred sample reanalysis (98.2% samples within limit), the short term and long-term stability of samples were acceptable.

3.2 Clinical PK and/or PD Assessments

Synopsis of PK study N002-CL-A3: This is a randomized, evaluator-blinded, four-treatment, crossover PK study conducted in healthy volunteers (male and female between 18 and 45 years old). The study consists of (i) a screening visit, (ii) four (4) dosing visits, Visit-1 to Visit-4 (separated by a 3 – 14 day period), and (iii) a follow-up phone evaluation (1-7 days after the completion of Visit-4, or study termination). This study aimed to evaluate PK and Safety/Tolerability profiles of the proposed intranasal (IN)product, N002. The PK parameters which characterize the N002 efficacy and safety evaluation were compared between IN deliveries of N002, and intramuscular (IM), or intravenous (IV)injections of Naloxone in healthy volunteers.

Study Product Information: Note: Only product V1 is the to-be-marketed formulation and the subject for review and approval and product V2 is a test treatment.

Table 5: Study Treatments Used in the PK Study.

Study Arms	V1	V2	C3	C4
Products				
Drug Formulation Code*	**N002-16-0.25**	**N002-40-0.25**	**Comparator**	**Comparator**
Manufacturer	IMS	IMS	Hospira (ANDA 070256)	IMS (ANDA 072076)
Naloxone Concentration (mg/mL)	16	40	0.4	1
Fill Volume, mL	0.25	0.25	1	2
Delivery				
Delivery Route	IN	IN	IM	IV
# of Nostrils for IN	1	1	-	-
Total volume delivered (mL)	0.25	0.25	1	2
Total Naloxone Dose (mg)	**4**	**10**	**0.4**	**2**

* Formulation code: Concentration (mg/mL) and fill volume (mL)

A total of 32 subjects aged 18 – 45 years healthy adult volunteers were enrolled and randomized in the study. The numbers of evaluable subjects are 25, 24, 27, and 26 for treatments V1, V2, C3, and C4, respectively.

Table 6: Demographic Profile of Subjects Recruited in the PK Study.

Items	V1	V2	C3	C4
Study Drugs	N002-16-0.25	N002-40-0.25	Naloxone HCl (ANDA 070256)	Naloxone HCl (ANDA 072076)
Delivery Route	IN	IN	IM	IV
Dose, mg	4	10	0.4	2
Volume, mL	0.25	0.25	1	2
Targeted # of Subjects, N	24			
# of Subjects Randomized, n1*	32 (12, 20)			
# of Subjects Treated, n2	27 (11, 16)	27 (11, 16)	28 (12, 16)	30 (12, 18)
# of Subjects, Evaluable, n3trt	25 (11, 14)	24 (11, 13)	27 (12, 15)	26 (12, 14)
# of Subjects, PPP-C3, n4trt3	25 (11, 14)	24 (11, 13)	27 (12, 15)	-
# of Subjects, PPP-C4, n4trt4	24 (11, 13)	23 (11, 12)	-	26 (12, 14)
Age (yr), mean ± std.	30.3 ± 6.8	29.9 ± 6.8	30.2 ± 6.7	29.9 ± 6.6
Age (yr), median (range)	30(18, 43)	29(18, 43)	30(18, 43)	29(18, 43)
Weight (kg), mean ± std.	74.1 ± 15.0	73.1 ± 13.5	74.4 ± 14.8	73.8 ± 14.0
Height (cm), mean ± std.	170.5 ± 10.2	170.4 ± 10.0	171.1 ± 9.9	171.6 ± 9.6
Race Group, N(%)				
White	10(37.0%)	10(37.0%)	10(35.7%)	10(33.3%)
Black or African-American	14(51.9%)	13(48.1%)	14(50.0%)	16(53.3%)
Asian	1 (3.7%)	1 (3.7%)	1 (3.6%)	1 (3.3%)
Others	2 (7.4%)	3 (11.1%)	2 (10.7%)	3 (10.0%)
Ethnicity, N(%)				
Hispanic	5(18.5%)	5(18.5%)	4(14.3%)	4(13.3%)
Non-Hispanic	22(81.5%)	22(81.5%)	24(85.7%)	26(86.7%)

* N is provided in the format N(M, F)=Number of Subjects (Number of male, female subjects)

The study protocol planned for a total of 21 blood sampling/data points for each subject at each study visit, and allowed each subject to miss certain post-dose sampling/data points. In the study, blood PK samples were collected at these scheduled time points: pre-dose baseline (-60 to 0 minutes), 1, 2, 3, 5, 10, 15, 18, 21, 24, 27, 30, 35, 40, 50, 60, 90, 120, 180, 240, and 360 minutes post-dose for each dosing visit. At each sampling point, blood samples (~2mL) was collected in ice-chilled K2-Ethylenediaminetetraacetic Acid (EDTA) collection tubes. All blood samples were centrifuged at 4°C, 2,000-3,000 g for 20 minutes for plasma isolation. Isolated plasma were transferred into one 2.0 mL cryo vial, so that the vial contains approximately 1 mL plasma per sample obtained. The plasma sample vials were frozen immediately on dry ice and then stored (within 60 minutes following plasma separation) in a freezer at -20°C or lower until analysis.

A minimum of 15 out of 20 post-dose PK measurements/data points for each subject per study period were required to be available for plotting the plasma concentration-time PK curves. There were no more than four (4) consecutive missing PK data points (including missed data points and disqualified samples for analyses) for a subject during the study period

There were seven (7) subjects had dropped out or were early terminated (ET) from the study. Two subjects withdrew their consent, one subject was early terminated due to drug leakage after injection, one subject was early terminated due to difficulty in PK blood sample collection, two subjects dropped

Table 7: Dropout Information

#	Subject ID/No.	Reason for dropout/Early Termanation (ET)	Treatment(s) Sequence *
1	(b) (6)	Unable to collect blood samples	C4-V1-V2-C3
2		Withdrew consent due to schedule conflict	C3-C4-V1-V2
3		No longer met inclusion #8: negative alcohol test	C4-V1-V2-C3
4		Withdrew consent due to adverse event	C3-C4-V1-V2
5		Study drug leakage	V1-V2-C3-C4
6		Positive pregnancy test	V1-V2-C3-C4
7		Met exclusion #8: abnormal ECG	C4-V1-V2-C3

* Visits marked in red represent missing study treatments (Refer to SAR Table 5.3.3.1.3-9-1124)

Table 8: Summary of Protocol Deviations

#	Deviation Description (Types)	# of Deviation(s) per Treatment				Subjects with Deviation shown by Subject ID or Sample ID *				
		V1	V2	C3	C4	V1	V2	C3	C4	Outside of Study Period
1	PK samples not collected	0	0	0	1	(b) (6)				
2	Study drug leakage	0	0	1	0					
3	PK sample collected out of time window *	1	13	0	12					
4	Post-dose repeat vital signs not collected	1	0	0	0					
5	Post-dose heart rate measurement was not collected	2	1	1	0					
6	Post-dose NOME conducted out of time window	1	0	1	0					
7	Post-dose Oropharyngeal Examination onducted out of time window	0	0	1	0					
8	The arm used for post-dose vital signs was not captured	2	2	2	1					
9	The arm used for pre-dose vital signs was not captured	0	0	0	2					
10	End-of-study clinical labs were not done	0	0	0	1					
11	End-of-study ECG and vital signs were not done	0	0	1	0					
12	Follow-up phone call was done out of window	0	0	0	0					
	Total	7	16	7	17					

* A unique sample ID was used to identify deviations related to individual PK samples, N2-PKA3-nn-XX, where XX is the two- digit time-point sequential number of the sample, where red colored subject ID represent SPD

out, as they no longer met the inclusion/exclusion criteria, and one subject was early terminated due to positive pregnancy test. Seven (7) subjects were disqualified from PPP analysis due to incorrect dosing, or missing PK data points. There were 12 types of protocol deviations documented in N002-CL-A3 study. The most common type of deviation was "PK sample collected out of time window" with 1 from Treatment-V1, 13 from Treatment-V2, and 12 from Treatment-C4, for a total of 26 deviations, or 54.2% (=26/48) of all protocol deviations. Out of the 26 deviations that were "PK sample collected out of time window", 16 deviations were classified as severe protocol deviations (SPD), due to the collecting time overlapping with the subsequent PK time point(s). As a result, these 16 PK samples were excluded from the primary PK analyses.

The sponsor defined the primary endpoints as follows:

1) AUC0-t*, (where t*= tmax of Treatment C3), defined as the partial area under the curve (AUC) in the plot of plasma Naloxone concentration versus time from time 0 to the tmax of Naloxone delivered by IM of Treatment C3.
2) ***t' (t prime)***, defined as the time at which the plasma naloxone concentration of a given IN treatment first reaches the peak plasma Naloxone concentration (*Cmax*) of the IM treatment. Namely, ***t'*** satisfies the following equation: $C^{IN}(t') < C^{IM}_{max}$ Where $t' < t^{max}_{IM}$

Assessments of PK parameters and relevant statistical analysis were conducted in two datasets:

- SPD-Included (SPD-I) dataset: All PK data points available (including SPD) were included for analysis;
- SPD-Excluded (SPD-E) dataset: PK data that are excluded due to SPD (collection time out-of-time-window) were considered as missing data. The missing data points due to SPD were calculated by interpolation. The SPD-E dataset, which excludes the SPD data, is considered as the primary analysis (described above in the main body of the review). Descriptive Statistics of naloxone PK (SPD-Excluded) following intranasal (Treatment V1 and V2), Intramuscular (Treatment C3), and Intravenous (treatment C4).

Table 9: Statistical analysis of endpoints defined in the protocol (Sponsor's analysis).

a. SPD-E Dataset

PK Parameter		Goal	V1	V2
Primary Endpoints			**N = 25**	**N = 24**
AUC_{0-t^*}	**The Ratio of Geometric Mean vs C3, %**		288.7	485.2
	90% LCI	> 80.0%	199.6	317.6
	90% UCI	-	417.6	741.4
t'	**The Ratio of Geometric Mean vs C3, %**		25.1	18.8
	90% LCI	-	17.5	12.2
	90% UCI	< 125.0%	36.1	28.8
Secondary Endpoints			**N = 24**	**N = 23**
$AUC_{0-\infty}$	**The Ratio of Geometric Mean vs C4, %**		66.3	159.8
	90% LCI	-	56.8	140.4
	90% UCI	< 125.0%	77.5	181.9
AUC_{0-6hr}	**The Ratio of Geometric Mean vs C4, %**		65.5	158.5
	90% LCI	-	55.8	139.0
	90% UCI	< 125.0%	76.9	180.7
C_{max}	**The Ratio of Geometric Mean vs C4, %**		26.7	65.0
	90% LCI	-	19.2	50.0
	90% UCI	< 125.0%	37.2	84.4
			N = 25	**N = 24**
C^{IN} (t*)	**The Ratio of Geometric Mean vs C3, %**		282.7	476.3
	90% LCI	> 80.0%	204.4	326.0
	90% UCI	-	390.9	695.9

(Refer to SAR **Table 5.3.3.1.3-9-2202a**, and **-2203a**)

b. SPD-I Dataset

PK Parameter		Goal	V1	V2
Primary Endpoints			**N = 25**	**N = 25**
AUC_{0-t^*}	**The Ratio of Geometric Mean vs C3, %**		288.7	466.4
	90% LCI	> 80.0%	199.6	303.7
	90% UCI	-	417.6	716.3
t'	**The Ratio of Geometric Mean vs C3, %**		25.1	19.6
	90% LCI	-	17.5	12.9
	90% UCI	< 125.0%	36.1	29.8
Secondary Endpoints			**N = 25**	**N = 25**
$AUC_{0-\infty}$	**The Ratio of Geometric Mean vs C4, %**		60.0	149.5
	90% LCI	-	50.5	128.4
	90% UCI	< 125.0%	71.2	174.1
AUC_{0-6hr}	**The Ratio of Geometric Mean vs C4, %**		59.1	148.1
	90% LCI	-	49.7	126.7
	90% UCI	< 125.0%	70.2	173.2
C_{max}	**The Ratio of Geometric Mean vs C4, %**		19.2	54.7
	90% LCI	-	12.5	36.8
	90% UCI	< 125.0%	29.4	81.2
			N = 25	**N = 25**
C^{IN} (t*)	**The Ratio of Geometric Mean vs C3, %**		282.7	460.8
	90% LCI	> 80.0%	204.4	314.6
	90% UCI	-	390.9	674.9

(Refer to SAR **Table 5.3.3.1.3-9-2202b**, and **-2203b**)

*Table 10: Descriptive Statistics of naloxone PK (SPD-Excluded) following intranasal (Treatment V1), Intramuscular (Treatment C3), and Intravenous (treatment C4). Post-hoc analysis by FDA reviewer where PK data was available from all subjects for treatments V1, C3 and C4. Units: Cmax – ng/mL; AUC – ng*min/mL; $T_{1/2}$ and Tmax – hours.*

Note: Treatment V1 is the to be marketed formulation. Analysis for Treatment V2 was excluded from this table because sponsor is not seeking approval it.

Variable	Treatment	NObs	Mean	SD	Min	Median	Max	Range	Geo Mean	Geo SD	Geo Lower 95% CI	Geo Upper 95% CI
Cmax	TreatmentC3	25	0.82	0.37	0.30	0.72	1.84	1.54	0.75	1.56	0.30	1.86
Cmax	TreatmentC4	25	45.87	151.54	3.44	12.05	769.73	766.29	13.60	3.11	1.31	141.79
Cmax	TreatmentV1	25	4.07	1.81	1.45	3.73	7.90	6.45	3.71	1.55	1.50	9.18
$T_{1/2}$	TreatmentC3	25	78.18	20.24	58.10	76.40	154.21	96.12	76.18	1.25	48.19	120.44
$T_{1/2}$	TreatmentC4	25	67.67	13.36	53.34	60.05	98.96	45.62	66.50	1.21	45.21	97.82
$T_{1/2}$	TreatmentV1	25	68.58	12.26	48.45	64.93	99.49	51.03	67.60	1.19	47.58	96.05
Tmax	TreatmentC3	25	30.88	22.0	3	21	90	87	22.8	2.4	3.7	140.2
Tmax	TreatmentC4	25	5.12	2.1	1	5	10	9	4.7	1.6	1.8	12.0
Tmax	TreatmentV1	25	35.88	17.8	15	30	90	75	32.1	1.6	11.9	86.8
AUC0-5	TreatmentC3	25	0.64	0.62	0.06	0.44	2.72	2.66	0.42	2.72	0.05	3.29
AUC0-5	TreatmentC4	25	105.09	350.38	4.97	24.88	1776.32	1771.35	28.07	3.46	2.17	362.72
AUC0-5	TreatmentV1	25	1.57	1.87	0.05	0.94	8.33	8.28	0.87	3.34	0.07	10.51
AUC0-10	TreatmentC3	25	2.84	2.03	0.62	2.08	8.39	7.77	2.24	2.04	0.51	9.77
AUC0-10	TreatmentC4	25	186.61	504.98	21.12	73.29	2594.31	2573.19	79.80	2.71	10.21	623.72
AUC0-10	TreatmentV1	25	9.37	8.38	0.74	6.88	33.61	32.87	6.60	2.44	1.05	41.68
AUC0-15	TreatmentC3	25	6.01	3.95	1.54	4.34	17.18	15.64	4.96	1.88	1.35	18.24
AUC0-15	TreatmentC4	25	218.02	506.58	31.83	111.47	2628.67	2596.84	113.37	2.42	18.22	705.39
AUC0-15	TreatmentV1	25	21.99	16.79	1.81	15.24	72.18	70.36	16.82	2.21	3.28	86.17
AUC0-18	TreatmentC3	25	7.97	5.00	2.24	5.89	21.96	19.72	6.70	1.83	1.93	23.20
AUC0-18	TreatmentC4	25	233.96	508.26	38.02	130.64	2649.89	2611.87	129.99	2.33	22.67	745.44
AUC0-18	TreatmentV1	25	31.34	22.13	2.77	22.36	93.68	90.92	24.65	2.13	5.18	117.22
AUC0-21	TreatmentC3	25	9.98	6.03	3.10	7.58	26.51	23.40	8.49	1.78	2.57	28.03

AUC0-21	TreatmentC4	25	249.45	509.85	43.90	148.72	2670.40	2626.50	146.20	2.25	27.33	782.09
AUC0-21	TreatmentV1	25	41.18	27.05	4.08	32.07	112.65	108.57	33.17	2.06	7.50	146.75
AUC0-24	TreatmentC3	25	11.94	6.98	4.03	9.37	31.04	27.01	10.27	1.74	3.26	32.38
AUC0-24	TreatmentC4	25	263.99	511.34	49.11	165.36	2689.62	2640.51	161.32	2.19	31.87	816.66
AUC0-24	TreatmentV1	25	50.63	31.36	5.61	42.71	130.98	125.37	41.59	1.99	10.04	172.29
AUC0-27	TreatmentC3	25	13.81	7.80	4.92	11.05	35.35	30.43	12.01	1.71	3.97	36.31
AUC0-27	TreatmentC4	25	277.38	512.48	53.71	182.17	2705.65	2651.94	175.10	2.15	36.11	849.09
AUC0-27	TreatmentV1	25	59.91	35.13	7.20	51.15	146.80	139.60	49.97	1.94	12.72	196.33
AUC0-30	TreatmentC3	25	15.73	8.60	5.78	12.64	39.57	33.78	13.80	1.68	4.72	40.33
AUC0-30	TreatmentC4	25	291.36	519.53	58.46	196.75	2750.97	2692.51	188.32	2.11	40.22	881.78
AUC0-30	TreatmentV1	25	69.24	38.34	8.83	59.98	160.53	151.71	58.57	1.90	15.62	219.58
AUCall	TreatmentC3	25	96.28	23.80	64.91	91.12	157.74	92.83	93.67	1.27	57.50	152.59
AUCall	TreatmentC4	25	649.72	583.68	250.44	564.60	3378.48	3128.04	558.39	1.59	215.03	1450.06
AUCall	TreatmentV1	25	400.20	114.78	220.20	382.54	644.49	424.28	384.89	1.33	213.36	694.33
AUCINF_obs	TreatmentC3	25	101.53	24.74	69.98	99.17	159.98	90.00	98.80	1.27	60.70	160.80
AUCINF_obs	TreatmentC4	25	661.85	583.45	259.60	571.21	3389.89	3130.28	571.51	1.58	223.31	1462.69
AUCINF_obs	TreatmentV1	25	412.45	115.28	231.84	395.86	662.30	430.45	397.53	1.32	224.25	704.69

Units: Cmax – ng/mL; AUC – ng*min/mL; T1/2 and Tmax – hours. Data excluded -06 (Missing V1), -08 (missing V1, C3), -15 (missing C3), -21 (missing C3), -24 (missing V1), -26 (missing V1 and C3))

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/s/

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Office of Clinical Pharmacology Review

NDA or BLA Number	208969
Link to EDR	\\cdsesub1\evsprod\NDA208969
Submission Date	4/19/2016
Submission Type	*[Standard review]*
Brand Name	(b) (4)
Generic Name	Naloxone Intranasal Spray
Dosage Form and Strength	Intranasal Spray (b) (4)
Route of Administration	Intranasal
Proposed Indication	Opioid Overdose Reversal
Applicant	Amphastar Inc.
Associated IND	*[124672]*
OCP Review Team	*[Srikanth C. Nallani, Ph.D.]*
OCP Final Signatory	*[Yun Xu, Ph.D.]*

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Recommendations

The submitted two PK studies are acceptable from a clinical pharmacology perspective. However, clinical division has decided to take a complete response action on this NDA due to unresolved product quality and human factors issues (b) (4)
As such, the review team will not have labeling negotiation with the Sponsor and labeling recommendations are not made from a clinical pharmacology perspective.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY CLINICAL PHARMACOLOGY REVIEW

2.1 Overview of the Product and Regulatory Background

Amphastar submitted (b) (4) NDA 208969 relying on Agency's previous findings of efficacy and safety for Narcan (NDA 016636) to the proposed intranasal (IN) delivery of naloxone (N002) by utilizing the 505(b) (2) pathway. NDA 016636 was discontinued not because of safety or effectiveness reasons. Two generic products were used as comparators in the relative bioavailability studies as Narcan is no longer marketed Hospira's Naloxone 0.4mg/1mL (ANDA 070256) and Amphastar/IMS's Naloxone 2mg/2mL (ANDA 072076). Both ANDAs are RLD's according to the Orange Book.

(b) (4) referred to as (b) (4) is a solution of naloxone HCl as (b) (4) concentration provided as (b) (4). Although other formulations (b) (4)) are labeled as N002 the product concentration is different and product fill volume is different. The investigated products are designated as a number as following: N002-(concentration as ng/mL)-(volume as mL) and the proposed product is (b) (4)

Naloxone HCl Nasal Spray, (b) (4)

Product Strength	**Naloxone HCl Nasal Spray, (b) (4)**
AMOUNT PER ML	
API:	
Naloxone HCl Dihydrate USP*	(b) (4) mg
Inactive Ingredients:	
Sodium Chloride, USP	(b) (4) mg
(b) (4)	pH adjustment as needed
Water for Injection, USP	QS Ad
(b) (4)	

Agency recognizes the life-saving nature of the treatment of opioid overdose indication. The sponsor was advised, in a pre-IND meeting, that the "The standard for approval for all naloxone products intended to be delivered in settings where opioids may be present (e.g., out-of-hospital/community settings) is to demonstrate that the proposed product achieves comparable or higher naloxone concentrations as the reference product at the Tmax of the reference product".

2.2 General Pharmacology and Pharmacokinetic Characteristics

Naloxone is a well-known opioid antagonist used commonly in a hospital setting to reverse opioid overdose via IM, SC and IV routes. New intranasal spray products have been approved for use by a family member to treat opioid overdose patients while waiting for first responders.

Naloxone has a short half-life (~1.5 hrs) and hence intranasal products as such are not a substitute for emergency medical care for the treatment of opioid overdose.

2.3 Clinical Pharmacology Review Questions

2.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The pharmacokinetic standard, described above, is based on the life-saving nature of the therapy in the setting of an opioid overdose in the community, the known efficacy of naloxone by the intramuscular and subcutaneous routes of administration, and the relatively wide safety margin for naloxone. This requirement ensures that there will not be a delay in onset of action after administration of your product compared to the reference product.

2.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The listed drug for this 505(b)(2) application, Narcan injection (NDA 016636), is available as a solution for intravenous, intramuscular and subcutaneous administration in three concentrations: 0.02 mg, 0.4 mg and 1 mg of naloxone hydrochloride per mL. For adults with known or suspected opioid overdose, an initial dose of 0.4 mg to 2 mg of NARCAN may be administered intravenously. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available. If the desired degree of counteraction and improvement in respiratory functions are not obtained, it may be repeated at two- to three-minute intervals.

The proposed dose for this new product is to administer the contents (b) (4) of a single unit of the Nasal Spray intranasally into one nostril with a dose of (b) (4) naloxone. If the patient does not respond or responds and then relapses into respiratory depression, additional doses of the Nasal Spray may be given after 2 minutes until emergency medical assistance arrives. (b) (4) The following two studies (PK only) were conducted to support the safety and efficacy of (b) (4) intranasal spray.

- Study (b) (4)

- Study (b) (4)

Since these two studies form the basis for clinical experience, inspection of Clinical site and Bioanalytical sites were conducted by OSIS. After reviewing the Establishment Inspection Report, inspection findings, and firm's response to Form FDA 483, the analytical data from the audited studies were found to be reliable by OSIS reviewers and the data were accepted for further review.

(b) (4)

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2.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

(b) (4)

Amphastar has indicated that they will develop a formulation with adequate dose volume for all age ranges, including pediatric patients. They have also indicated in their pediatric plan that if a new pediatric formulation is deemed necessary and developed, its PK will be characterized in healthy adults.

Conclusions:

Amphastar has demonstrated that (b) (4) (or (b) (4) is effective only when used as directed.

However, during the review process human factors study identified the (b) (4)

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3. APPENDICES

[Please note: The appendices listed below are examples only; appendices should be tailored to the review of a particular submission.]

3.1 Summary of Bioanalytical Method Validation and Performance

(b) (4)

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3.4 Clinical pharmacology Filing memo.

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	208969	**SDN**	1
Applicant	Amphastar	**Submission Date**	4/19/2016
Generic Name	Naloxone HCl	**Brand Name**	(b) (4) (Changed to (b) (4)
Drug Class	Opioid Antagonist		
Indication	Emergency treatment of opioid overdose		
Dosage Regimen	Call 911 and administer as needed before emergency response.		
Dosage Form	Spray	**Route of Administration**	Intranasal
OCP Division	DCP2	**OND Division**	DAAAP
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	Srikanth C. Nallani, Ph.D.	Yun Xu, Ph.D.	
Pharmacometrics			
Genomics			
Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	6/21/2016	**74-Day Letter Date**	6/30/2016
Review Due Date	1/15/2017	**PDUFA Goal Date**	2/19/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☑ Yes

☐ No

If yes explain

The NDA is supported by a bioavailability data compared to previously approved IM naloxone product. Hence, OSI inspection of the sole support for the NDA is required and the consult was submitted on 4/26/2016.

Clinical Pharmacology Package

Tabular Listing of All Human	☑ Yes ☐	Clinical Pharmacology	☑ Yes ☐

Studies Bioanalytical and Analytical Methods	No ☑ Yes ☐ No	Summary Labeling	No ☑ Yes ☐ No

Clinical Pharmacology Studies		
Study Type	**Count**	**Comment(s)**
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		
☐ Distribution		
☐ Drug-Drug Interaction		
In Vivo Studies		
Biopharmaceutics		
☐ Absolute Bioavailability		
☑ Relative Bioavailability	2	Study (b) (4)
☐ Bioequivalence		
☐ Food Effect		
☐ Other		
Human Pharmacokinetics		
Healthy Subjects ☑ Single Dose	2	Study (b) (4)
Healthy Subjects ☐ Multiple Dose		
Patients ☐ Single Dose		
Patients ☐ Multiple Dose		
☐ Mass Balance Study		
☐ Other (e.g. dose proportionality)		
Intrinsic Factors		
☐ Race		
☐ Sex		
☐ Geriatrics		
☐ Pediatrics		
☐ Hepatic Impairment		
☐ Renal Impairment		
☐ Genetics		
Extrinsic Factors		
☐ Effects on Primary Drug		
☐ Effects of Primary Drug		
Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		

☐ Patients					
☐ QT					
Pharmacometrics					
☐ Population Pharmacokinetics					
☐ Exposure-Efficacy					
☐ Exposure-Safety					
Total Number of Studies		**In Vitro**		**In Vivo**	2
Total Number of Studies to be Reviewed					2

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☑Yes ☐No ☐N/A	Bioavailability study compares partial AUCs of naloxone with the proposed product with previously approved IM injection.
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☐Yes ☐No ☑N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☑Yes ☐No ☐N/A	See above.
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-	☑Yes ☐No ☐N/A	

BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?		
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo
This is optional, discuss with your TL content and format

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