CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208411Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, MD
Subject	Division Director Summary Review
NDA #	208411
Applicant Name	Adapt Pharma, Inc.
Date of Submission	July 20, 2015
PDUFA Goal Date	January 20, 2016
Proprietary Name / Established (USAN) Name	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
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
CDTL Review	Joshua Lloyd, MD
Pharmacology Toxicology Review	Newton Woo, PhD, R. Daniel Mellon, PhD
OPQ Review	Venkat Pavuluri, PhD, Christina Capacci-Daniel, PhD, Erika Pfeiler, PhD, Grace McNally, PhD, Edwin Jao, PhD, Steve Kinsley, Julia Pinto, PhD
CDRH Review CDRH OCP	Ryan McGowan, Rick Chapman Juandria Williams
Clinical Pharmacology Review	Suresh Naraharisetti, PhD, Yun Xu, PhD
OSI	Arindam Dasgupta, PhD, Yiyue Zhang, PhD, Melkamu Getie-Kebtie, PhD, RPh, Charles Bonapace, PharmD
OSE/DMEPA	Millie Shah, PharmD, BCPS; Vicky Borders-Hemphill, PharmD; Quynh Nhu Nguyen; MS, Irene Chan, PharmD, BCPS
OPDP/DCDP	L. Shenee Toombs
OMP/DMPP	Nathan Caulk, MS, BSN, RN; Barbara Fuller, RN, MSN, CWOCN; LaShawn Griffiths, MSHS-PH, BSN, RN
Pediatric Maternal Health Staff	Mona Khurana, MD: Hari Cheryl Sachs, MD; Linda Lewis, MD

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
OPQ= Office of Pharmaceutical Quality
CDRH=Center for Device and Radiological Health
OCP = Office of Combination Products
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Errors Prevention
OSI=Office of Scientific Investigations
OPDP=Office of Prescription Drug Promotion, DCDP=Division of Consumer Drug Promotion
OMP=Office of Medical Policy Initiatives, DMPP=Division of Medical Policy Programs

Signatory Authority Review Template

1. Introduction

The current application is a 505(b)(2) application for Narcan (naloxone hydrochloride) Nasal Spray which cross references the efficacy and safety information from Narcan, (NDA 016636). This application represents the first nasal naloxone spray to meet the criteria for novel naloxone products described by the Agency during the public meetings held in 2012 and in 2015. The application was accepted for rolling review and was granted priority review status upon submission of the final sections reflecting the importance this product from the public health perspective. The application relies on a relative bioavailability study in healthy volunteers. As the marketing of Narcan has been discontinued, the Applicant used a generic product, International Medicinal System's naloxone HCl injection USP pre-filled syringe (ANDA 072076) for the relative bioavailability study necessary to create a scientific bridge to the Agency's prior findings for Narcan. This review will focus on the pharmacokinetic parameters, local adverse events, and the potential for use in pediatric overdose situations.

2. Background

Naloxone HCl was first approved in 1971(Narcan, NDA 016636), for intravenous, intramuscular, and subcutaneous administration. The current labeling of Narcan recommends an initial dose of 0.4 mg to 2 mg, followed by repeated doses up to 10 mg in the setting of suspected opioid overdose. The off-label use of commercially available naloxone hydrochloride by the intranasal route of administration using a nasal atomizer is growing in popularity as many programs and communities seek to address the public health problem of prescription and illicit opioid abuse and the overdoses that occur in these settings. The need for a naloxone product for use outside of a controlled medical setting extends beyond the setting of abuse. As the management of chronic pain in the US relies heavily on the use of chronic opioid treatment, there is risk for overdose for patients and household contacts. The first product approved to address the risk of opioid overdose in all settings was Evzio (naloxone HCl injection), approved on April 3, 2014. Evzio is an autoinjector with audible and written instructions for use, and delivers 0.4 mg of naloxone in 0.4 mL to the subcutaneous or intramuscular space.

There is evidence that the off-label use of naloxone by the intranasal route has been effective in reversing opioid overdose in many cases. However, there are no data that specifically quantitate the success rate, leaving the question of whether there are situations that could have benefited from a higher dose of naloxone. Unpublished pharmacokinetic data suggest that naloxone levels following off-label use by the intranasal route are lower than by the approved routes of administration. The lowest effective dose of naloxone is unclear, and is likely dependent on a number of factors, including dose, route of administration, and the amount and

type of opioid involved in the overdose. In discussion with the Applicant during product development, it was determined that designing an efficacy study to define an effective range of naloxone use in the proposed setting would be difficult to justify as it would require administration of opioids to create an overdose, albeit in a controlled setting. The use of pharmacodynamic measurements such as pupil dilation or response to inhaled carbon dioxide may demonstrate an effect of naloxone, however, because the relationship between experimental opioid effects and reversal of a clinically meaningful overdose is not well defined, could not be relied upon for dose selection. Furthermore, there is an approved dosing regimen for naloxone. Therefore, the approach required by the division was to match the naloxone exposure achieved by administration of naloxone using an approved dose and route. This is done by conducting a relative bioavailability study that demonstrates the new product matches or exceeds the pharmacokinetic parameters of Cmax and Tmax for naloxone by an approved route, intramuscular, intravenous, or subcutaneous injection. The first few minutes are of particular importance, because if the overdose has led to apnea, time is of the essence if the brain is to be spared permanent hypoxic injury. Therefore, in addition to Cmax and Tmax, it is necessary to demonstrate that the naloxone levels are comparable to the approved route during the first minutes after dosing. Given the known safety profile of naloxone, the relative bioavailability study can be conducted in a normal healthy volunteer population without risk to the study participants. This approach has been discussed at two public meetings hosted by FDA.[1,2]

In patients managed with opioid analgesics, an opioid overdose leading to death can occur in a variety of settings. Patients may inadvertently take too much trying to better manage pain, or through errors in dose or frequency. Initiating a new concomitant medication that inhibits the metabolic pathway of an opioid, or discontinuation of a concomitant medication that induces the metabolic pathway can result in overdose in a patient who has used their opioid analgesic according to instructions. Addition of a new medication with the adverse effect of central nervous system depression, or an error in judgment surrounding the use of alcohol can also create a situation of over sedation in a patient previously stable on an opioid. Overdose can occur in household contacts of a patient prescribed opioids by accidental exposure or through intentional misuse or abuse. Individuals abusing prescription opioid analgesics or illicit opioids can also inadvertently overdose. With the range of potency of available opioids, death from overdose can occur with the first attempt at abuse. Death due to overdose from most opioids may be preventable with the immediate administration of an opioid antagonist such as naloxone. However, there are limitations in the prevention of death 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 no substitute for seeking emergency medical help.

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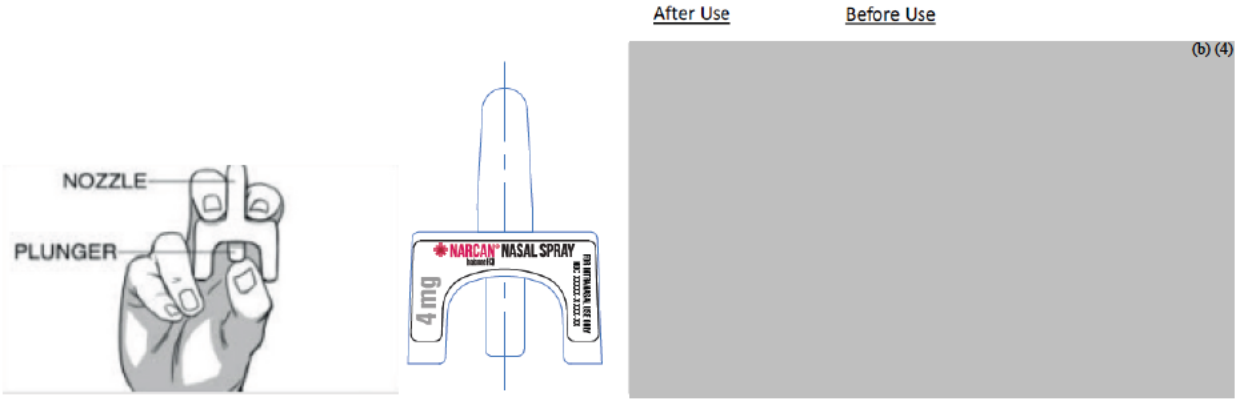
[1] Exploring Naloxone Uptake and Use – A Public Meeting, July 1 and 2, 2015. http://www fda.gov/Drugs/NewsEvents/ucm442236.htm

[2] Role of Naloxone in Opioid Overdose Fatality Prevention; Request for Comments; Public Workshop, April 12, 2012. http://www fda.gov/Drugs/NewsEvents/ucm277119.htm

3. OPQ/Device

Narcan Nasal Spray consists of the formulated drug product filled into a unit-dose vial which is stoppered and placed within a Unit-dose Delivery Device produced by (b) (4). This unit-dose device is then placed into a single blister pack. The container closure-spray device is a single-entity combination (drug/device) product. The device contains 100 microliters of a 40 mg/mL solution of naloxone hydrochloride, and is intended to deliver a dose of 4 mg with one spray. The device is displayed in the following figures:



From the Office of Pharmaceutical Quality review:

> 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 40mg/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 temperature. Further, the Office of Process and Facilities, has made an overall recommendation of adequate for all facilities related to this application. Therefore, from a quality perspective, this NDA is recommended for approval.

Mr. McGowan performed an evaluation of the design of the device constituent parts of the combination product and covered the intended design and design control information for the subject device constituent part. From Mr. McGowan's review:

> The device consultant authoring this review memorandum has performed a design review of submission materials intended to support the safety and functionality of the of the device constituent parts of the subject combination product. After examination of the original new drug application (NDA), cross-referenced drug master files (DMF), and responses to information requests, the consulting reviewer has determined that the device constituent parts of the

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