CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208411Orig1s000

MEDICAL REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of Drug Evaluation IV
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M E M O R A N D U M

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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

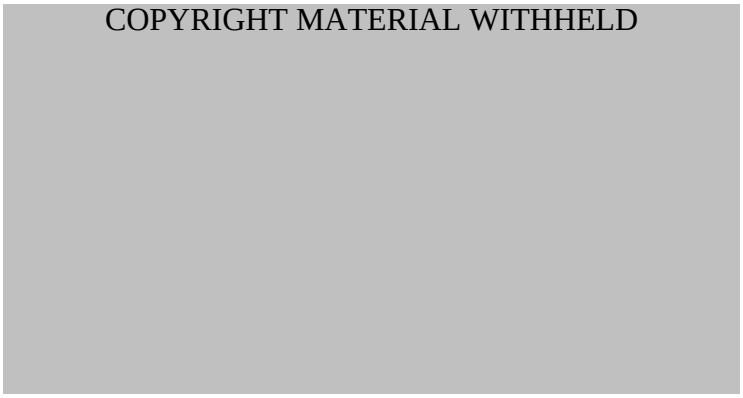
[1] Del Pizzo J and Callahan JM. Intranasal Medications in Pediatric Emergency Medicine. Pediatric Emergency care 30: 496-504, 2014.

[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

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