CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208411Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	(electronic stamp)
From	Joshua M. Lloyd, MD
Subject	Cross-Discipline Team Leader Review
NDA	208411
Applicant	Adapt Pharma, Inc.
Date of Submission	July 20, 2015
PDUFA Goal Date	January 20, 2016
Proprietary Name / Established (USAN) names	Narcan nasal spray / Naloxone hydrochloride
Dosage forms / Strength	Intranasal spray / 40 mg/ml
Proposed Indication(s)	1. Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression 2. Intended for immediate administration as emergency therapy in settings where opioids may be present 3. Not a substitute for emergency medical care
Recommended:	Approval

1. Introduction

Adapt Pharma, Inc. ("Applicant"), submitted this new drug application (NDA) for Narcan (naloxone hydrochloride) nasal spray for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. Narcan nasal spray is a single-use, drug-device combination product intended for use in the community. It is designed for use in non-healthcare settings by laypersons to rescue patients experiencing the life-threatening effects of an accidental or intentional opioid overdose while awaiting emergency medical attention. The Applicant conducted the clinical development program under IND 114,704 in collaboration with the National Institutes for Drug Abuse (NIDA) and proposes to market Narcan nasal spray in one strength (i.e., 40 mg/ml) that delivers 0.1 ml (4 mg) in a single intranasal spray and is for use in patients of all ages, both adult and pediatric. The investigational new drug (IND) application was submitted by Lightlake Therapeutics, Inc. (also referred to as the "Applicant" throughout this review), on July 18, 2014, and the ownership of the IND was transferred to Adapt Pharma, Inc., on December 16, 2014. This IND was granted fast track designation on January 27, 2015, for the proposed indication.

The Applicant submitted bioavailability data to cross-reference their NDA for Narcan[1] (naloxone hydrochloride; NDA 16636), an injectable formulation of naloxone. Narcan was approved April 13, 1971, and is available for subcutaneous, intramuscular, and intravenous use

[1] The Narcan NDA was transferred from Endo Pharmaceuticals, Inc., to the Applicant effective May 26, 2015

for the complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids, including propoxyphene, methadone and certain mixed agonist-antagonist analgesics: nalbuphine, pentazocine, butorphanol, and cyclazocine. Narcan is also indicated for diagnosis of suspected or known acute opioid overdosage. The indication and usage section of the labeling further states that Narcan may be useful as an adjunctive agent to increase blood pressure in the management of septic shock. Narcan has been discontinued from marketing; however, the Agency determined that it was not withdrawn from sale for reasons of safety or effectiveness (74 FR 22751). Therefore, the Applicant used a generic naloxone product manufactured by (b) (4) in the pivotal relative bioavailability study to create a scientific bridge to their NDA for Narcan to establish the safety and efficacy of Narcan nasal spray for the proposed indication. Although the Applicant owns the Narcan NDA, this NDA for Narcan nasal spray is relying on the published literature to support the safety and efficacy of the product in the pediatric population and, therefore, was submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.

This NDA was accepted for rolling review and was granted priority review status upon submission of the final sections of the application reflecting the importance of this product from the public health perspective, as, currently, there are no approved intranasal naloxone products intended for use in the community.

Both Narcan nasal spray and Narcan contain naloxone, and the proposed population for Narcan nasal spray (i.e., known or suspected opioid overdose) is encompassed by the indicated population for Narcan. However, several important differences exist between Narcan nasal spray and Narcan. Narcan nasal spray represents a change in the route of administration from intravenous (IV), intramuscular (IM), or subcutaneous (SC) injection to intranasal (IN). Therefore, the Applicant evaluated the potential for local toxicity in the relative bioavailability studies. Narcan nasal spray also represents a change in the intended setting. Narcan is generally used in healthcare settings by healthcare professionals, whereas Narcan nasal spray is intended to be used in a community setting by laypersons. The Applicant submitted a human factors evaluation to support use in this different setting. Lastly, the proposed dosing for Narcan nasal spray represents a change in dosing regimen for pediatric patients. Narcan labeling recommends weight-based dosing in pediatric patients, whereas Narcan nasal spray contains a fixed dose of naloxone. This review will explore these issues in greater detail, in addition to confirming that Narcan nasal spray achieves comparable or greater systemic exposures to naloxone as compared to Narcan, particularly in the period immediately after drug administration, as this represents a critical period in which the patient's opioid overdose must be reversed to avoid irreversible injury or death.

2. Background

Accidental or intentional overdose and death associated with the use, misuse, and abuse of illicit and/or prescription opioids is a public health crisis in the United States. Opioid overdose can occur in a patient prescribed an opioid medication or in household contacts of the patient and in people who misuse or abuse opioids. Opioid overdose is characterized by life-threatening respiratory and central nervous system (CNS) depression that, if not immediately

treated, may lead to significant morbidity and mortality due to irreversible hypoxic injury. Naloxone is a nonselective opioid receptor antagonist, with the greatest affinity for the mu-opioid receptor that, if immediately administered, can reverse these life-threatening effects in an opioid overdose and prevent hypoxia-associated injury and death. However, there are limitations to the use of naloxone in this setting. The effects of some opioids, such as buprenorphine, may be difficult to antagonize. Larger doses of antagonist may be necessary than are available and the opioid overdose must be reversed before hypoxia results in irreversible injury. Also, it is important to realize that the duration of antagonists such as naloxone are generally shorter than the duration of action of most opioids. Therefore, even when an antagonist is available, it is not a substitute for seeking emergency medical help.

The US Department of Health and Human Services (HHS) has made addressing this public health crisis a top priority and has outlined a targeted initiative to do so that includes providing training and educational resources, increasing the use of naloxone, and expanding the use of medication-assisted treatment. The availability of an approved intranasal naloxone product intended for use in the community would contribute towards meeting these goals and is of great importance from a public health perspective.

Generic versions of Narcan are currently available; the approved Narcan labeling recommends initial doses of 0.4 mg to 2 mg for known or suspected opioid overdose in adults with repeat doses every two to three minutes up to a total of 10 mg. In children, initial doses of 0.01 mg/kg with repeat doses of 0.1 mg/kg are recommended. Additionally, Evzio, an injectable naloxone product that delivers 0.4 mg of naloxone HCl intramuscularly or subcutaneously intended for use in the community, was approved on April 3, 2014, and is available.

Naloxone has also been increasingly available in the community through a variety of public health programs, which have generally supplied an injectable formulation of naloxone (i.e., either a vial or syringe) along with a needle or mucosal atomizer device (MAD) to provide access to this life-saving medicine. The MAD allows for the injectable formulation to be delivered as an intranasal spray (currently, an off-label route of administration), typically from an injectable solution containing 2 mg of naloxone HCl in 2 ml of solution. The bioavailability of this off-label intranasal route of administration using an MAD may be less than the exposure following approved routes of administration for naloxone, based on reports in the literature, but there are also reports in the literature and from addiction treatment programs that naloxone administered this way has been successful in reversing opioid overdose. Therefore, the minimum effective dose of naloxone is unclear.

Evaluating the efficacy of a new formulation or route of administration of naloxone to establish an effective dose range presents significant logistical and ethical challenges, as already-approved naloxone-containing products are available for treatment of this life-threatening condition, which, if not immediately treated, could result in substantial morbidity and mortality. The Division has determined that it would not be ethical to deliver an experimental naloxone (i.e., through a novel formulation or via a novel route of administration) to an actual patient suffering from opioid overdose and potentially delay life-saving treatment with an already-approved naloxone product in the context of a clinical

efficacy study. Furthermore, intentionally administering enough opioid to actually create a clinically meaningful opioid overdose is not ethical.

Therefore, the Division has outlined a path for the clinical development of novel naloxone products, including those intended to be used in the community, which consists of demonstrating comparable or greater systemic exposure to naloxone with the new naloxone product, particularly in the early critical period after drug administration. This relative bioavailability study would be conducted in healthy volunteers, thus obviating the need to conduct a study in patients suffering from an opioid overdose. The necessary clinical development program was discussed with the Applicant at a Pre-IND meeting held May 24, 2012. It was further discussed that, although the proposed product represents a new route of administration, nonclinical studies to evaluate local toxicity would not be required given the clinical experience with intranasal naloxone, lack of any novel excipients, the acute use of the drug product, and the potentially life-saving indication, provided that the Applicant includes adequate clinical monitoring of local tissues in the relative bioavailability studies. A Pre-NDA meeting was held March 27, 2015.

3. CMC/Device

The Quality Assessment review consisted of the following disciplines: Drug Substance and Drug Product (Venkat Pavuluri, PhD), Process (Christina Capacci-Daniel, PhD and Edwin Jao, PhD), Microbiology (Christina Capacci-Daniel, PhD, and Erika Pfeiler, PhD), Facility (Christina Capacci-Daniel PhD and Grace McNally, PhD), Regulatory Business Process Manager (Steve Kinsley), Application Technical Lead (Julia Pinto, PhD), and CDRH OC Combination Products (Juandria Williams). CDRH was also consulted (Ryan McGowan and Rick Chapman). The information for the naloxone drug substance is referenced in DMF (b) (4) for which (b) (4) is the holder, and the information for the nasal spray device is referenced in DMF (b) (4) for which (b) (4) is the holder. Both DMFs were found to be adequate. The quality review team recommended approval for this NDA. The following is a summary of the quality review.

The quality review team noted that:

> The naloxone API is supplied by (b) (4). The drug product is formulated in (b) (4) comprising the following excipients: sodium chloride, (b) (4) and benzalkonium chloride, in a concentration of 40 mg/ml. The container closure system is a glass vial with a (b) (4) stopper, which is then encased within a nasal actuator and container holder. The nasal spray device is by (b) (4), under DMF (b) (4), and has been reviewed by CDRH and OPQ, for use with the naloxone drug product. Each unit dose device, formulated to deliver one dose of naloxone, is placed within a blister package. Two units or blister packages are then stored per carton. Adequate data to assess the device delivery of the drug product and to assure the identity, strength, purity, and quality of the drug product is provided. The drug product is granted an expiry of 24 months, when stored at room

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