Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Cross-Discipline Team Leader and Division Director Summary Review

Date	August 7, 2024
From	Rigoberto Roca, MD
NDA Number	218590
Applicant	Purdue Pharma, LP
Date of Submission	February 7, 2024
PDUFA Goal Date	August 7, 2024
Proprietary Name	Zurnai
Established or Proper Name	Nalmefene hydrochloride injection, auto-injector
Dosage Form	Autoinjector delivers 1.5 mg nalmefene (equivalent to 1.7 mg nalmefene hydrochloride) in 0.5 mL solution.
Applicant Proposed Indication/Population	Emergency treatment of known/suspected opioid overdose induced by natural/synthetic opioids in adults and pediatric patients aged 12 years and older.
Applicant Proposed Dosing Regimen	(b) (4)
Regulatory Action	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**	
Medical Officer Review	Zachary Dezman, MD	
OPQ Review	Drug Substance:	Zhixing Shan, PhD / Katie Duncan, PhD
	Drug Product/Labeling:	Jizhou Wang, PhD / Valerie Amspacher, PharmD / Julia Pinto, PhD
	Manufacturing:	Sugandha Saboo/ Cassie Abellard, BSc
	RBPM:	Teicher Agosto, PharmD, RPh
	ATL:	Valerie Amspacher, PharmD
Pharmacology Toxicology Review	Min Zhang, PhD / Newton Woo, PhD / R. Daniel Mellon, PhD	
Clinical Pharmacology Review	Srikanth Nallani, PhD / Deep Kwatra, PhD	
Pharmacometrics Review	Mike Bewernitz, PhD / Atul V. Bhattaram, Ph.D.	
DARS Review	John Mann, PhD / Anik Chaturbedi, PhD / Zhihua Li, PhD	
OSE/DMEPA	Damon Birkemeier, PharmD, FISMP, NREMT Valerie S. Vaughan, PharmD / Murewa Oguntimein, PhD, MHS, CPH, MCHES / Ariane O. Conrad, PharmD, BCACP, CDCES, FISMP / Jason Flint, MBA, PMP / Mishale Mistry, PharmD, MPH	
OSE/DPV II	Sarah Kang, PharmD, MS, BCPS / Mallika Mundkur, MD, MPH S. Christopher Jones, PharmD, MPH, MS	
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CDTL=Cross-Discipline Team Leader
DARS = Division of Applied Regulatory Science
DMEPA=Division of Medication Error Prevention and Analysis
DPV II = Division of Pharmacovigilance II
OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OSE= Office of Surveillance and Epidemiology

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

I concur with Dr. Dezman's Analysis of Condition and Current Treatment Options. This application is for a drug-device combination product designed to deliver 1.5 mg of nalmefene hydrochloride in 0.5 mL solution of in a single-use prefilled autoinjector.

The Applicant, Purdue Pharmaceuticals, has submitted an application that relies on the Agency's previous finding of safety and effectiveness for Revex (nalmefene hydrochloride injection), NDA 020459. They have submitted data from clinical pharmacology studies that demonstrates that, based on dose-normalized area under the curve to infinity (AUCinf), the bioavailability of Zurnai Autoinjector was 113% relative to IM injection and 115% relative to IV bolus of nalmefene. In addition, the Applicant submitted data to address the onset of action of nalmefene, and the generally slow onset of intramuscular and subcutaneous injections.

The safety profile of nalmefene has been previously evaluated, and the additional safety information submitted by the Applicant did not identify any safety issues of concern with their product.

I concur with the review team's assessment that this application can be approved at this time, with the postmarketing requirements and postmarketing commitments as described in Section 13 of this review.

Benefit-Risk Dimensions

The following table is reproduced from Dr. Dezman's review.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• There were 106,699 drug overdose deaths in 2021 in the United States, resulting in an age-adjusted rate of 32.4 per 100,000 persons.[13] • Around 80% of these drug overdose deaths involved an opioid.[13] • From 2001 to 2021, almost 630,000 people have died from a drug overdose.[13] • On average, 230 Americans die every day from opioid overdoses.[13]	Opioid overdose and death continue to be a public health crisis and a leading cause of death in the US. While nalmefene hydrochloride can reverse the acute opioid intoxication of a patient, patients require emergency department evaluation afterwards, and receiving nalmefene hydrochloride is not a permanent solution for opioid abuse, misuse, and addiction.
Current Treatment Options	• There are a number of currently approved and available community-use nalmefene hydrochloride and naloxone hydrochloride products.[8] • Evzio (both 0.4 mg and 2 mg intramuscular [IM/SC]) were discontinued.[14] • NARCAN Nasal Spray (NNS) and Revive, both 4 mg IN (intranasal) are considered safe for non-prescription use.[15, 16] • Anecdotally, some overdoses have required multiple administrations of standard doses of naloxone. It is not known whether these represent failures of the products approved for use in the community, the increasing prevalence of synthetic opioids (e.g., fentanyl and analogs), or co-ingestions without mu-opioid receptor activity (e.g., xylazine).	Patients and advocates have been clear in their desire for a broad array of opioid reversal products, including a multiple doses and routes of administration. While there are a number of FDA-approved treatment options available to treat opioid overdose, there are currently no approved autoinjector products on the market.
Benefit	• The efficacy of this product for community use is supported by a scientific bridge between the proposed product (ZURNAI, 1.5 mg delivered in 0.5 mL via IM/SC injection) and the reference product, REVEX, administered as 1.0 mg IM/SC, as shown in the pharmacokinetic (PK) study NAL 1005. • The pharmacokinetic data demonstrated that a single dose of ZURNAI results in the same or greater systemic naloxone* hydrochloride concentration compared to the reference product REVEX given 1.0 mg IM. This includes earlier time points that are most relevant to the	The Applicant provided literature and PK data to support the effectiveness of ZURNAI for the proposed indication intended for community use for those 12 years and older. The application contains no evidence that this product will result in improved outcomes in reversing synthetic opioids compared to other approved products.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	immediate treatment of opioid overdose (e.g., 0-5 min post-dose), as demonstrated in the pharmacodynamic study NAL 1005. • The efficacy and safety of this product has not been shown in the entire pediatric age range (i.e., there is no data for those from birth to 12 years of age). • There are no clinical efficacy data for this product to assess its efficacy in treating overdoses from synthetic opioids. • There are no comparative efficacy data between this product and other approved opioid reversal products for community use.	
Risk and Risk Management	• There is literature and modelling data to support the safety of nalmefene hydrochloride doses similar to the proposed dose for this product in adults and in the children 12 years and older. • Nalmefene hydrochloride administration causes withdrawal symptoms in opioid dependent individuals. Precipitated withdrawal may be severe and if left untreated, it can lead to dehydration, electrolyte abnormalities, and renal failure. These products are intended to save the lives of persons who use illicit opioids, but they may be less accepting and less likely to use products that frequently precipitate withdrawal. • Similar to naloxone hydrochloride, there are reports of patients suffering from noncardiogenic pulmonary edema after receiving nalmefene hydrochloride.[17] • Proposed product labeling includes language about the serious risks of precipitating acute opioid withdrawal. There are no comparative safety data between this product and other currently-available reversal products to inform prescribing decisions.	The Applicant has not provided data to describe the frequency of precipitated opioid withdrawal in patients who are treated with the proposed device and have opioid dependence. Based on evidence from the literature and other Applicants/NDAs, we would expect the current application to have safety on-par with existing opioid reversal products. Future trials may provide additional insight. Approval of this product would provide an additional approved opioid reversal product and would be the only autoinjector available to civilian use.

* Note: this should read “nalmefene” and not “naloxone.”

2. Background

The analysis of condition, current therapeutic options, and regulatory background are very well documented in Dr. Dezman's review; please refer to his review for the details. Particularly notable items regarding the regulatory history are noted below (reproduced from Dr. Dezman's review).

> The Division held a Type B PIND meeting with the Applicant during the pre-IND stage of development on June 19, 2018. The topics discussed that were relevant to this clinical review were how to apply for Fast Track designation, how to pick a relevant reference drug (and how to address the unique pediatric and reproductive concerns related to nalmefene hydrochloride), how to choose and create the data needed to support the device portion of their application (specifications [including needle length], reliability testing, storage, human factors).
>
> On June 3rd, 2020, the Applicant requested a Type C meeting. The Agency further clarified how to bridge to the Agency's prior finding of nalmefene hydrochloride's safety and efficacy, provided initial guidance on the Applicant's choice of using an autoinjector for their product, and described the data that would be needed to be submitted to support the addition of $MgCl_2$ (an excipient new to the IM/SC route of administration). The Agency stressed the importance of the initial resuscitation period (i.e., 0-5 and 0-10 minutes after administration) and provided guidance on how the Applicant may demonstrate their product has overcome known issues with 1) the onset of action of nalmefene hydrochloride and 2) the generally slow onset of IM/SC injections. The Agency provided guidance on the safety of the Applicant's FIRD protocol.
>
> There was an end-of-phase 1 meeting held on October 4th, 2021. The Agency requested the Applicant's FIRD model be revised for safety. The Applicant discussed some of the changes they enacted in their FIRD protocol to provide more reliable results (See Section 6.2 for more on this point). It was stated that the Agency did not agree the proposed study in healthy recreational opioid users, NAL 1004, would adequately explore issues related to precipitated withdrawal. Other topics of discussion included proposed nonclinical animal tolerance/toxicology studies, labelling,
>
> The Office of Pharmaceutical Quality held a separate end-of-Phase 1 meeting with the Applicant on March 31st, 2022. The conversation revolved around how to provide the appropriate data for their product's stability, extractable/leachables, and reliability.
>
> At the pre-NDA meeting on November 2nd, 2023, the Applicant largely discussed how to divide and present the data within the NDA and confirmed the process to apply for Priority Review and the 505(b)(2) pathway.

3. Product Quality

For complete details regarding the submission, please refer to the review by the Office of Pharmaceutical Quality. The review team concluded that adequate information was submitted to recommend approval of this application.

The review team's summary regarding the drug substance is reproduced below:

Assessment Recommendation: *Adequate*

Assessment Summary:

The CMC information for the drug substance, Nalmefene Hydrochloride, is cross referenced to Type II DMF [redacted]. Nalmefene Hydrochloride is manufactured by the Holder of the referenced DMF – [redacted].

The DMF was originally submitted on 15-OCT-2001. Since then, the DMF has been reviewed three times. The latest review on the most recent quality amendment (SD 28) was completed on 18-JAN-2022 with the conclusion of Adequate; Yongjun Gao, Ph.D.

The Applicant refers to the DMF and provides a brief description of the general properties, specification, impurities, analytical methods and validations, batch analyses, stability, etc. for the drug substance. All the information is adequate.

Based upon the information disclosed in the DMF, the controls on the impurities in the Nalmefene Hydrochloride drug substance are adequate. There are no concerns of potential genotoxic impurities [redacted] for the drug substance, [redacted]

Based upon stability data in the DMF, the DMF Holder assigned a retest period [redacted] for Nalmefene Hydrochloride stored [redacted] in the proposed container closure system.

List Submissions being assessed (*Table*):

Document(s) Assessed	Date Received
Original NDA_SD 01	07-FEB-2024

Highlight Key Issues from Last Cycle and Their Resolution:
N/A

Concise Description of Outstanding Issues (*List bullet points with key information and update as needed*):
None

Their summary regarding the drug product is reproduced below:

Assessment Recommendation: *Adequate* ***With PMC***

Nalmefene Hydrochloride Injection, Auto-Injector, 1.5 mg (NAI) has been developed as a sterile, nonpyrogenic solution to be administered as a single-dose injection for intramuscular (IM) or subcutaneous (SC) delivery. NAI has a rapid onset of therapeutic effect and is suitable to be used by non-medically trained responders.

The intended regulatory pathway for NAI is via the 505(b)(2) route using the FDA's assessment of safety and efficacy of Revex® (Nalmefene Hydrochloride Injection 1.0 mg base/mL) as the listed drug (LD) for which the Sponsor does not have a right of reference.

A quality target product profile (QTPP) was defined based on the properties of the drug substance, intended route of administration, patient population, and product performance expectations. The release specifications of the drug product have been adequately controlled as per USP General Chapters, ICH guidelines and in-house data trend. The specification of the

release batches meet the specification. The impurities were adequately justified either by ICH Q3B (R2) or inhouse toxicity studies.

The product contact components of the primary packaging comply with USP requirements. The applicant has also performed extractables and leachables studies to further verify the suitability. The extractables studies were guided with an acceptable analytical evaluation threshold (AET) based on a SCT of 5 mcg/day, a maximum daily dose (2 x 0.5 mL) and a 50% uncertainty factor.

The extractables studies are acceptable in terms of solvents (aqueous buffer to bracket the pH 3-10), and 50% IPA (simulate the worst case scenario), extraction technique and extraction temperature, extraction duration (refluxing for 24 hours), analytical method sensitivity (LOQ < AET), but not for the sample preparation (i.e. not cut into pieces). The extractables studies results are also not convincing. Multiple semi-volatile extractables were found from the parts of the glass barrel with needle. It is unusual to see these extractables coming from glass. Additionally very few nonvolatiles were found in the rubber stoppers. Therefore, the extractables studies need to be re-run as recommended. In addition, no leachables data from earlier time points (3, 6, 9 month) were provided. The 12, 24 month leachables data cannot provide the leachables trend throughout the shelf-life. Therefore, leachables studies at earlier, middle and late time points should also be re-done based on the updated extractables studies via validated methods to catch the leachables trend throughout the shelf-life. In light of the overall leachables risk is not high because all the leachables from 0, 12 and 24 month time points are lower than the AET. **Therefore, a post market commitment (PMC) is issued to ensure that any residual risk has been mitigated**.

The stability specifications are slightly wider than those of the release specifications in terms of the acceptance criterion of assay, pH, and specified impurity [redacted] (b) (4), total impurity. Stability studies are being conducted on the prefilled syringe (PFS) and the assembled Nalmefene Auto-Injector (NAI) using both horizontal (the worst case scenario) and needle-tip up (inverted) storage orientations under Long term 25°C ± 2°C / 60%RH ± 5%RH, intermediate 30°C ± 2°C /75%RH ± 5%RH and accelerated condition 40°C ± 2°C /75%RH ± 5%RH per ICH Q1A(R2). Six (6) month accelerated stability data, up to 30 month long term stability data for PFS and 12 month long term stability data for assembled auto-injector are available. All the data are well within specification in both the horizontal and inverted configuration. Twelve (12) months of stability data for Nalmefene Hydrochloride Injection Auto-Injector, 1.5 mg, from the 25°C/60%RH storage condition and 6 months of accelerated stability data from storage at 40°C/75%RH support a proposed **shelf-life of 24 months** when stored at 20°C to 25°C (68°F to 77°F) (Controlled Room Temperature) per ICH Q1E.

Overall, this NDA is deemed adequate from a CMC drug product perspective, with a PMC listed below.

The outstanding issue that could be addressed with a PMC is reproduced below:

The extractables studies were not appropriately designed to produce a complete extractables profile, but the overall leachables risk is not high because all the leachables from 0, 12 and 24 month time points are lower than the AET, a post market commitment (PMC) is issued to ensure that any residual risk has been mitigated. In addition, applicant needs to address some flaws of the HPLC method validation for identification, assay and impurities.

PMC

1. We note that only three (3) non-volatile, but no volatile or semi-volatile extractables [redacted] (b) (4) were observed in the extractables studies, while multiple semi-volatile extractables are noted [redacted] (b) (4). It is unusual to see these extractables [redacted] (b) (4). Therefore, your extractables

studies may not be appropriately designed to produce a complete extractables profile to guide leachables studies.

In order to obtain a complete extractables profile, re-run the extractables studies in 5% IPA, 50% IPA, pH 3 and 9 buffer solutions and reflux the samples in each media for 12-24 hours to achieve an equilibrium. We recommend that you size the components or materials (for example, by cutting the samples to smaller pieces, or grinding them) to increase the surface area and extraction stoichiometry before extraction. Ensure all the limits of quantitation (LOQs) of the reference standards are at or lower than the analytical evaluation threshold (AET). In addition, at least a confident level of structural identification should be achieved if a confirmation level is not possible as defined in USP <1663>.

2. Re-do the leachables studies based on the revised extractables study results. To mitigate the interference from the drug product matrix or from low response or low recovery of the compound from the drug product matrix, the leachables method should be fully validated. If full validation of the leachables methods for all the extractables over AET observed in the extractables studies is not possible or feasible, multiple representative compounds (≥3) from each chemical class (i.e., antioxidants, plasticizers, curing agents, additive degradants, and fatty acids) for volatile, semivolatile and non-volatile extractables, should be chosen for method validation. Ensure all the limits of quantitation (LOQs) of the reference standards are at or lower than the analytical evaluation threshold (AET).

   In the IND 137597 EOP2 meeting dated 5/25/2023, Agency recommended, “Evaluate at least three batches of your to-be-marketed drug product for leachables and include assessments at each timepoint over the course of your stability studies in order to identify trends in leachable levels over time (including early middle, and late time points). The materials tested should include any secondary container closure systems, if present, and be subjected to the same sterilization methods, as appropriate. These data are essential to determine the appropriate shelf life of your product”. Therefore, your proposal to do leachables testing [redacted] (b) (4) is not sufficient to obtain a trend of leachables throughout the shelf-lifeof the product. Provide leachables study results for the first 3 commercial batches manufactured for the assembled auto injector under accelerated and long term conditions following ICH Q1A time points (i.e. 0, 3, 6 for accelerated studies and 0, 3, 6, 9, 12, etc. for long term stability studies) with validated analytical methods.

3. We acknowledge Method Validation Report for Identification, Assay and Impurities of Nalmefene in Nalmefene Hydrochloride Injection in Prefilled Syringe or Autoinjector, 1.5 mg/0.5 mL by High Performance Liquid Chromatography (HPLC) (DOC No.: [redacted] (b) (4)-REP-2481), we note Table 4 Assay Level Linearity/Accuracy Solutions Results. Per FDA guidance “Validation of Chromatographic Methods” available at: https://www.fda.gov/regulatory-information/search-fda-guidancedocuments/ reviewer-guidance-validation-chromatographic-methods, provide accuracy data in triplicate.

There were no outstanding issues regarding the manufacturing facilities or sterility assurance that would preclude approval.

I concur with the OPQ review team that the Applicant has submitted adequate information to support approval of this application, with the PMC as noted above.

4. Nonclinical Pharmacology/Toxicology

In their review, Drs. Zhang, Woo, and Mellon noted the following in their discussion of the nonclinical findings:

> In support of the nalmefene autoinjector, the Applicant submitted several nonclinical toxicology studies that evaluated the safety of the higher nalmefene concentration and MgCl2 excipient, as well as qualify a drug product degradant specification. The Applicant is seeking approval for an adult and pediatric population, 12 years and older. The Applicant has committed to conducting two juvenile animal studies (JAS), as PREA PMRs.
>
> The Applicant's specifications for the drug substance/drug product impurity and residual solvents are deemed acceptable. The drug substance specification (b) (4), exceeds ICH Q3A(R2) recommended qualification threshold but is qualified by the 14-day repeat-dose and local tolerance studies that evaluated nalmefene, which contained supportive (b) (4) impurity levels. The drug product stability specification (b) (4) exceeds the ICH Q3B(R2) recommended qualification threshold. The Applicant submitted a 14-day IV rat study, local tolerance IM/SC rabbit study, and a (Q)SAR assessment, which were reviewed and adequately qualifies the proposed specification (b) (4). All analyzed elemental impurities are within respective parenteral PDEs recommended in ICH Q3D.
>
> To support safety of the container closure system, the Applicant submitted an extractables/leachables assessment. Issues have been identified by the CMC review team regarding the extractables and leachables data. However, given there are no leachable compounds identified above the 5 mcg/day threshold, components of the autoinjector have been used in other FDA approved products, and that this product is for a life-saving indication, the identified issues do not preclude approval and will be addressed through postmarketing commitment (PMC) studies.
>
> Systemic and local toxicity of the drug product were evaluated in two GLP 14-day repeat-dose general toxicology studies in rats and dogs with IM administration route and in local tolerance studies in rats and rabbits with IM or SC administration route. These studies were conducted to support the higher nalmefene concentration and the levels of MgCl2 as this excipient. is not currently in any FDA approved IM/SC products.
>
> In the 14-day repeat-dose toxicity studies, animals received daily IM injections of nalmefene or the vehicle of MgCl2 (0.94%). There were no test article-related adverse systemic effects observed at high exposure multiples compared to the human nalmefene exposure after administration of two doses (see Table 22 for exposure multiples). Test article-related local effects were observed at the IM dosing site, including minimal to mild edema, fibrosis and hemorrhage; minimal to marked myofiber necrosis and associated minimal to moderate inflammatory changes (mixed cell and/or macrophages). Minimal to mild local effects were generally observed in the vehicle (0.94% MgCl2) and the low dose-treated group with similar incidence, but there was a dose-related increase in incidence and severity at the mid-dose and the high dose groups. The local findings at the mid-dose and the high dose of nalmefene were considered exacerbation of vehicle/procedure-related local toxicity. By Day 29, the local changes observed on Day 15 had partially or completely resolved. It is noted that these repeat-dose studies characterized the exaggerated local toxicity profiles given that the nalmefene autoinjector is intended for single acute use.
>
> The local safety of the drug product was primarily characterized in acute local tolerance studies. In these studies that included a 14-day recovery period, rats or rabbits received a single IM or SC administration of saline, several doses of MgCl2 alone or combination of MgCl2 and nalmefene. In the local tolerance rat study, minimal to moderate local effects

including necrosis, inflammation and hemorrhage were observed at the IM or SC injection site across all groups. Recovery of the local effects were observed on Day 15. Test article-related minimal to mild local effects were observed at nalmefene concentrations up to 5.2 times and 2.6 times the clinical nalmefene concentration, respectively; and up to 2.8 times and 5 times the clinical MgCl2 concentration, respectively. In the local tolerance rabbit study, minimal to mild local effects were observed at the IM or SC dosing site in all treatment groups with nalmefene or MgCl2 concentration up to 2.5 times the corresponding clinical concentration. These local effects were considered procedure related as opposed to MgCl2 or nalmefene related, given that the local findings are commonly seen secondary to injection procedures, lacked a dose-response in incidence and severity, and occurred at similar incidence and severity across all treatment groups (including the saline group).

Taken together, the submitted pivotal nonclinical studies described above have adequately characterized the local and systemic safety of the nalmefene auto-injector.

For additional details, please refer to their review. Their final recommendation was for approval of the application with the following postmarketing requirement (PMR) studies:

The following juvenile animal studies are recommended as a PREA PMRs to support the clinical pediatric study outlined in the agreed Pediatric Study Plan (PSP).

- Conduct juvenile animal studies in rats to support the initiation of clinical studies in pediatric patients from (b) (4) to less than 12 years of age. This study will evaluate the effect of the drug on growth and development, specifically reproductive performance/sexual maturation and central nervous system histopathology and long-term behavioral effects.

- • Conduct (b) (4) study in juvenile rats (b) (4) (b) (4) This study will evaluate the effect of the drug on neuroapoptosis and central nervous system histopathology (b) (4) (b) (4).

I concur with the pharmacology toxicology review team that this can be approved at this time with the PMR studies as described above.

5. Clinical Pharmacology

The summary of the clinical pharmacology team's assessment of the application is reproduced below.

2.1 Pharmacology and Clinical Pharmacokinetics

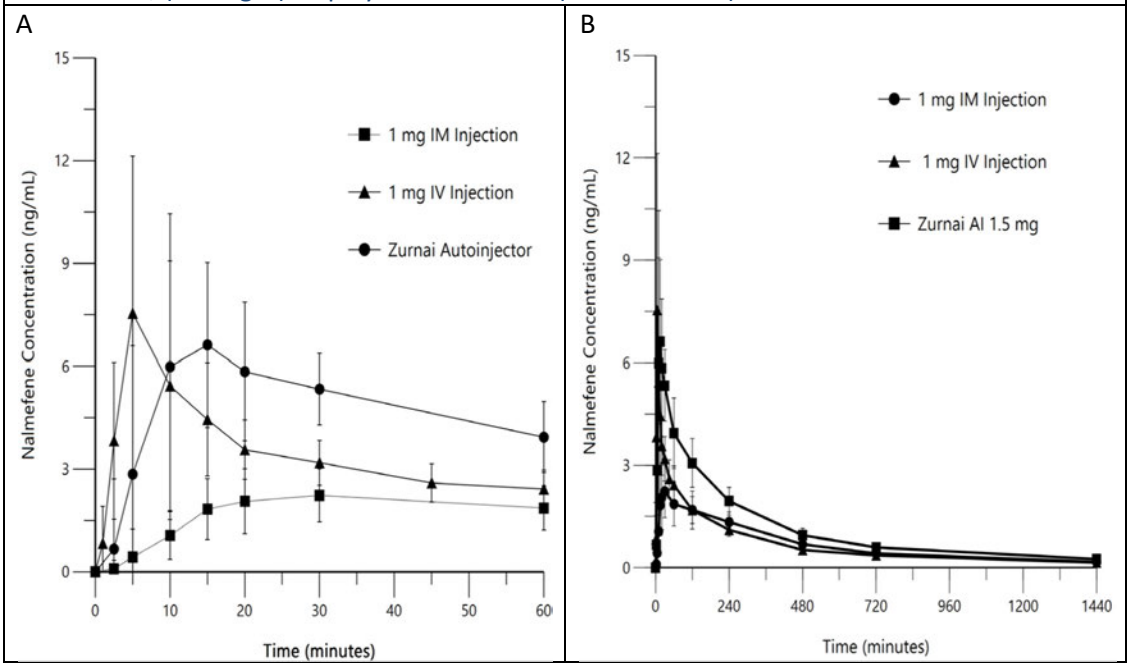
This is a 505(b)(2) NDA application for Zurnai Autoinjector, which relies on the previous Agency findings of safety and efficacy for the reference listed drug REVEX (nalmefene hydrochloride injection), NDA 020459. Zurnai (b) (4) is the brand name for the nalmefene hydrochloride (HCl) intramuscular (IM) autoinjector that delivers 1.5 mg nalmefene base which is equivalent to 1.7 mg nalmefene HCL in 0.5 mL solution. REVEX, nalmefene HCl injection, is indicated for the complete or partial reversal of opioid drug effects, including respiratory depression, induced by either natural or synthetic opioids. REVEX is also indicated in the management of known or suspected opioid overdose. The pharmacokinetics (PK) and pharmacodynamics (PD) of Zurnai Autoinjector following IM

administration have been characterized in one relative bioavailability study (NAL1005) and one pharmacokinetic-pharmacodynamic (PK-PD) study (NAL1004) as well as a population PK report investigating the effect of body weight and height effect on PK of Zurnai. Additional dose-selection studies (NAL1002 and NAL1003) and simulations of multiple dose administrations were also submitted to the NDA.

Mechanism of Action: Nalmefene is a well-known opioid antagonist that binds to opioid receptors and prevents or reverses the effects of opioids, including respiratory depression, sedation, and hypotension.

Summary of Pharmacokinetics of Zurnai: Following single IM dose administration of Zurnai Autoinjector, quantifiable plasma nalmefene levels were observed at the first time point of blood collection at 2.5 minutes (**Figure 1**).

Figure 1: Pharmacokinetics of nalmefene (mean ± SD) following Zurnai Autoinjector administration from relative bioavailability study NAL1005 (A – Left) truncated to the first 60 minutes; (B – Right) displayed to 24 hours (1440 minutes).



Plasma levels of single IM injection of Zurnai were higher at all time points compared to 1 mg IM injection of nalmefene (generic nalmefene injection ANDA 212955) in healthy volunteers (n=24). In addition, the applicant evaluated PK of 1 mg nalmefene HCl following intravenous administration (generic nalmefene injection ANDA 212955) in a subset (n=12) of the healthy volunteers. Dose-normalized peak plasma levels (Cmax) of nalmefene Zurnai Autoinjector were higher compared to IM injection and lower compared to IV bolus in study NAL1005 (See **Table 2** and **Table 3**). Based on dose-normalized area under the curve to infinity (AUCinf), bioavailability of Zurnai Autoinjector was 113% relative to IM injection and 115% relative to IV bolus of nalmefene (See **Table 2** and **Table 3**).

It is anticipated that if the patient does not respond to the first dose, opioid overdose reversal products may be administered repeatedly until emergency services arrive. The applicant

conducted pharmacokinetic simulations of various scenarios comparing exposure (Cmax and AUC) following repeat dose administration of Zurnai autoinjector, IM injection of nalmefene or IV bolus of nalmefene. Based on Revex injection (NDA 20459) label, nalmefene exhibited dose proportional pharmacokinetics following intravenous administration of 0.5 mg to 2.0 mg. Kaplan J.L. et al., (1999) evaluated safety of up to four doses of nalmefene following 1 mg and 2 mg IV injections administered every five minutes. Since the Kaplan 1999 publication did not evaluate pharmacokinetics, the pharmacokinetic simulations helped provide an understanding of the bracket for safety. As described in section 4.4.3, many scenarios of repeated dose administration were simulated; however, PK parameters from one pertinent scenario are presented in the **Table 1** below. The PK data from repeat dose simulations suggests that following administration of two doses of Zurnai Autoinjector administered 2 minutes apart, the systemic exposure (both Cmax and AUC) will be below two doses of 2 mg IV administered 5 minutes apart.

Table 1: Mean ± SD systemic exposure of nalmefene simulated with Zurnai autoinjector and nalmefene 2 mg IV injection.

Parameter	Zurnai Autoinjector 1.5 mg Observed Single Dose	Nalmefene IM Injection 1 mg Observed Single Dose	Nalmefene IV Injection 1 mg Observed Single Dose	Zurnai Autoinjector 1.5 mg Simulated Repeat doses 2-minute interval			Nalmefene 2mg IV Bolus (Kaplan 1999) Simulated Repeat doses 5-minute interval		
				2 doses	3 doses	4 doses	2 doses	3 doses	4 doses
Cmax (ng/mL)	8.14 ± 3.86	2.51 ± 0.82	7.81 ± 4.35	15.5 ± 6.9	22.3 ± 9.34	28.62 ± 11.5	26.5 ± 15.3	35.6 ± 18.1	42.6 ± 19.1
AUCt (ng.hr/mL)	28.76 ± 4.99	16.46 ± 3.66	16.42 ± 2.46	60.1 ± 9.4	90.2 ± 14.1	120.3 ± 18.8	65.7 ± 10.1	98.5 ± 15.1	131.3 ±20.1
AUC0-∞ (ng.hr/mL)	30.91 ± 4.95	18.37 ± 3.86	18.42 ± 2.82	61.9 ±10.3	92.9 ± 15.4	123.91 ± 20.6	71.3 ± 11	107 ± 16.5	142.6 ± 22

Source: Adapted from Table 20 from repeated dose simulations report. Data is Arithmetic Mean ± Standard deviation.

Pharmacodynamics: Onset of reversal of fentanyl-induced respiratory depression with Zurnai Autoinjector was observed within 2.5 to 5 minutes in the experimental clinical pharmacology study NAL1004 conducted in opioid-experienced, non-dependent healthy volunteers. Naloxone (Narcan nasal spray) was included as a positive-control or validity measure. Maximum reversal effect of nalmefene in reversing respiratory depression was noted in 15 minutes. OCP's independent modeling & simulation using a previously developed systems pharmacology model further support the applicant's claim that nalmefene IM 1.5 mg has an onset of action at least as fast as naloxone IN 4 mg which is an approved opioid antagonist formulation for reversal of opioid overdose in a community setting.

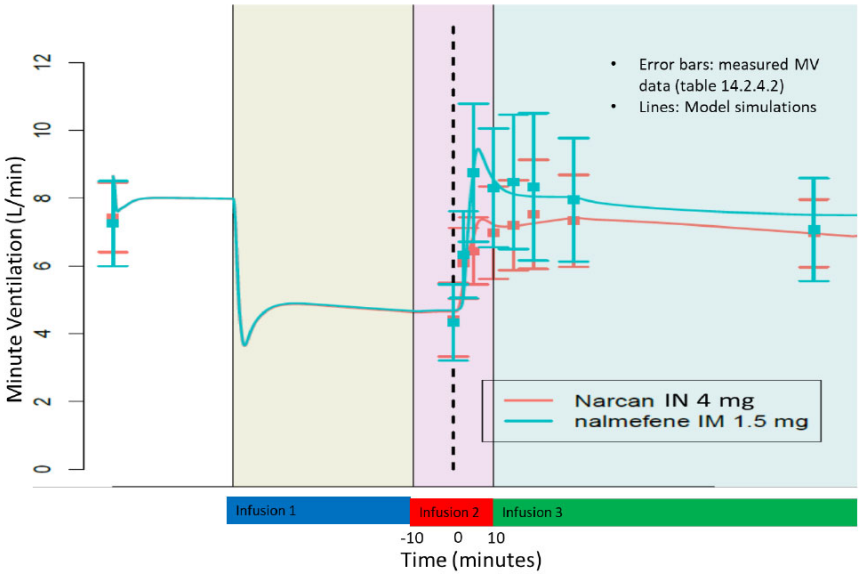


Figure 2: Comparison of the pharmacologic effects on minute ventilation (MV) from nalmefene IM 1.5 mg and naloxone IN 4 mg in NAL1004.

Error bars: mean and standard deviation of minute ventilation in the naloxone IN 4 mg group (red) and nalmefene IM 1.5 mg group (blue) from the study NAL1004. Solid lines: OCP systems pharmacology model simulation of a typical subject. During "infusion 1", fentanyl IV infusion was started at a rate of 5 mcg/min and was stopped when there was a 50% decrease in MV for the individual subject. The duration of infusion 1 was adjusted for each individual subject. After "infusion 1", "infusion 2" started at a rate lower than infusion 1. The rate for fentanyl infusion in "infusion 2" was calculated according to the Applicant's prespecified table so that the predicted plasma concentration of fentanyl at the end of infusion 1 would be maintained during the course of infusion 2. During the study, subjects were breathing air with supplemental oxygen at a rate of at least 2 L/min. Ten minutes after the initiation of infusion 2, IM nalmefene 1.5 mg (blue) or IN naloxone 4 mg (red) was administered (reported as time 0 in the **Figure 2**), leading to a recovery (increase) of MV. Twenty minutes after the initiation of "infusion 2", the fentanyl infusion at the "infusion 2" rate was stopped and "infusion 3" initiated, which had an even lower infusion rate according to the Applicant's prespecified dosing table (not shown in this review).

OCP's evaluation also supports that the proposed dose of 1.5 mg nalmefene IM may not require titration or re-administration to significantly decrease the incidence of opioid-associated cardiac arrest or brain hypoxia in a community setting, as long as the 1st dose of nalmefene is administered early enough (See DARS review appended in 4.3 DARS review:).

Zurnai Autoinjector was not evaluated in any specific populations. Considering the acute course of therapy, no dosage adjustment is needed elderly, renal impairment patients, or hepatic impairment patients. The basis for the recommendation is reliance on label for nalmefene injection. Based on population PK simulations, 12- to 17-year-old virtual subjects with a median weight of 62 kg are expected to have 8% to 27% higher Cmax and 4% to 15% higher AUC0-inf. Such anticipated exposures may not adversely affect safety while providing effective plasma nalmefene concentrations and hence Zurnai Autoinjector can be administered in adolescent patients without dose adjustment.

As noted above, the Division of Applied Regulatory Science within the Office of Clinical Pharmacology conducted a modeling and simulation exercise to evaluate the onset of action of intramuscularly administered nalmefene IM to intranasal administration of naloxone.

Their conclusions were noted as follows in their review:

> OCP's conducted independent modeling & simulation using a previously developed systems pharmacology model to evaluate the onset of action of nalmefene IM 1.5 mg compared to naloxone IN 4 mg. The analyses support that the onset of action for nalmefene IM 1.5 mg was at least as rapid as naloxone IN 4 mg, supporting that this nalmefene product is also appropriate for use in a community setting. OCP's evaluation also supports that the proposed dose of 1.5 mg nalmefene hydrochloride IM is unlikely to require titration or re-administration to decrease the incidence of opioid-associated cardiac arrest or brain hypoxia in a community setting, as long as the 1st dose of nalmefene was administered soon enough.

I concur with the conclusions and recommendations of the clinical pharmacology review team.

6. Clinical Microbiology

The proposed product is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

7. Clinical/Statistical- Efficacy

The Applicant did not conduct any clinical trials to support the efficacy of their product. As a 5050(b)(2) application, the Applicant is relying on the FDA's finding of efficacy for the listed drug, Revex (NDA 20459)

8. Safety

The Applicant is relying on the FDA's finding of safety for the listed drug, Revex (nalmefene hydrochloride injection; NDA 020459). However, the Applicant submitted the clinical safety data from the clinical pharmacology studies that were supporting this application, Study NAL 1004 and Study NAL 1005.

The number of subjects exposed to the to-be-marketed product in these two studies is summarized in the following table, reproduced from Summary of Clinical Safety.

	NAL1004	**NAL1005**			**Pooled**	
	Fentanyl/ NAI 1.5 mg IM	NAI 1.5 mg IM	Nalmefene HCl 1.0 mg IM	Nalmefene 1.0 mg IV Bolus	Pooled NAI 1.5 mg IM	Pooled Nalmefene
N	23	21	24	12	44	47

Dr. Dezman's assessment of the safety is summarized in the Integrated Assessment of Safety section of his review, reproduced below.

> The Applicant has submitted safety data from their pharmacokinetic study, their pharmacodynamic study, the results of a computer model extrapolating the effects of their product from adults to those down to 12 years of age, and a review of the literature in support of the safety of ZURNAI. This data was reviewed from February 2024 to July 2024.
>
> The safety for this product is based on the agency's prior findings for REVEX (nalmefene hydrochloride) solution for injection. The PK data showed the systemic exposure level of ZURNAI (1.5 mg nalmefene hydrochloride in 0.5 ml for injection IM/SC) is higher than the reference product, 1.0 mg REVEX (nalmefene hydrochloride, NDA 16636) administered IM/SC. Within the limits of cross-study comparisons, the PK of ZURNAI seems to approximate those of 1.0 mg REVEX administered IV. (b) (4) (b) (4) (b) (4). The Applicant also submitted data from the literature to support the safety of the systemic exposure observed with ZURNAI, including several studies to support the safety of higher doses of nalmefene hydrochloride than observed in the current submission.
>
> We reviewed the NDAs of other recent opioid reversal products while preparing this review, both those containing nalmefene hydrochloride (OPVEE [NDA 217470], REVEX [NDA 20459]) and those relying upon naloxone hydrochloride (NARCAN [NDA 208411], KLOXXADO [NDA 212045], REVIVE [NDA 217722], REZENOPY [NDA 215487], and (b) (4)). Allowing for differences in the dose of the active substance, the incidence, types, and severity of AEs documented in those applications were similar those seen in the current application. Consistent with the current application, a minority of subjects in those applications experienced symptoms including, but not limited to, nausea, vomiting, headache, dizziness, and flushing, all of which were recorded as mild and short-lived. Based on the bridging study and the literature review included in the submission, we believe the proposed product would be safe at reversing an opioid overdose in healthy individuals.
>
> The safety of safety of ZURNAI in persons who are physically dependent on opioids is less clear. Limited clinical trial data [12] from emergency department patients suffering from presumed opioid overdose suggests there is similar efficacy and safety between 1.0 mg REVEX IV, 2.0 mg REVEX IV, or 2 mg naloxone hydrochloride IV when used for their approved indication. Extrapolating this evidence to the current application, ZURNAI would be expected to precipitate withdrawal in opioid dependent persons at a rate comparable to existing approved naloxone hydrochloride products. Well controlled trials in the future may provide further insight.
>
> The post-marketing experience of nalmefene hydrochloride is limited, making it difficult to gauge the likelihood of severe complications like noncardiogenic pulmonary edema. Extrapolating from the naloxone hydrochloride experience, we expect the incidence of noncardiogenic pulmonary edema to low and related to the amount of drug administered.
>
> Additionally, OPVEE nasal spray (2.7 mg of nalmefene hydrochloride) has higher pharmacokinetic parameters than ZURNAI and OPVEE was found to be safe and effective in 2023.[11]
>
> In aggregate, these potential safety concerns are outweighed by several factors: the benefit of reversing a life-threatening opioid overdose, ensuring that a diverse array of reversal drug products with multiple routes of administration is available to the public, and the general population health benefit of increasing access to additional opioid overdose products.

I concur with Dr. Dezman's assessment. For additional details, please refer to his review.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application as there were no issues in this application that required presentation or discussion at an advisory committee meeting.

10. Pediatrics

As noted in Dr. Dezman's review, the Applicant provided simulation data that demonstrated that the pharmacokinetics of nalmefene hydrochloride could be extrapolated down to 12 years of age. The Division had previously advised the Applicant that efficacy cannot be extrapolated for subjects under 12 years of age and that additional PK, safety, and efficacy data would be needed to support an indication in < 12 years old. Moreover, nonclinical PK and repeat dose toxicity studies will need to be completed prior to initiation of clinical studies in < 12 years old.

In consultation with the Pediatric Review Committee (PeRC), the Division agreed to the initial pediatric study plan that was submitted with this application.

11. Other Relevant Regulatory Issues

Review of the device

The Executive Summary and recommendations from the CDRH review team indicate that the application can be approved with a PMC is noted below. The summary table below is reproduced from the CDRH team's review:

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	X			
Labeling	X			
Design Controls	X			
Risk Analysis	X			
Design Verification	X			Design verification is extensively documented. Cap removal torque reliability data indicates that the manufacturing process for this device component is poorly controlled, although all samples tested are well within the specification.
Consultant Discipline Reviews			X	No consults issued.
Clinical Validation			X	Deferred to CDER
Human Factors Validation			X	Deferred to CDER/DMEPA
Facilities & Quality Systems	X			

The following comment was provided by the CDRH review team regarding one of the essential performance requirements (EPRs):

> Reliability testing data indicates that cap removal torque is significantly different (b) (4) (b) (4) Because pooling data from different (b) (4) produces non-normal distributions, tolerance intervals cannot be computed using routine statistical analysis from pooled samples. The sponsor has segregated data (b) (4) for analysis to demonstrate reliability. For cap removal torque, the control strategy includes variable testing on release for (b) (4) and the final finished combination product. This testing data should also be analyzed per (b) (4) (b) (4) to ensure that the reliability specification for this EPR is maintained.

The CDRH review team did not identify any outstanding deficiencies that would preclude approval of the application, they did have the following recommended postmarketing requirement:

> Stability testing documents indicate that the 24 month real-time aging study should have been completed on July 5, 2024. Provide completed test reports for device EPRs for review by October 5, 2024. Please analyze cap removal torque test results (b) (4) .

12. Labeling

Consultation was obtained from the Division of Medication Error Prevention and Analysis (DMEPA) and their comments regarding labeling were conveyed to the Applicant.

13. Postmarketing Requirements

The Applicant has agreed to the following six post-marketing requirements and commitments.

4665-1 Conduct a clinical pharmacokinetic, pharmacodynamic, and safety study of Zurnai in pediatric patients aged birth to less than 12 years of age.

The timetable you submitted on August 1, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	07/2025
Final Protocol Submission:	12/2025
Study Completion:	10/2028
Final Report Submission:	04/2029

4665-2 Conduct a juvenile animal study in rats to support the initiation of clinical studies in pediatric patients from 3 years to less than 12 years of age. This study will evaluate the effect of the drug on growth and development, specifically reproductive performance/sexual maturation and central nervous system histopathology and long-term behavioral effects.

The timetable you submitted on August 1, 2024, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/2024 (Submitted)
Study Completion:	03/2025
Final Report Submission:	09/2025

4665-3 Conduct a juvenile animal study in rats to support the initiation of clinical studies in pediatric patients from birth to less than 3 years of age. This study

will evaluate the effect of the drug on development, specifically neuroapoptosis and central nervous system histopathology.

The timetable you submitted on August 1, 2024, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/2024 (Submitted)
Study Completion:	03/2025
Final Report Submission:	09/2025

4665-4 Conduct a 24-month real-time aging study which includes an analysis of cap removal torque test results (b) (4) , and provide completed test reports for device Essential Performance Requirements (EPRs).

The timetable you submitted on August 1, 2024, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	02/2024 (Submitted)
Study Completion:	08/2024
Final Report Submission:	10/2024

4665-5 Conduct a study or studies to detect any non-volatile, semi-volatile, or volatile extractables from the container closure used in this product; then, based on the revised results, repeat the leachable studies.

The timetable you submitted on July 22, 2024, states that you will conduct this study according to the following schedule:

Interim Report #1: 12/2025
(Extractables study and initial leachables timepoint)

Interim Report #2: 12/2026
(1-,3- and 6-month leachables timepoints)

Final report submission: 12/2027
(including 9- and 12-month leachables timepoints)

4665-6 Provide accuracy data in triplicate for the Identification, Assay and Impurities of Nalmefene analytical method per the FDA guidance for industry *Validation of Chromatographic Methods*[1] for nalmefene in nalmefene hydrochloride injection in prefilled syringe or autoinjector, 1.5 mg/0.5 mL by High Performance Liquid Chromatography (HPLC).

[1] https://www.fda.gov/media/75643/download

The timetable you submitted on July 22, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2025

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RIGOBERTO A ROCA
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