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APPLICATION NUMBER:

215457Orig1s000

CLINICAL REVIEW(S)

DIVISION OF PULMONOLOGY, ALLERGY AND CRITICAL CARE (DPACC)
MEDICAL OFFICER CONSULTATION

Date:	February 1, 2022
To:	Jane Mun, DAAP
From:	Elisabeth Boulos, Clinical Reviewer, DPACC
Through:	Kelly Stone, Associate Director for Therapeutic Review, DPACC
Through:	Banu Karimi-Shah, Deputy Division Director, DPACC
Subject:	Naloxone Auto-Injector 10mg for Opioid Overdose

General Information

NDA:	215457
Sponsor:	Kaleo, Inc.
Drug Product:	Naloxone Auto-Injector 10mg
Request From:	Jane Mun, DAAP
Date of Request:	August 31, 2021
Sponsor Meeting:	February 28. 2021
Reviewed:	NDA 215457, eCTD# 0001, 08/08/2021 • Clinical Overview • Clinical summary NDA 215457 Clinical Pharmacology Review

Executive Summary

This is a Medical Officer response to a request for consultation from DAAP regarding the development of Naloxone Auto-Injector 10mg (NAI) for both prophylaxis and emergency treatment of high-potency opioid toxicity in settings where chemical weapon use is suspected or for treatment of overdoses of large quantities of potent opioids; at the time of this review, the final label indication is to be determined. DAAP requests DPACC's comments regarding the Sponsor's *in silico* model of opioid-induced respiratory depression (OIRD).

Since it is infeasible to conduct clinical trials for this indication, to support the NDA via a 505(b)2 pathway, the Sponsor relied on nonclinical data, published literature, information for other naloxone products (Narcan NDA 016636, Evzio NDA 209862), and an *in silico* mechanistic pharmacokinetic-pharmacodynamic (PK-PD) model of OIRD. The primary metric for this model was ventilation, measured as a percent of baseline ventilation. The Division of Applied Regulatory Science (DARS) advised the Sponsor to create this model and has advised the Sponsor on its development in several IRs since 12/29/2020. In addition, DARS developed its own model to support the validity of this approach. Key differences are outlined in the clinical pharmacology review and discussed below. Both models rely, at least in part, on percent baseline ventilation as a metric of OIRD.

The Sponsor proposes to include data generated by the *in silico* simulations in Section 12.2 (pharmacodynamics) of the label; the label does not include a Section 14. DPACC does not have prior regulatory experience with *in silico* modeling. Upon review of materials provided by both the Sponsor and DARS, we find the data generated to be appropriate for supporting pharmacodynamic claims. We do not find the metric of percent baseline ventilation to be directly clinically meaningful; however, given the intended use of this product and the leveraging of this data to support pharmacodynamic rather than clinical efficacy, we find this information useful and reasonable to include.

Regulatory History

Kaleo submitted NDA 218457 for NAI on 08/28/2021 in conjunction with the Department of Defense (DoD) as part of medical countermeasures against opioids. The initial proposed indications (which are still under review) were:

(b) (4)

Naloxone has been FDA approved since 1971 (NDA 016636) and is available as intramuscular (IM), intravenous (IV), subcutaneous (SC), and intranasal (IN) formulations. Naloxone has been approved up to doses of 8 mg IN (NDA 212045) and 5mg IM/SC (NDA 212854) for patients down to birth.

In line with other recent naloxone development programs conducted via a 505(b)2 pathway, the Sponsor relied on a PK bioavailability study in healthy volunteers (HVs) to demonstrate greater bioavailability of 10mg NAI compared to 2mg autoinjector (Evzio, NDA 209862). This study demonstrated a greater than 5-fold increase in several PK parameters with 10 mg NAI. Efficacy of this dose was then demonstrated using the PK/PD model developed in conjunction with DARS.

Naloxone is widely used in clinical practice in community, pre-hospital, emergency room, and intensive care unit settings for the treatment of OIRD. In the absence of opioid receptor agonists, naloxone has no effect. Naloxone is generally safe, and the primary risks pertain to re-narcotization and need for repeat doses, limited efficacy against partial agonists, and precipitation of acute withdrawal symptoms in opioid-dependent patients[2]. Whether naloxone may induce acute pulmonary edema (PE) is controversial, and the

[1] Kaleo, proposed USPI NDA 215457.
[2] https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212854s000lbl.pdf

mechanism, via catecholamine surge and acute increase in afterload[1], is poorly understood. There are many clinical confounders (e.g., risk of aspiration, drug inhalation), and it is well-known that opioid agonists themselves cause pulmonary edema[2]. In clinical practice, naloxone is usually administered in small, incremental doses (starting at 0.04 mg IV or 2 mg IN) or as a titratable infusion[3].

Questions from DAAP

DAAP is requesting a pulmonary consult to review the Applicant's modeling data and respiratory/ventilatory endpoints. DAAP wants to know if the endpoints chosen by the Applicant are clinically relevant and if they will be able to rely on these for their proposed indications.

DPACC Response

Sponsor Model and Ventilation Threshold

As previously stated, DPACC has no regulatory experience evaluating *in silico* PK/PD simulation models. For a detailed assessment of the strengths and limitations of this model, we defer to the DARS team and refer to the clinical pharmacology review. Incorporating input from DARS, the Sponsor developed a model simulating reversal of OIRD caused by a range of different opioids at different doses. The simulations compared the time courses for reversal of OIRD with NAI 10mg and 2mg, administered as both rescue treatment and prophylaxis.

The Sponsor chose 40% of baseline ventilation (or reduction by 60% from baseline ventilation) as the threshold for NAI administration and for the definition of reversal of OIRD, i.e., recovery. This threshold was set for morphine, fentanyl, and carfentanil models; for buprenorphine, a threshold of 70% ventilation (or reduction by 30% from baseline) was set because of the slower dissociation of buprenorphine from opioid receptors[4]. The results of these simulations led to the following summary conclusions:

- 10 mg NAI (compared to 2 mg or no naloxone) results in a greater proportion of subjects recovering from OIRD caused by medium or high dose opioids;
- 10 mg NAI is less effective in achieving recovery from OIRD caused by high dose carfentinal;
- Prophylactic administration of 10 mg NAI may prevent OIRD caused by high dose fentanyl or carfentanil;
- Early administration of 10 mg NAI is critical for achieving reversal of OIRD.

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[1] Farkas A, Lynch MJ, Westover R, Giles J, Siripong N, Nalatwad A, Pizon AF, Martin-Gill C. Pulmonary Complications of Opioid Overdose Treated With Naloxone. Ann Emerg Med. 2020 Jan;75(1):39-48. doi: 10.1016/j.annemergmed.2019.04.006. Epub 2019 Jun 8.

[2] Sporer KA, Dorn E. Heroin-related noncardiogenic pulmonary edema : a case series. Chest. 2001 Nov;120(5):1628-32. doi: 10.1378/chest.120.5.1628.

[3] Panchal AR, Bartos JA, Cabañas JG, Donnino MW, Drennan IR, Hirsch KG, Kudenchuk PJ, Kurz MC, Lavonas EJ, Morley PT, O'Neil BJ, Peberdy MA, Rittenberger JC, Rodriguez AJ, Sawyer KN, Berg KM; Adult Basic and Advanced Life Support Writing Group. Part 3: Adult Basic and Advanced Life Support: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2020 Oct 20;142(16_suppl_2):S366-S468.

[4] Kaleo, Integrated Summary of Efficacy, NDA 215457.

It appears that the pre-defined threshold of 40% ventilation is derived from a study of respiratory volume monitoring in opioid-anaesthetized, post-operative patients[1]. The rationale for 40% of baseline ventilation is stated as such:

> "Since the ARDSnet protocol uses a cutoff of 40% of the predicted value for normal respiration to indicate inadequate ventilation, unsuitable for extubation (albeit in [tidal volume] TV instead of [minute ventilation] MV), this became the criteria for designating a patient with an MV of less than 40% predicted as "unsafe." For example, in an 80-kg patient with a low normal [respiratory rate] RR of 8, an MV of 40% MVPRED would translate to 2.6 L/min. If one would not consider such a mechanically ventilated patient to be safe for extubation with sole reliance on spontaneous breathing, we assumed spontaneous breathing below this cutoff to be inadequate (unsafe) and with potential to result in respiratory complications if left untreated." (Voscopoulos, 2014.)

We note that in clinical practice in the ICU, in which ARDSnet ventilation strategies are frequently implemented, clinicians do not routinely use percent baseline ventilation as a metric for clinical decision making. Other measurements that assess similar concepts and are more clinically meaningful include a rapid shallow breathing index (RSBI), end-tidal CO2 monitoring (EtCO2), and PaCO2, for example. All of these metrics, however, arrive at the same fundamental idea of quantifying ventilatory burden and drive. Therefore, we find this threshold definition reasonable in this context, since its use is for a physiologic model to support pharmacodynamic effects, rather than to directly inform clinical decision making.

Limitations and Alternative Approaches

After a literature review, we are not aware of other more persuasive models or obviously superior alternative definitions of ventilatory recovery.

We do acknowledge several limitations of the Sponsor's model, including the somewhat arbitrary threshold of 40% baseline ventilation based on a single study, the assumption of isocapnic breathing (stable CO2), the assumption of healthy, normal respiratory function at baseline, and the assumption that naloxone is administered immediately after opioid exposure, which is not practically possible. We understand that these limitations have been addressed extensively by the DARS team and accounted for in their alternative model. The FDA model, which looks at clinically meaningful endpoints, such as proportion of patients suffering cardiac arrest and brain partial pressure of O2 (PO2)[2] has supported claims made by the Sponsor regarding NAI 10 mg efficacy and safety.

Overall Assessment

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[1] Voscopoulos, Christopher J. MD; MacNabb, Colin Marshall MS; Freeman, Jenny MD; Galvagno, Samuel M. Jr. DO, PhD; Ladd, Diane DNP; George, Edward MD, PhD Continuous noninvasive respiratory volume monitoring for the identification of patients at risk for opioid-induced respiratory depression and obstructive breathing patterns, Journal of Trauma and Acute Care Surgery: September 2014 - Volume 77 - Issue 3 - p S208-S215

[2] Clinical Pharmacology / DARS presentations, NDA 215457, \\fdsfs01\ODE2\DAAAP\NDA and sNDA\NDA 215457 (Naloxone_Kaleo)\Meetings\Internal Discussion 02.08.22

We find that the endpoint of ventilatory recovery or “rescue”, defined as reversal of OIRD to at least 40% of baseline ventilation is imperfect, but provides useful data for understanding the pharmacodynamic effects of 10mg NAI. We do not find percent baseline ventilation to be directly clinically meaningful; however, the derivation of this threshold and the justification for its use are reasonable. We are not aware of superior alternatives, and clinical trials for this indication are not practicable or ethical. We agree that data obtained from this model are appropriate to include in Section 12.2 of the label.

There are several uncertainties regarding the intended use of 10 mg NAI. Among them are the route of administration, dose, and type of opioids that may induce OIRD. Therefore, it is impossible to predict the exact clinical effectiveness of 10 mg NAI in real world use. Naloxone has a favorable safety profile in opioid-naïve patients (as we would expect most first-responders or military personnel to be), and in opioid-dependent patients, the sequelae of acute withdrawal are more manageable with appropriate medical care than fatal OIRD and death. Therefore, we agree with an overall favorable risk-benefit profile for this product based on the data available, provided the relevant limitations are communicated clearly in the label.

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/s/

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