Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, MD
Subject	Division Director Summary Review
NDA #	208411/S-001
Applicant Name	Adapt Pharma, Inc.
Date of Submission	March 25, 2016
PDUFA Goal Date	January 25, 2017
Proprietary Name / Established (USAN) Name	Narcan nasal spray / Naloxone hydrochloride
Dosage Forms / Strength	Intranasal spray / 20 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	N/A
Pharmacology Toxicology Review	Carlic Huynh, PhD, Newton Woo, PhD, R. Daniel Mellon, PhD
OPQ Review	Venkat Pavuluri, PhD, Julia Pinto, PhD
CDRH/GHDB/DAGRID Review	John McMichael, Alan Stevens, LCDR, USPHS
Clinical Pharmacology Review	Suresh Naraharisetti, PhD, Yun Xu, PhD
OSI	N/A
OSE/DMEPA	Millie Shah, PharmD, BCPS; Vicky Borders-Hemphill, PharmD; Quynh Nhu Nguyen; MS, Irene Chan, PharmD, BCPS
OPDP/DCDP	Koung Lee, Olga Salis, L. Shenee Toombs
OMP/DMPP	Morgan Walker, PharmD, MBA, CPH; Barbara Fuller, RN, MSN, CWOCN; LaShawn Griffiths, MSHS-PH, BSN, RN
Pediatric Maternal Health Staff	Mona Khurana, MD; Leyla Sahin, MD; Hari Cheryl Sachs, MD; Miriam Dinatale, DO, LCDR, USPHS, John Alexander, MD, MPH

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 supplemental NDA for Narcan (naloxone hydrochloride) Nasal Spray 2 mg. Narcan Nasal Spray 4 mg was approved on November 18, 2015, as a 505(b)(2) application, which cross referenced the efficacy and safety information from Narcan, (NDA 016636). The formulations for the approved 4 mg product and proposed 2 mg product (b) (4)

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 has been 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 U.S. relies heavily on the use of chronic opioid treatment, there is risk of 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 (NDA 205787) 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. A higher dose version, Evzio 2 mg (NDA 209862) was approved on October 19, 2016.

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. Highly potent opioids have been found mixed into heroin, in particular fentanyl and carfentanil, and this has led to a number of overdose deaths among those abusing heroin. Also, it is important to realize that the duration of antagonists such as naloxone is generally shorter than the duration of action of most opioids.

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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

Therefore, even when an antagonist is available, it is no substitute for seeking emergency medical help.

3. OPQ/Device

Narcan Nasal Spray 2 mg [redacted] 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 20 mg/mL solution of naloxone hydrochloride, and is intended to deliver a dose of 2 mg with one spray. The device is displayed in the following figures:

[redacted]

The drug substance, DMF [redacted], remains acceptable to support the product. As noted in the OPQ review, page 3:

> The proposed drug product, intended for intranasal delivery of naloxone hydrochloride, 2 mg per spray, contains naloxone hydrochloride dihydrate as active ingredient [redacted] in a [redacted] aqueous solution along with disodium edetate as stabilizer and benzalkonium chloride as [redacted] preservative. The composition of proposed drug product, [redacted] is similar to the approved NARCAN® metered nasal spray, 4 mg / spray and thus there are no scientific or regulatory concerns on the components and composition.

From the OPQ review, page 22:

> Based on the data presented above for clinical and registration batches of naloxone formulations at concentration of 20 mg/mL, the worst case scenario for the formulation at the concentration of 10 mg/mL out to 24 months, and the 12 month stability data from the 40 mg/mL clinical and registration batches, sponsor proposed an expiration date of twenty four (24) months for the to be marketed 20 mg/mL Naloxone Nasal Spray concentration.
>
> ***3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment***
>
> Sponsor commits to place the first three production (validation) batches and at least one production batch each year thereafter on stability in the final container closure system according to the stability protocol described in section 3.2.P.8.1. Sponsor also commits to perform the microbiological contamination tests (TAMC, TYMC, E. coli, S. aureus, P. aeruginosa and B. cepacia) on an annual basis

for the first three (3) production batches [redacted].

From Mr. McMichael's CDRH review, p.4:

> The sprayer system is manufactured by a third part sponsor named [redacted] This third party sponsor has provided a number of non-clinical resources to support approval of NDA 208411. The specific sprayer devices used within the subject NDA is stated as also used [redacted] spray products in the U.S. [redacted]

And from page 9 of the CDRH review:

> The Design Controls of the NARCAN Nasal Spray was reviewed and established to be adequate under the original approved NDA submission NDA 208411. This supplement includes no changes to the design controls of the device constituent parts of the combination product, however due to the newly proposed dosage of 2 mg Naloxone, performance testing and stability data was required to re-verify the essential performance requirements of the device with the lower dosage form. It should be noted that the deliverable volume of the nasal spray remains the same for both dosage forms.
>
> The Sponsor submitted updated stability testing for the 2 mg combination product that is adequate to the consultant reviewer.
>
> A post-market requirement for reliability of the NARCAN nasal spray was established for the original NDA submission [redacted]
> After discussion with the CDER review team the same rationale applies for this supplemental dose that applied for the original NDA dosage in that the safety and efficacy of the drug product dosage is not in question and the concerns regarding the reliability of the device constituent do not outweigh the potential benefit of the device reaching market. [redacted]

The postmarket requirement in place from the original application is as follows:

1. Establish reliability requirements for the combination product and complete testing which verifies combination product reliability [redacted]:

   - Establish reliability requirements for your combination product. It is recommended that reliability be directly specified as R(t) = x%, where t = time and x% = probability of meeting essential performance requirements. These requirements should be objective and relate to the ability of a population of devices to meet essential performance requirements after pre-conditioning to elements outlined within c, below. The reliability requirements should be verified with a high degree of statistical confidence.

   - Provide rationale and justification supporting the clinical acceptability of the established reliability requirements.

   - Perform a test to verify the reliability requirements specified in above.

   - Devices assessed within the reliability test should be preconditioned to worst-case reasonably foreseeable conditions. The Agency has conceived the following recommended preconditioning activities, however you should provide rationale supporting the final precondition elements chosen, and the order in which the products are conditioned. Your assessment of the preconditioning

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