CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208411Orig1s000

MEDICAL REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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M E M O R A N D U M

From:	Mona Khurana, M.D., Medical Officer Division of Pediatric and Maternal Health Office of Drug Evaluation IV
Through:	Hari Cheryl Sachs, M.D., Team Leader
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To:	Division of Anesthesia, Analgesia, and Addiction Products
Drug:	Naloxone
Therapeutic Category:	Opioid antagonist
Application number:	NDA 208411 (IND 114704)
Subject:	Adequacy of Pediatric Assessment
Applicant:	Adapt Pharma Limited
Proposed Indication:	Emergency treatment of known or suspected opioid overdose as manifested by respiratory and/or central nervous system depression
Formulation:	Single 4 mg dose of naloxone hydrochloride in a 0.1 milliliter intranasal spray delivered via (b) (4) Unit-Dose Nasal Device

Materials Reviewed

- Modules 1.9.6, 2.2 (Introduction) and 2.5 (Clinical Overview) of NDA 208411

- Orange Book (accessed 10/14/15; Rx active ingredient search term: "naloxone")
- Drugs@FDA (accessed 10/14/15; search term: "Narcan")
- UptoDate (accessed 10/15/15; search term: "naloxone")
- PubMed (accessed 10/15/15; search terms: "nasal" AND ""airway" AND "anatomy" OR "development"; "intranasal" AND "drug" AND "delivery" with limits: human, English, pediatric age [birth to 18 years], review; "intranasal drug" AND "neonates")
- Retrieval and review of referenced publications in pediatric assessment (10/16/15)
- DARRTS for IND 114704 Application History (accessed 10/19/15)

Consult Request

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted the Division of Pediatric and Maternal Health (DPMH) to comment on the following:

- The adequacy of the pediatric assessment submitted with new drug application (NDA) 208411
- Recommend which pediatric age ranges, if any, for whom naloxone should be approved based on the pediatric assessment
- Recommend what additional studies could be done to fulfill the Pediatric Research Equity Act (PREA) requirements for those pediatric age ranges in which the pediatric assessment is inadequate

I. Intranasal Drug Delivery

A. Anatomical Considerations

The goal of intranasal (IN) drug delivery is to maximize drug deposition in the portion of the nasal cavity primarily responsible for systemic drug entry while minimizing runoff of the drug into the pharynx and lungs.[1] The main site of systemic entry of IN drugs is a highly vascularized region near the inferior turbinate, known as the respiratory zone, which has a large surface area of 120-150 squared centimeters (cm^2) in adults (see Figure 1).[2] Residual drug that is not absorbed after 30 minutes may be cleared by ciliary cells.[1] The olfactory epithelium is an appealing site for delivery of central nervous system (CNS)-acting drugs because the blood-brain barrier is bypassed allowing direct CNS access.[3] However, the olfactory epithelium does not

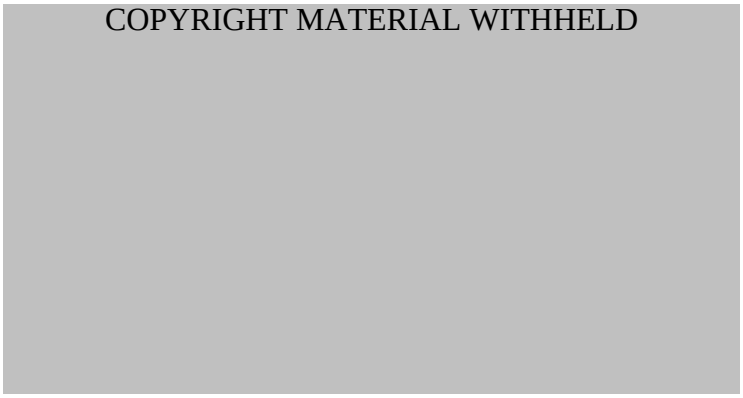
[1] Del Pizzo J and Callahan JM. Intranasal Medications in Pediatric Emergency Medicine. Pediatric Emergency care 30: 496-504, 2014.

[2] Grassin-Delyle, Buenestado A, Naline E, et al. Intranasal Drug Delivery: An Efficient and Non-Invasive Route for Systemic Administration. Focus on Opioids. Pharmacology & Therapeutics 134: 366-379, 2012.

[3] Wolfe TR and Braud DA. Intranasal Medication Delivery for Children: A Brief Review and Update. Pediatrics 126(3): 532-537, 2010.

appear to be significantly involved in systemic absorption of IN drugs since the small surface area (1-5 cm^2) in adults accounts for only 3-5% of the total surface area of the nasal cavity and is difficult to reach via IN delivery.[1] Venous drainage of the nasal cavity occurs directly into the superior vena cava and then into the systemic circulation via the internal jugular veins, thereby avoiding first-pass hepatic metabolism.[1]

Figure 1. Different anatomical regions of the nasal cavity[2]



B. Factors Affecting Intranasal Delivery

Optimizing delivery of IN drugs requires interactions between the formulation, the device, the mode of administration, and patient technique.[4] The highest IN absorption occurs with drugs that are characterized by low molecular weight, high lipophilicity, and no net charge at physiologic pH.[1] Additional factors affecting IN drug absorption include the following:[1]

- Amount of time the drug is in contact with the nasal mucosa. For example, epistaxis or a large amount of nasal secretions will reduce contact of the drug with the mucosal surface and reduce the mucosal surface area available for absorption.
- Deposition of the drug in the wrong part of the nasal cavity may result in not only reduced absorption but also increased runoff into the posterior pharynx with subsequent entry into the lungs.
- Due to the low surface area of the nasal mucosa, IN administration of volumes greater than 200 microliters (µL) may be associated with increased runoff into the pharynx.[2]
- Individual variations in the structure and function of the nasal cavity may prevent the same IN dose from having a uniform effect in all individuals.[5] For example, underlying

[4] Foo MY, Cheng Y, Su w, et al. The Influence of Spray Properties on Intranasal Deposition. Journal of Aerosol Medicine 20(4): 495-508, 2007.

[5] Mygind N and Dahl R. Anatomy, Physiology and Function of the Nasal Cavities in Health and Disease. Advanced Drug Delivery Reviews 29: 3-12, 1998.

co-morbidities that affect ciliary function (i.e. cystic fibrosis) or nasal anatomy (i.e. nasal polyps) may reduce absorption of intranasally administered drugs.

C. Intranasal Drug Products Approved for Pediatric Use

Multiple IN drug products are approved for pediatric use in the United States. None are approved for use down to birth and only one is approved for use within the first year of life (see Table 1). Additionally, the intranasal influenza vaccines, FluMist Quadrivalent and the trivalent FluMist, are biologic drug products approved for use in pediatric patients' only down to age 2 years.[6] Both IN influenza vaccines products were tested in patients less than 2 years of age and were not approved in this age group because of an increased risk of wheezing and hospitalization.

DPMH Comments: Multiple drugs are also currently being used intranasally off-label in pediatric patients for the following reasons:[1]

- *Pediatric sedation as an anxiolytic or amnestic (e.g. midazolam)*
- *Pain associated with orthopedic injuries (e.g. fentanyl citrate)*
- *Status epilepticus or febrile seizure (e.g. midazolam, lorazepam)*
- *Pre-operative sedation (e.g. ketamine, sufentanil)*

The extent of this off-label use and the age ranges of the treated pediatric patients are difficult to determine.

[6] https://www.flumistquadrivalent.com/consumer/; accessed 10/19/15

Table 1. Examples of intranasal drug products approved in the United States with pediatric ages specified in labeling

Drug	Nasal Formulation	Pediatric Indication	Pediatric Age Range
Prescription			
Minirin (desmopressin acetate) N021333	Metered Spray: 100 µL/actuation	Antidiuretic therapy in central diabetes insipidus	3 months to 12 years
Nasonex (mometasone furoate monohydrate) N020762	Metered spray: 100 µL/actuation	Nasal symptoms of allergic rhinitis, nasal congestion associated with seasonal allergic rhinitis, prophylaxis of seasonal allergic rhinitis	2 years and older
Qnasl (beclomethasone) N202813	Aerosol spray: Volume/actuation unspecified	Treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis	4 years and older
Atrovent (ipratropium bromide) N020393	Metered spray: 70 µL/actuation	Symptomatic relief of rhinorrhea associated with allergic and non-allergic perennial rhinitis	6 years and older
Rhinocort (budesonide) N020746	Metered spray: Volume/actuation unspecified	Temporary relief of hay fever or other upper respiratory allergies	6 years and older
Beconase AQ (beclomethasone dipropioante monohydrate) N019389	Metered spray: Volume/actuation unspecified	Relief of seasonal or perennial allergic and nonallergic rhinitis	6 years and older
Patanase (olapatadine HCl) N021861	Metered spray: 100 µL/actuation	Relief of symptoms of seasonal allergic rhinitis	6 years and older
Over-the-Counter			
Nasacort Allergy 24 Hour (triamcinolone acetonide) N020468	Metered spray: Volume/actuation unspecified	Temporary relief of hay fever or other upper respiratory allergies	2 years and older

(Source: created by this reviewer)

DPMH Comments: These approved IN drug products administer volumes per actuation ranging from 75 to 125 µL and appear to be well-tolerated. The applicant is proposing a 100 µL volume per actuation that is within the volumes per actuation of these currently approved drug products.

IN drugs, particularly those given chronically, have the potential for causing local toxicity such as anosmia, epistaxis, and numbness depending on their active ingredient and excipient contents. For example, over-the-counter (OTC) IN drugs containing zinc for treatment of common cold symptoms have been associated with reports of anosmia while oral zinc tablets and lozenges have not been implicated in these reports.[7] Many affected consumers stated that the loss of sense of smell occurred with the first dose of IN zinc products, although some report anosmia after later doses. Some OTC IN antihistamines contain labeling cautioning consumers to stop product use and ask a doctor if they have severe or frequent nosebleeds.[8] Approved prescription IN steroids contain labeling language cautioning about the potential for local nasal effects such as epistaxis and nasal ulceration.[9]

No local nasal effects were observed in the pilot pharmacokinetic (PK) study conducted by the applicant, but 12 adult subjects in the pivotal PK study experienced at least one adverse event (AE) thought to be at least possibly related to naloxone. The most frequent naloxone-related AEs were local effects including nasal erythema (n=5) and nasal edema (n=4). The occurrence of these AEs in pediatric patients may be of greater concern than in adults if the proposed product were to be used chronically rather than as intended for single use in an emergency setting.

II. Clinical Pharmacology

A. Naloxone Hydrochloride

Naloxone is essentially a pure opioid antagonist that lacks intrinsic agonist properties.[10] Naloxone has not been shown to produce tolerance or cause physical or psychological dependence but will produce acute withdrawal symptoms in adults who are physically dependent

[7] http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm166931.htm; accessed 10/29/15

[8] http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020468Orig1s040lbl.pdf; accessed at Drugs@FDA 10/29/15

[9] http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022004s013lbl.pdf; accessed at Drugs@FDA 10/29/15

[10] http://www.accessdata.fda.gov/drugsatfda_docs/label/2002/016636s052s054lbl.pdf; accessed at Drugs@FDA 10/21/15

on opioids,[13] including neonates born to opioid-dependent mothers.[11] Withdrawal symptoms may appear within minutes of naloxone administration and persist for two hours.[13] The intravenous (IV) onset of action is generally apparent within two minutes but is slightly less rapid when given intramuscularly (IM) or subcutaneously (SC).[13] The duration of action depends on both the dose and route of naloxone administration with the IM route producing a more prolonged effect than the IV route. Repeated naloxone doses may be needed to reverse the effects of some opioids which have longer duration of action than naloxone.

B. Composition of Proposed Intranasal Formulation

Component	Grade	Concentration 40 mg/mL	
		Quantity per mL	Quantity per unit dose (100 µL)
Naloxone HCl dihydrate (corresponding to naloxone HCl)	USP/Ph. Eur	44.0 mg (40.0 mg)	4.4 mg (4.0 mg)
Benzalkonium chloride (b) (4) (b) (4)	Ph. Eur/USP/NF	(b) (4)	
Disodium edetate	USP		
Sodium chloride	MULTI-COMPENDIAL; USP, BP, Ph. Eur, JP		
Hydrochloric acid	Ph. Eur/USP		
(b) (4)	USP/Ph. Eur		

USP = United States Pharmacopeia
q.s. ad = a sufficient quantity to make

(Source: Table 2.2-1 page 11 of Module 2.2 Introduction to Summaries for NDA 208411)

The drug product solution will be filled into 0.1 mL (100 µL) Type I glass vials which are closed with (b) (4) plungers. The vials are mounted into an (b) (4) nasal spray device designed to deliver 100 µL with each actuation. The device is a non-pressurized dispenser delivering a single 100 µL spray containing a metered dose (4 milligrams [mg]) of the active ingredient.

DPMH Comments: The excipients at the proposed concentrations do not appear to raise safety concerns from DPMH's perspective, but we defer to Chemistry, Manufacturing, and Control (CMC) colleagues in DAAAP. Disodium edetate is the disodium salt form of edetate, which is a

[11] American Academy of Pediatrics Committee on Drugs. Naloxone Use in Newborns. Pediatrics 65: 667-669, 1980.

(b) (4)[12] *While the amount of edetate in other development programs has raised safety concerns* (b) (4) *the relatively lower concentration present in the proposed IN formulation does not appear to raise similar safety concerns. A single actuation of the proposed product will deliver a 100 µL volume containing* (b) (4) *of edetate disodium. Approved drugs contain edetate in amounts ranging from 0.05 mg to 2.5 mg per dose.*

III. Regulatory History of this Application

The program was developed under investigational new drug (IND) 114704, and the proposed IN naloxone formulation received Fast Track designation on January 26, 2015.

The applicant submitted a 505(b)(2) NDA for IN naloxone for emergency treatment of known or suspected opioid overdose as manifested by respiratory and/or central nervous system depression. The proposed drug is intended for use in community settings. This NDA relies on previous findings of safety and efficacy submitted in NDA 016636 for the reference listed drug (RLD), Narcan® (naloxone hydrochloride) for injection, and on relevant clinical data published since Narcan's 1971 approval. The RLD is approved for IV, IM, or SC use in pediatric patients of all ages, including neonates, to reverse the effects of opiates.[13] Importantly, an auto-injector containing naloxone (Evzio Auto-Injector, NDA 205787) was approved in adults and pediatric patients of all ages on April 3, 2014 for IM or SC use for emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression, and for immediate administration as emergency therapy in settings where opioids may be present.[14] The Evzio labeling contains no limitations of use but does caution that IM or SC absorption of naloxone in pediatric patients may be delayed or erratic (Section 8.4 Pediatric Use).

NDA 208411 is supported by two PK bridging studies conducted to compare the bioavailability of the proposed IN formulation to IM naloxone, the generic form of the RLD. The bridging studies consist of a pilot PK study (Naloxone-Ph1a-001) and a pivotal PK study (Naloxone-Ph1a-002) which used the to-be-marketed IN formulation. The applicant has not conducted any additional non-clinical or clinical studies. DAAAP had previously conveyed to the applicant that additional clinical efficacy studies would not be required if the bioavailability of the proposed IN

[12] http://pubchem.ncbi.nlm.nih.gov/compound/8759; accessed 10/21/15

[13] http://www.accessdata.fda.gov/drugsatfda_docs/label/2002/016636s052s054lbl.pdf; accessed at Drugs@FDA 10/21/15

[14] http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/205787Orig1s000ltr.pdf; accessed at Drugs@FDA 10/29/15

formulation is the same or greater than a parenteral naloxone comparator at an approved labeled dose (0.4 mg to 2 mg).[15] DAAAP also conveyed that additional safety data may be needed depending on how much the PK profile of the proposed IN formulation differs from that of parenteral naloxone.

IV. Pediatric Development Program

The initial pediatric study plan (iPSP) was presented to the Pediatric Review Committee (PeRC) on May 6, 2015. At the meeting, DAAAP clarified that the applicant has proposed not to conduct any clinical studies and plans to rely upon demonstration of relative bioavailability. DAAAP concurred with the applicant that non-clinical juvenile animal studies would not be warranted based on the indication and significant safety margin for acute naloxone use. The PeRC agreed that a 2 mg IN dose could be acceptable if DAAAP is satisfied with the data provided in the NDA submission. However, PeRC was not convinced there was sufficient data to show that the proposed dosage volume and method of administration via a nasal spray device would consistently deliver a 2 mg dose to younger pediatric patients and opined that, without these data, pediatric studies may need to be deferred. PeRC stated the applicant must provide justification that a 2 mg dose would be safe for all pediatric patients and that, if adequate safety data are provided, then no clinical safety studies would be needed. PeRC also recommended the following:

- The applicant should provide information about whether the proposed device can be used to administer the drug to all pediatric patients including neonates.
- The applicant must demonstrate that the volume administered via the proposed device will have the same absorption characteristics in pediatric patients as in adults.

The PeRC's recommendations were conveyed to the applicant on May 13, 2015. FDA subsequently issued an Agreed iPSP Agreement to the applicant on June 22, 2015.

V. Considerations for Pediatric Approval

A. PK and Dosing Considerations

The applicant conducted two bridging PK studies in adults that consisted of a pilot study (Naloxone-Ph1a-001) and a pivotal study (Naloxone-Ph1a-002) which used the to-be-marketed IN formulation. Pilot study Naloxone-Ph1a-001 was designed as an inpatient three-treatment crossover study to compare the PK parameters of 2 mg and 4 mg IN doses to the approved 0.4

[15] June 18, 2012 Meeting Minutes for Pre-Investigational New Drug (IND) Type B Meeting (DARRTS Reference ID 3146923)

mg IM dose in order to find an appropriate IN dose that could achieve systemic exposure comparable to an approved parenteral dose. Per the applicant, both the 2 mg and 4 mg IN doses produced naloxone plasma concentrations and exposures that were significantly higher than that produced by the 0.4 mg IM dose in the same subjects. The applicant also noted that the time from obtaining the IN device to administration of the first IN dose was less than one-third the time needed to prepare the IM injection. The pivotal study Naloxone-Ph1a-002 was designed as an inpatient, open-label, randomized, 5-period, 5-treatment, 5-sequence, crossover study in 28 healthy adult volunteers to determine the PK of four IN doses (2 mg, 4 mg [2 nostrils], 4 mg [1 nostril], 8 mg [2 nostrils]) compared to the approved 0.4 mg IM dose; the study's goal was to determine an appropriate IN dose that could achieve systemic exposure comparable to a 2 mg IM dose. Results suggested that, based on dose-normalized values, the relative bioavailability of the intranasally administered naloxone compared to the IM naloxone ranged from 43.9% to 53.6%.

Based on these PK data, the applicant is proposing a non-weight based dose of 4 mg IN naloxone for all age groups from birth to adults. The applicant asserts this dose will provide immediate rescue with onset that would be just as rapid as with an IM dose and will achieve plasma concentrations and exposures that approximates a 2 mg IM dose. The applicant contends that 2 mg is the most often used and the most effective out-of-hospital naloxone dose given IV or IM. The applicant states the PK data suggest a single 4 mg IN dose would provide effective levels for at least 120-180 minutes, allowing emergency medical services up to 120 minutes to arrive after a caregiver has administered the IN dose. The applicant proposes a second 4 mg IN dose could be given if the patient remains unresponsive.

DPMH Comments:

A standard, non-weight based 4 mg IN dose for low birth weight neonates will potentially result in the delivery of a naloxone dose per body weight that is nearly 100-fold higher than the pediatric dose currently recommended in the RLD labeling and ten-fold higher than the recommendations by the American Academy of Pediatrics' (AAP) Committee on Drugs (COD). Based on the assumption that 50% of the proposed 4 mg IN dose is absorbed, then neonates at the second percentile for weight (2 kilogram [kg]) who receive a 4 mg IN naloxone dose may receive up to 1 mg/kg of naloxone.[16] *The RLD labeling recommends an initial pediatric dose of 0.01 mg/kg body weight IV. The AAP COD recommends a parenteral naloxone dose of 0.1*

[16] http://www.cdc.gov/growthcharts/who_charts.htm; accessed 10/15/15

mg/kg for pediatric patients from birth to age 5 years or 20 kg of body weight and a dose of 2 mg for pediatric patients older than age 5 years or weighing more than 20 kg.[17]

The applicant conducted a review of the published literature since the 1971 approval of the RLD to identify any new clinical data relevant to this NDA. The applicant retrieved seven publications describing PK studies of naloxone which the applicant says did not reveal any pharmacological issues that impact labeling.

DPMH Comments:

Two retrieved publications were PK studies examining IV and IM naloxone delivery in newborns[18] *and IV naloxone delivery in very low birth weight (VLBW) infants*[19]*. The authors who conducted the PK study in newborns concluded the IM route (200 µg) resulted in higher plasma concentrations and longer time to reach peak plasma levels than either of two IV doses (35 µg and 70 µg) administered to term newborns. Notably, the plasma half-life of naloxone in the newborns was two to three times longer than that reported for adults. The authors attributed the longer half-life to decreased ability of the newborns to eliminate naloxone via glucuronide conjugation. Results from the PK study in 10 VLBW infants suggested the mean (range) serum half-life of IV naloxone was 70.8 (26 to 122) minutes which the authors stated is comparable to IV naloxone's reported half-life of 64 ± 12 minutes in adults.*[20]

A third retrieved publication describing the PK of naloxone administered IV and orally on separate occasions to the same adult male subject showed that oral naloxone has a significant first-pass effect and is 1/50th as potent as IV administered naloxone.[21] *Oral naloxone's poor bioavailability due to the first-pass effect may have clinical efficacy implications for the proposed IN formulation if the delivered dose is inadvertently swallowed.*

[17] Committee on Drugs Naloxone Dosage and Route of Administration for Infants and Children: Addendum to Emergency Drug Doses for Infants and Children. Pediatrics 86(3): 484-485, 1990.

[18] Moreland TA, Brice JE, Walker CH, et al. Naloxone Pharmacokinetics in the Newborn. British Journal of Clinical Pharmacology 9(6): 609-612, 1980.

[19] Stile IL, Fort M, Wurzburger RJ, et al. The Pharmacokinetics of Naloxone in the Premature Newborn. Developmental Pharmacology and Therapeutics 10(6): 454-459, 1987.

[20] Ngai SH, Berkowitz BA, Yang JC, et al. Pharmacokinetics of Naloxone in Rats and in Man: Basis for its Potency and Short Duration of Action. Anesthesiology 44(5): 398-401, 1976.

[21] Fishman J, Roffwarg H, Hellman L. Disposition of Naloxone-7,8-^{3}H in Normal and Narcotic-Dependent Men. The Journal of Pharmacology and Experimental Therapeutics 187(3): 575-580.

B. Efficacy Considerations

The applicant relied upon adult naloxone use, published case studies, and RLD labeling for pediatrics to support the safety, efficacy, and dose of IN naloxone for use in pediatric patients. According to the applicant,[22] naloxone's 1971 approval for use in pediatric patients was supported by evidence from adequate and well-controlled studies in adults with additional data from 15 clinical studies (controlled and uncontrolled) in which neonates and older pediatric patients received parenteral naloxone in doses ranging from 0.005 mg/kg to 0.01 mg/kg.

DPMH Comments: The applicant cited six additional published efficacy studies to support their conclusions that 2 mg is the most effective and most often used out-of-hospital dose given IV or IM and that the IN route will achieve the same beneficial effects as IM or IV naloxone. None of these studies enrolled young pediatric patients. Four studies were conducted in patients' age 13 years or older. [23,24,25,26] *Subjects' ages were not specified in one study.* [27] *Although a sixth study did enroll pediatric patients as young as age 3 years, the age range of the study population was very broad (3 to 96 years) and the total number of enrolled pediatric patients was not specified.*[28]

C. Safety Considerations

1. Safety Considerations Related to Non-Weight Based IN Dose of 4 mg

[22] Page 24 in Section 2.5 Clinical Overview NDA 208411

[23] Kerr D, Kelly A, Dietze P, et al. Randomized Controlled Trial Comparing the Effectiveness and Safety of Intranasal and Intramuscular Naloxone for the Treatment of Suspected Heroin Overdose. Addiction 104: 2067-2074, 2009.

[24] Merlin MA, Saybolt M, Kapitanyan R, et al. Intranasal Naloxone Delivery is an Alternative to Intravenous Naloxone for Opioid Overdoses. The American Journal of Emergency Medicine 28: 296-303, 2010.

[25] Kelly A, Kerr D, Dietze P, et al. Randomised Trial of Intranasal Versus Intramuscular Naloxone in Prehospital Treatment for Suspected Opioid Overdose. Medical Journal of Australia 182(1): 24-27, 2005.

[26] Barton ED, Colwell C, Wolfe T, et al. Efficacy of Intranasal Naloxone as a Needleless Alternative for Treatment of Opioid Overdose in the Prehospital Setting. The Journal of Emergency Medicine 29(3): 265-271, 2005.

[27] Barton ED, Ramos J, Colwell C, et al. Intranasal Administration of Naloxone by Paramedics. Prehospital Emergency Care 6(1): 54-58, 2002.

[28] Robertson TM, Hendey GW, Stroh G, et al. Intranasal Naloxone is a Viable Alternative to Intravenous Naloxone for Prehospital Narcotic Overdose. Prehospital Emergency Care 13(4): 512-515, 2009.

The applicant states the safety of naloxone is well-established in pediatric patients and concluded there was no significant new information regarding the safety of naloxone following their review of the published clinical literature.

DPMH Comments: This reviewer's search of the PubMed database retrieved several published case reports, also referenced by the applicant, that do describe young pediatric patients in the first five years of life who received IV naloxone to reverse opioid effects without adverse events. However, only two patients received a single dose, the remaining patients received doses over time periods exceeding one hour (see Table 2).

Table 2. Published case reports of pediatric patients in first five years of life who received the recommended IV naloxone dose or higher without adverse events.

Publication	Patient Age	Total Naloxone Dose	Total Naloxone Dose Per Body Weight	Time Period
Simons 1973[29]	6 months	2.48 mg	0.3 mg/kg	Over 40 hours
Rumack 1974[30]	2.5 years	20 mg	Weight unreported	Single dose
Sesso 1975[31]	7 months	1.04 mg	0.1 mg/kg	Over 5.5 hours
Gober 1979[32]	4 weeks	2.73 mg	0.8 mg/kg	Over 27 hours
Moore 1980[33]	2.5 years	2.1 mg	Weight unreported	Over 1.5 hours
Lewis 1984[34]	31 months	4.1 mg	0.3 mg/kg	Over 9 hours
Glatstein 2009[35]	11 months	Total dose unreported	0.1 mg/kg	Single dose

(Source: created by this reviewer)

[29] Simons P. The Treatment of Methadone Poisoning with Naloxone (Narcan). The Journal of Pediatrics 83(5): 846-847, 1973.

[30] Rumack BH and Temple AR. Lomotil Poisoning. Pediatrics 53(4): 495-500, 1974.

[31] Sesso AM and Rodzvilla JP. Naloxone Therapy in a Seven-Month-Old with Methadone Poisoning. Clinical Pediatrics 14(4): 388-389, 1975.

[32] Gober AE, Kearns GL, Yokel RA, et al. Repeated Naloxone Administration for Morphine Overdose in a 1-Month-Old Infant. Pediatrics 63(4): 606-608, 1979.

[33] Moore RA and Rumack BH. Naloxone Underdosage after Narcotic Poisoning. American Journal of Diseases in Children 134:156-158, 1980.

[34] Lewis JM, Klein-Schwartz W, Benson BE, et al. Continuous Naloxone Infusion in Pediatric Narcotic Overdose. American Journal of Diseases in Children 138: 944-946, 1984.

[35] Glatstein M, Finkelstein Y, Scolnik D. Accidental Methadone Ingestion in an Infant. Pediatric Emergency Care 25: 109-111, 2009.

Notably, two published case reports in neonates have described serious adverse events with parenteral naloxone use. One case report describes a female newborn born to an opioid-dependent mother who developed a generalized seizure two minutes after receiving 0.2 mg IM naloxone for no spontaneous respiratory effort by four minutes of life.[36] Her seizure failed to respond to three anticonvulsants but, after 30 minutes, resolved with a morphine bolus which was then continued as an infusion. The other case report describes a 27 week female newborn with a birth weight of 485 grams who developed cardiac arrest immediately after receiving 0.1 mg/kg of IV naloxone for suspected morphine overdose.[37] She responded to resuscitative efforts, but life support was withdrawn at age 4 weeks due to severe bronchopulmonary dysplasia and continued need for maximum ventilatory support.

Published case reports describing serious adverse events following naloxone use in older pediatric patients appear to be limited to four cases of acute pulmonary edema following parenteral naloxone administration to reverse the effects of perioperative opioid analgesia in otherwise healthy adolescents with orthopedic injuries.[38, 39,40] These patients received parenteral naloxone at total doses of 0.1 mg,[38] 0.5 mg,[38], 0.08 mg,[39] and 0.2 mg[40] before the onset of symptoms consistent with acute pulmonary edema.

The applicant cited a systematic review of nine randomized controlled trials comparing naloxone to placebo or no drug to newborns with transplacental narcotic exposure to support their claim that the safety of naloxone in the pediatric population is well-established.[41] The cited review focused only on the neonatal age group and not on older pediatric patients and did not address the safety and efficacy concerns with neonatal use of the proposed drug for the following reasons:

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[36] Gibbs J, Newson T, Williams J, et al. Naloxone Hazard in Infant of Opioid Abuser. The Lancet 159-160, 1989.

[37] Deshpande G and Gill A. Cardiac Arrest Following Naloxone in an Extremely Preterm Neonate. European Journal of Pediatrics 168: 115-117, 2009.

[38] Prough DS, Roy R, Bumgarner J, et al. Acute Pulmonary Edema in Healthy Teenagers Following Conservative Doses of Intravenous Naloxone. Anesthesiology 60: 485-486, 1984.

[39] Johnson C, Mayer P, Grosz D. Pulmonary Edema Following Naloxone Administration in a Healthy Orthopedic Patient. Journal of Clinical Anesthesiology 7: 356-357, 1995.

[40] Harrington LW. Acute Pulmonary Edema Following Use of Naloxone: A Case Study. Critical Care Nurse 8(8): 69-73, 1988.

[41] McGuire W, Fowlie P. Naloxone for Narcotic Exposed Newborn Infants: Systematic Review. Archives of Disease in Childhood 88(4): F308-F311, 2003.

- *None of the trials collected data on clinically important outcomes such as the need for assisted ventilation or admission to a neonatal intensive care unit (NICU).*

- *The trials broadly compared naloxone use to placebo or no drug in newborns with transplacental opioid exposure, regardless of the presence of respiratory depression. None of the trials restricted entry to newborns with respiratory depression following narcotic exposure, the sub-population for which the AAP COD recommends parenteral naloxone. The trials evaluated naloxone doses ranging from 0.01 to 0.04 mg/kg except for one trial which evaluated a total naloxone dose of 0.2 mg/kg. All of these weight-based doses are lower than that which would be delivered with the proposed 4 mg IN dose. For instance, newborns weighing 2.5 kg (50th percentile weight for age)[16] would receive 1.6 mg/kg of naloxone with administration of the proposed 4 mg IN dose.*

- *None of the trials examined IN naloxone delivery. Four trials evaluated the IM route, and five trials evaluated the umbilical vein route.*

Finally, to further support the safety of naloxone in pediatric patients, the applicant cited a randomized, double-blind, placebo controlled trial in 193 newborns with low one minute Apgar scores due to intrauterine asphyxia who received 0.4 mg/kg IM naloxone or normal saline.[42] Naloxone administration did not have a significant effect on spontaneous respiratory frequency or heart rate up to 30 minutes after injection or at 24 hours of age. Increased muscle tone of the upper and lower extremities was associated with naloxone use, which the authors opined was not desirable in the context of inadequate oxygen delivery to vital organs. The authors concluded that naloxone has no readily apparent benefit in the resuscitation of the asphyxiated newborn.

DPMH Comment: This trial was conducted exclusively in asphyxiated newborns, and newborns whose mothers had been given an opioid analgesic within four hours of delivery were excluded. Therefore, the safety findings are not necessarily generalizable to the intended population.

An additional publication retrieved by this reviewer described a retrospective chart review designed to evaluate the cardiorespiratory changes and complications following naloxone treatment in 195 pediatric patients, ages' birth to 18 years, with known or suspected opioid-induced CNS and/or respiratory depression.[43] One group consisted of patients who had undergone fentanyl-supplemented general anesthesia for different surgical procedures (n=116);

[42] Chernick V, Manfreda J, De Booy V, et al. Clinical Trial of Naloxone in Birth Asphyxia. Fetal and Neonatal Medicine Journal of Pediatrics 113: 519-525, 1988.

[43] Hasan RA, Benko AS, Nolan BM, et al. Cardiorespiratory Effects of Naloxone in Children. Annals of Pharmacotherapy 37: 1587-1592, 2003.

these patients were given naloxone by an anesthesiologist post-operatively. Another group consisted of patients who were given naloxone in the emergency room or pediatric intensive care unit (n=79). None of the patients in this study developed arrhythmias, hypotension, seizures, emesis, or cardiac arrest after naloxone administration at total doses ranging from 0.01 to 7 mg (0.001 to 0.5 mg/kg body weight) with a median dose of 0.1 mg. One 17 year old male developed progressive hypoxia and bradycardia requiring tracheal intubation within five minutes of 2 mg IV naloxone administration by emergency medical services; acute pulmonary edema was subsequently confirmed radiographically.

2. Safety Considerations Related to IN Delivery

In addition to local safety concerns, another key safety consideration is the possibility of treatment failure from inadequate IN delivery of the proposed dose. The efficacy of the proposed IN formulation is based on the premise that the full 4 mg intended dose is able to be effectively delivered and absorbed via the IN route in pediatric patients of all ages.

Effective IN delivery of the proposed drug may be compromised if the actuator tip is too large for insertion into the nares of neonates and other young pediatric patients. While the applicant did conduct two human factors validation studies to determine if subjects could correctly insert the actuator tip into the nostril and press the plunger to release the naloxone dose, neither study included pediatric patients under age 12 years. Inadvertent swallowing of the drug rather than inhalation due to improper IN delivery is likely to lead to treatment failure given the poor oral bioavailability of naloxone.

QNASL and Sprix are two specific examples of IN drugs approved in adults and/or older pediatric patients for which sponsors encountered safety issues when studying IN delivery in younger pediatric patients. QNASL (beclomethasone nasal aerosol) is approved for the treatment of allergic rhinitis in patients' ages 6 years and older. The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) noted that the (b) (4) nasal actuator appeared too large to fit in the nostrils of younger pediatric patients and might pose concerns regarding accurate dose delivery and, more importantly, issues of local and ocular safety in young children.[44] Consequently, the sponsor evaluated the suitability of the nasal actuator in pediatric patients by conducting a nasal actuator "fit" study and found a substantial number of pediatric patients' age 2 years to 3 years in whom the actuator tip would not fit in the nose adequately. The sponsor attempted to develop a nasal actuator nose tip with a smaller outside diameter of approximately (b) (4). However, the nosepiece resulted in low delivery and

[44] 11/13/12 Medical Officer Review of Sponsor's Request for Partial Waiver of Pediatric Studies for NDA 202813 (Anthony Durmowicz; DARRTS Reference ID 3216225)

unacceptable dose uniformity (DDU) variability and did not pass FDA Nasal Guidance DDU requirements due to excessive drug retention inside the nosepiece (b) (4) . Based on this information, DPARP granted the sponsor's request to extend the waiver for pediatric studies to include patients' age 2 years to 3 years since a smaller nasal tip was not possible for this product given the lack of dose delivered uniformity.

Since the actuator diameter of (b) (4) for the proposed IN naloxone product exceeds that of QNASL, the actuator tip may not fit pediatric patients' age 2 years to 3 years (see actuator tip diameter in Table 3, Module 3.2 P). (b) (4) .

Table 3. Release specifications for the proposed unit dose nasal device

Test	Requirements
Container holder	
Visual control	Equivalent to reference – Pass
General appearance	Equivalent to reference – Pass
Length	(b) (4)
Full diameter	
Inside diameter	
Verification of material	
Actuator	
Visual control	Equivalent to reference – Pass
General appearance	Equivalent to reference – Pass
Length	(b) (4)
Width diameter	
Depth diameter	
Tip diameter	
Ledge to tip	
Verification of material	

(Source: Table 10 in Section 4.1 of Module 3.2 P Unit Dose Nasal Device for NDA 208411)

Sprix (ketorolac) is a prescription IN drug product which was approved for short-term management of moderate to moderately severe pain in adults requiring opioid analgesia in adults. At the time of approval, studies evaluating the PK and safety of this drug in all pediatric age groups were planned and subsequently initiated.[45] (b) (4)

[45] http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/022382s000ltr.pdf; accessed at Drugs@FDA 11/1/15

Pediatric Review Committee subsequently agreed to a (b) (4) waiver for pediatric studies in patients (b) (4) for safety reasons.[46]

Both the size and shape of the nasal airways vary significantly with age, and the most dramatic growth in the upper respiratory tract appears to occur in the first five years of life. There is some published evidence that these differences in nasal morphology are also associated with large variability in the pattern of deposition of intranasally administered particles not only among pediatric patients under age 5 years but also when compared to adults. The applicant referenced a 2012 study evaluating age-related effects on nasal airflow and particle deposition to support their conclusion that intranasal drug absorption is similar between adults and pediatric patients even though pediatric patients have smaller nasal volumes.[47] However, a more recent publication from the same authors seems to refute these findings.[48] Both studies used a computer method to develop nasal-laryngeal airway models based on computed tomography and magnetic resonance images. The authors in the more recent study noted that the four pediatric patients they studied had smaller nostrils, shorter turbinate regions, and narrower nasopharynx than the single adult studied. The authors found large variability in the pattern of deposition of intranasally-administered particles among the pediatric patients and adult. The authors concluded that, from the drug delivery perspective, the differences in nasal morphology, nasal cavity dimensions, and pattern of intranasal particle deposition they noted imply that adult deposition results might not guarantee an accurate dose for pediatric patients.

If DAAAP is satisfied that the actuator tip may be properly positioned (i.e., does not need to be inserted fully into the nostril) and can deliver a minimally effective dose in pediatric patients under age 5 years, then PK data in this pediatric age group should be obtained as a post-marketing commitment to confirm the amount of the intended IN dose that is actually delivered. Confirming the extent to which the IN dose is systemically absorbed in the youngest pediatric patients is important since limited published evidence suggests that nasal morphology and intranasal particle deposition in pediatric patients in the first 5 years of life may be different from older pediatric patients and adults. Understanding the amount that is intranasally absorbed in neonates is particularly important for the following reasons:

[46] July 29, 2015 PeRC Meeting Minutes for NDA 022382 (DARRTS Reference ID 3803939)

[47] Xi J, Berlinski A, Zhou Y, et al. Breathing Resistance and Ultrafine Particle Deposition in Nasal-Laryngeal Airways of a Newborn, and Infant, a Child, and an Adult. Annals of Biomedical Engineering 40(12): 2579-2595, 2012.

[48] Xi J, Si X, Zhou Y, et al. Growth of Nasal and Laryngeal Airways in Children. Implications in Breathing and Inhaled Aerosol Dynamics. Respiratory Care 59(2): 263-273, 2014.

- Administration of the proposed non-weight based 4 mg IN dose to low birth weight neonates will potentially result in the delivery of a naloxone dose per body weight that is nearly 100-fold higher than the pediatric dose currently recommended in the RLD labeling[10] and nearly 10-fold higher than that recommended by the AAP COD[17] if the full dose is systemically absorbed.

- The plasma half-life of naloxone in newborns has been shown to be two to three times longer than that reported for adults.[18] The longer half-life is possibly attributed to decreased ability of the newborns to eliminate naloxone via glucuronide conjugation.

- Systemic absorption of a high naloxone dose with a prolonged half-life to neonates born to opioid-dependent mothers may precipitate acute withdrawal symptoms which, if not recognized, can be life-threatening. For this reason, the most recent American Heart Association and AAP Neonatal Resuscitation Guidelines advise that naloxone should not be administered to infants of opioid-dependent mothers as part of initial resuscitative efforts.[49] The RLD labeling likewise also recommends cautious administration to newborns of mothers who are known or suspected to be physically dependent on opioids because naloxone can cause an abrupt and complete reversal of opioid effects and may precipitate an acute withdrawal syndrome. Acute withdrawal in neonates may include convulsions, excessive crying, and hyperactive reflexes.

3. Off-Label Use

In supervised medical settings such as delivery rooms, emergency rooms, or intensive care units, preference should be given to administering weight-based dosing using available parenteral naloxone formulations rather IN administration of the proposed drug in patients under age 5 years. This approach is consistent with AAP COD statement which has expressed concerns about the reliability of naloxone administration in hospital settings via routes other than IV and intratracheal.[17] While aligned with the American Heart Association and AAP neonatal resuscitation guidelines about the recommended naloxone dose in pediatric patients, the AAP COD recommends consistent use of the IV and intratracheal routes only and has expressed concern that absorption of IM or SC administered naloxone may be erratic, delayed, or both in patients who are hypotensive, hypoperfused, and/or peripherally vasoconstricted.[17] Accordingly,

[49] Kattwinkel J, Perlman JM, Aziz K, et al. Special Report – Neonatal Resuscitation: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 122: S909-S919, 2010.

Narcan labeling contains language about the AAP's position on the recommended routes of naloxone administration.

VI. Conclusions

Given the intended use for treatment of a life-threatening condition, the relative ease of use of the proposed IN formulation compared to the IM formulation, and the established wide safety margin for naloxone, administration of a non-weight based IN naloxone dose of 4 mg seems reasonable for pediatric patients from birth to under age 17 years for emergency treatment of known or suspected opioid overdose until emergency medical services can be provided by trained professionals. Approval in younger pediatric patients should be contingent upon DAAAP being satisfied that IN delivery with the proposed unit dose device will result in absorption of a minimally effective dose in pediatric patients of all ages. Since young infants are obligate nose breathers with the potential for respiratory distress with IN instrumentation, DPMH encourages DAAAP to consider issuing a post-marketing requirement (PMR) to capture any serious AEs of airway obstruction, respiratory distress, or respiratory arrest with product use in pediatric patients under age 1 year. Since some published evidence suggests that nasal morphology and intranasal particle deposition in pediatric patients in the first 5 years of life may be different from older pediatric patients and adults, DPMH also encourages DAAAP to consider issuing a post-marketing commitment (PMC) to evaluate the PK of this novel delivery system to confirm how much of the IN dose is actually absorbed in pediatric patients under age 5 years.

The most likely scenario of pediatric naloxone use for the proposed indication would be to reverse opioid effects in young pediatric patients who inadvertently ingest large amounts of opioid medications as an isolated instance of accidental overdose. These pediatric patients are unlikely to be opioid-dependent and should not develop withdrawal symptoms or seizures with naloxone use. Compared to older, ambulatory pediatric patients who may more readily find opioids in household settings, neonates are unlikely to accidentally ingest opioids in the community setting.

In supervised medical settings such as delivery rooms, emergency rooms, or intensive care units, preference should be given to administering weight-based dosing using available parenteral naloxone formulations rather IN administration in pediatric patients under age 5 years. This approach is consistent with AAP COD statement which has expressed concerns about the reliability of naloxone administration in hospital settings via routes other than IV and intratracheal.

VII. Recommendations

1. If DAAAP is satisfied that IN delivery with the proposed unit dose device will result in absorption of a minimally effective dose in pediatric patients of all ages, DPMH

recommends approval for the proposed indication for pediatric patients from birth to under age 17 years for emergency treatment of known or suspected opioid overdose until emergency medical services can be provided by trained professionals.

2. We recommend issuing a safety PMR to capture any treatment failures or serious AEs of airway obstruction, respiratory distress, or respiratory arrest with product use, particularly in pediatric patients under age 1 year. In addition, this review should capture local AEs involving the nasal cavity such as epistaxis, anosmia, or numbness in older patients since younger patients may not be able to recognize or articulate the AE occurrence.

3. Consider issuing a PMC to evaluate the PK profile of this novel delivery system to confirm how much of the IN dose is actually absorbed in pediatric patients under age 5 years. This information will help inform use for not only the proposed product but also for future IN products. If this product is approved in all pediatric age groups, then "opportunistic" PK data could be collected from pediatric patients who receive this product as part of standard medical care. Alternatively, potential sub-populations in whom PK may be ethically studied include patients requiring procedural sedation in whom rapid opioid reversal would not pose a safety concern (e.g., sedation for an imaging study).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MONA K KHURANA
11/08/2015

HARI C SACHS
11/09/2015
I agree with these recommendations. Labeling is in the process of being negotiated, DPMH input will be reflected in final labeling.

LINDA L LEWIS
11/10/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 208411 **Applicant:** Adapt Pharma, Inc. **Stamp Date:** July 20, 2015

Drug Name: Naloxone HCL **NDA/BLA Type:** 3 (new dosage form)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			The annotated labeling that the Applicant submitted with the application contained reference to a product (i.e., Evzio) that the Applicant did not list as a reference product for this 505(b)(2) application. The Division held a teleconference with the Applicant on 8/21/15 to discuss this issue, and the Applicant clarified that their NDA was not relying on the Evzio application. The Applicant subsequently submitted annotated draft labeling that did not contain references to Evzio.
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			The Applicant did not submit an ISS with the

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					application. This issue was discussed with the Applicant at the 8/21/15 teleconference. The Applicant subsequently submitted the ISS, which refers back to the summary of clinical safety.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			The Applicant did not submit an ISE with the application. This issue was discussed with the Applicant at the 8/21/15 teleconference. The Applicant subsequently submitted the ISE, which refers back to the summary of clinical efficacy.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	X			505(b)(2)
505(b)(2) Applications					
13.	If appropriate, what is the relied upon listed drug(s)?			X	The Applicant is relying upon literature to support the use of their product in all pediatric age ranges. The Applicant is also cross-referencing NDA 016636 (Narcan), which they own
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?	X			
15.	Describe the scientific bridge (e.g., BA/BE studies)				Relative BA study
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?			X	No efficacy studies were required

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1 Indication: Pivotal Study #2 Indication:				
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			The Applicant collected safety data in their relative BA studies, including the pivotal relative BA study, to support this application. The data include information collected from nasal examinations.
26.	Has the applicant submitted the coding dictionary[2] used for	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	mapping investigator verbatim terms to preferred terms?				
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			There were no deaths or serious adverse events. There was one discontinuation due to an adverse event. However, the Applicant did not submit a narrative for this subject with the application. This issue was discussed with the Applicant at the 8/21/15 teleconference, and the Applicant subsequently submitted a narrative for this subject.
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Pediatric assessment
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	

as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			There were no deaths or serious adverse events. There was one discontinuation due to an adverse event. However, the Applicant did not submit a case report form for this subject with the application. This issue was discussed with the Applicant at the 8/21/15 teleconference, and the Applicant subsequently submitted a case report form for this subject.
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___YES_____

Clinical Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOSHUA M LLOYD
09/03/2015