

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217470Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 19, 2023
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 217470
Product Name, Dosage Form, and Strength:	Opvee (nalmeфene) nasal spray, 2.7 mg
Applicant/Sponsor Name:	Opiant Pharmaceuticals Inc. (Opiant)
TTT ID #:	2022-2538-2 and 2022-2888-1
DMEPA 1 Human Factors Safety Evaluator:	Avani Bhalodia, PharmD, BCPS
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD
DMEPA 1 Human Factors Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label, blister labeling, carton labeling, Quick Start Guide (QSG), and instructions for use (IFU) received on May 16, 2023 and May 18, 2023, for Opvee. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container label, blister labeling, carton labeling, QSG, and IFU for Opvee (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during our previous label and labeling and human factors study results reviews.^{ab}

^a Birkemeier, D. Label and Labeling Review for Opvee (NDA 217470). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 MAR 16. TTT ID No.: 2022-2538.

^b Bhalodia, A. Human Factors Study Report Review for Opvee (NDA 217470). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 MAY 05. TTT ID No.: 2022-2888.

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/

AVANI BHALODIA
05/19/2023 08:54:47 AM

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05/19/2023 09:35:08 AM

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05/19/2023 10:19:07 AM

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM

Date	5/10/2023		
To:	Sandy Truong		
Requesting Center/Office:	CDER/OND	Clinical Review Division:	Other
From	Porsche Bennett OPEQ/OHT3/DHT3C		
Through (Team)	Courtney Evans, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	NDA217470, (b)(4) (nalmeferene) nasal spray ICC2300074_ICC2201077 ICCR00893266 ICCR00886193		
Recommendation	Filing Recommendation Date: 1/10/2023 ☐ CDRH did not provide a Filing Recommendation ☒ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies Mid-Cycle Recommendation Date: 3/2/2023 ☐ CDRH did not provide a Mid-Cycle Recommendation ☒ CDRH has no approvability issues at this time. ☐ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A. Final Recommendation Date: 4/28/2023 ☒ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA217470
Sponsor	Opiant pharmaceuticals, Inc.
Drug/Biologic	(b) (4) (nalmefene) nasal spray
Indications for Use	For the complete or partial reversal of opioid drug effects, including respiratory depression, induced by either natural or synthetic opioids; In the emergency treatment of known or suspected opioid overdose; Not a substitute for emergency medical care
Device Constituent	Nasal Spray
Related Files	N/A

Review Team		
Lead Device Reviewer	Porsche Bennett	
Discipline Specific Consults	Reviewer Name (Center/Office/Division/Branch)	CON #
Biocompatibility	Papatya Kaner	CON230925

Important Dates	
Discipline-Specific Review Memos Due	04/19/2023
Final Lead Device Review Memo Due	04/28/2023
Interim Due Dates	Meeting/Due Date
Filing	01/10/2023
Mid-Cycle	03/02/2023
Primary Review	04/28/2023

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

- ☐ Approvable – the device constituent of the combination product is approvable for the proposed indication.
☐ Approvable with PMC or PMR, [See Section 2.3](#)
☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, [see Section 2.2](#).

Section	Adequate			Reviewer <u>Notes</u>
	Yes	No	NA	
Device Description	X			
Labeling	X			
Design Controls	X			
Risk Analysis	X			
Design Verification	X			
Device Reliability	X			
Consultant Discipline Reviews	X			
Clinical Validation	X			
Human Factors Validation			X	
Facilities & Quality Systems	X			

2.1. **Comments to the Review Team**

- ☒ CDRH does not have any further comments to convey to the review team.
☐ CDRH has the following comments to convey to the review team:

2.2. **Complete Response Deficiencies**

- ☒ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.
☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. **Recommended Post-Market Commitments/Requirements**

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☒

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3. PURPOSE/BACKGROUND

3.1. Scope

Opiant pharmaceuticals, Inc. is requesting approval of (b) (4) (nalmefene) nasal spray. The device constituent of the combination product is a Nasal Spray.

CDER/OND has requested the following [consult](#) for review of the device constituent of the combination product:

Please review device facilities and see if inspections are needed.

Please review the reliability of the device function. Please also check if Applicant submitted irritation and sensitization endpoints. During the IND phase, we informed the Sponsor irritation and sensitization study needs to be submitted with the NDA.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following [review areas](#):

Device Performance and Shelf life
Device Biocompatibility
Device Reliability
Device Facilities Compliance

This review will not cover the following review areas:

Device Human Factors: Deferred to DMEPA
Drug Product: Deferred to CDER
Drug Substance: Deferred to CDER
Overall Labeling Adequacy: Deferred to CDER

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. [Prior Interactions](#)

IND136851: Pre-NDA (Excerpts for all device related comments provided in meetings have been included below). Refer to Module 1.6.3 Correspondence regarding meetings for complete meeting minutes.

Type B, PIND Meeting (February 8, 2018, 3:30 p.m. (Eastern))

As indicated at the meeting, advice from the CDRH, Office of Compliance (OC), Division of Manufacturing and Quality (DMQ) would follow in a post-meeting note (below in bold font).

*****Post-Meeting Note**

Combination products are subject to the current good manufacturing practices (CGMP) requirements applicable to each constituent part (drug, device, biological product) of the combination product. However, as reflected in the final rule on CGMPs for combination products (21 CFR Part 4), manufacturers have the option to demonstrate compliance both with the

drug CGMP regulations (21 CFR Parts 210, 211) and with the device quality system (QS) regulation (21 CFR Part 820) through a streamlined approach. If utilizing a streamlined approach, you must demonstrate compliance with either the drug CGMPs or the QS regulation in its entirety and also with those provisions specified in Part 4 from the other of these two sets of requirements. Alternatively, you may demonstrate compliance with both the drug CGMPs and QS regulation in their entirety (non-streamlined approach).

Further information on 21 CFR Part 4 is available at,
<https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products>.

Related final guidance is available at,
<http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm>.

Information to include in NDA Form 356h –

- List the manufacturing facilities for the combination product and its constituent parts and identify what activities occur at each site (e.g., assembly, filling, sterilization, packaging other) involving which constituent's parts (e.g., drug only, device only, both drug and device).
- For facilities that have manufacturing activities for both drug and device constituent parts, identify which CGMP operating system is being used at the site for the combination product (streamlined or non-streamlined) and if it is a streamlined system, whether it is a drug-CGMP-based or QS-regulation-based system.

Information to include in your application –

- If you are using a drug-CGMP-based system, you must demonstrate compliance with the following provisions from the QS regulation.
- Provide the following information in your marketing application with respect to these requirements. Review of this material will enable the Agency to determine whether inspection is needed with respect to these requirements and, if so, to enhance the efficiency of this inspection. Using the eCTD format, this information should be provided in Section 3.2.P.3. for all manufacturing facilities responsible for manufacturing the combination product or device constituent.
 - Management Responsibility (21 CFR 820.20)

product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4). Also, provide a description of the functions and responsibility of each facility involved in the manufacturing of the combination product and its constituent parts.

o **Design Control, General (21 CFR 820.30)**

Explain how you utilized the design control process to develop the combination product under review and provide a description of your design control procedures. The description must include how requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file are fulfilled. Provide a copy or a summary of the plan used to design the combination product.

o **Purchasing Controls (21 CFR 820.50)**

Provide a summary of the procedure(s) for purchasing controls. The summary should (a) describe your supplier evaluation process and describe how it will determine type and extent of control you will exercise over suppliers, (b) define how you maintain records of acceptable suppliers and how you address the purchasing data approval process, and (c) explain how you will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.

Explain how the procedure(s) will ensure that changes made by contractors/suppliers will not affect the final combination product. Provide a description of how you apply the purchasing controls to the suppliers/contractors used in the manufacturing of the combination product. (e.g., through supplier agreement).

o **Corrective and Preventive Action (21 CFR 820.100)**

Summarize the procedure(s) for your Corrective and Preventive Action (CAPA) System. Your CAPA system should require the following:

a. Identification of sources of quality data and analysis of

- a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products
-

- b. Investigation of nonconformities and their causes
- c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities
- d. Verification or validation of the actions taken

Clinical Questions

Question 5

Opiant plans to use the Aptar Unit Dose Sprayer (UDS), which is the same device used for Narcan Nasal Spray. Does the Agency agree that the Aptar UDS is an appropriate device for delivery of intranasal nalmefene as an emergency use product?

FDA Response

Yes, we agree that the Aptar UDS may be an appropriate device for delivery of intranasal nalmefene as an emergency use product.

Please see additional comments regarding device information and test requirements that should be included in your marketing application for your proposed combination product.

Devices

Provide the following information to support the device constituent parts of the combination product. We recommend that you refer to the eCTD Technical Conformance Guide published in September 2016, available at, <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissions/Requirements/ElectronicSubmissions/UCM465411.pdf>, when determining the location of the following information within your submission.

For more information regarding cGMP requirements for combination products please refer to the January 2017 FDA guidance for industry and FDA staff, *Current Good Manufacturing Practice Requirements for Combination Products*, available at, <https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf>.

Provide the following information to support the device constituent parts of the combination product:

- 1) A complete and detailed description of your device constituent design and delivery system, including any features and functionalities unique to your device. This should also include engineering drawings and detailed descriptions of the individual device constituent components.
- 2) Detailed descriptions of the principles of operation of your device, from beginning to end of the activation process, in which you explain the mechanical drug delivery mechanisms of your device constituent in order for it to achieve its intended use.
- 3) A complete and detailed device constituent design requirements and specifications document, including design inputs and outputs in accordance with 21 CFR 820.30 design controls. Ensure that you clearly describe the acceptability of your design control inputs within the context of the intended use of your combination product. Be sure to identify the essential performance requirements of your device. The essential performance requirements of any device constituent parts are the design outputs necessary for your device constituent to safely and effectively achieve the product's intended use. The essential performance requirements of the should be developed in accordance with the risk profile of the entire combination product and may vary depending on the indications for use, patient and/or user population, and design of the constituent parts of the combination product. Your design requirements and essential performance requirements should consider the desired level of reliability of the product and level of risk associated with failure to meet the essential performance requirements.

For nasal sprays we expect the essential performance requirements to include, at a minimum, the following:

- Pump Delivery (Spray Weight)
- Spray Pattern and Plume Geometry Shape
- Spray Content Uniformity (SCU)
- Droplet / Particle Size Distribution
- Activation Force

Refer to the July 2002, FDA guidance for industry, *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation*, available at, <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070575.pdf>, for more details.

- 4) **Design verification documentation.** Verification testing documentation may include summary test results of established test methods for the product (e.g., recognized consensus standards, FDA guidance, etc.) or complete verification test reports for unique or unrecognized test methods. All verification testing should be directly traced to the design requirements of the device. Ensure that you utilize test methods and preconditioning that simulate the intended use of your product. Conduct testing to verify the essential performance requirements of the combination product with the to-be-marketed version of the device constituent and the intended biologic/drug product; however, if you plan to rely on verification testing conducted with a different test fluid be sure to provide a scientific rationale for the acceptability of the test fluid as a surrogate for the intended biologic/drug product (i.e., fluid characteristics, viscosity, etc.). Valid justifications for any test results not being able to pass its acceptance criteria should be provided, if applicable. Furthermore, you

should utilize a sufficient number of device constituent test samples that will be statistically relevant for your performance testing.

- 5) **Design validation documentation.** Design validation documentation should be performed to ensure that the device constituent parts of the combination product meet the intended use of the combination product as a whole. Design validation documentation may be in the form of clinical studies with the to-be-marketed presentation of the device, bridging studies that successfully validate the to-be-marketed presentation of the device constituent through clinical and/or bench top studies of the essential performance requirements of the device constituent in the context of the intended use of the combination product, literature review regarding the use of the to-be-marketed device constituent presentation in the context of the intended use of the combination product, human factors studies, and/or simulated actual-use studies. We highly recommend that you conduct clinical studies with the to-be-marketed presentation of the combination product and capture any device constituent failures/malfunctions as part of the clinical study protocol in order to successfully validate the device constituent parts of the combination product.
- 6) **Provide a risk analysis associated with the final finished combination product** that is inclusive of risks associated with the device constituent parts of the combination product. Your risk analysis should include all identified risks, potential hazards that are apparent to your device, risk control measures and/or mitigation strategies, verification of risk control and/or mitigation measures, and the clinical acceptability of any residual risk associated with the device. Outline the methods in which you identified the risks of the product within your risk analysis documentation (e.g., DFMEA, UFMEA, Fault Tree Analysis).
- 7) **Biocompatibility evaluation.** Provide documentation to support the biocompatibility of your device constituent including test reports and protocols to ensure that the system components are biocompatible commensurate with the level and duration of patient contact. Refer to the June 2016 FDA guidance for industry, *Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process*, available at, <https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf> for more details.
- 8) **Stability and shelf-life testing.** Provide documentation that ensures the final finished combination product maintains its essential performance requirements up to the labeled date of expiry.

- 9) **Shipping studies.** Provide documentation that ensures that the final finished combination product maintains its essential performance requirements after actual or simulated shipping.
- 10) **Lot release specifications.** Provide the lot release specifications associated with the device constituents of the combination product, including all essential performance requirements.
- 11) We recommend that a traceability matrix is provided to ensure each design requirement has been adequately verified and validated. The following is an example traceability matrix for the essential performance requirements of the device constituent as a summary of the testing completed to support the device constituents of the combination product:

Essential Performance Requirement	Specification	Verification	Validation	Shelf Life / Stability (Y/N)	Shipping/ Transportation (Y/N)	Lot Release Testing (Y/N)
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- 12) As the owner of the combination product it is expected that you maintain the requirements for your product within your marketing application. If you intend to refer to documentation (e.g., verification testing) held within another submission and/or master file be sure to provide a letter of authorization or right of reference alongside a detailed description of the location of the information within the file (i.e., volume, page number, section header, etc.). We recommend that you provide a brief overview of how the referenced information is intended to support the review of your submission.
- 13) Given the intended use your proposed product (i.e., emergency use) we expect you to establish a clinically-based reliability specification (e.g. failure rate < 1/10,000) and verify this reliability through both design and manufacturing data analysis. We recommend that you utilize a fault tree analysis, or similar methodology, to identify all aspects of the design and manufacturing of the product that support the reliability specification and quantify the probability data to support the reliability specification. Previously conducted verification testing and/or validated manufacturing controls may be leveraged to support the reliability specification, if applicable. We recommend that you provide a draft reliability report for review that includes the following information:
- a) Establish reliability requirement(s) for the combination product and produce data which supports the combination product reliability as described in detail below:
- i) Establish a reliability requirement for your combination product. We recommend that reliability be directly specified as $R(t) = x\%$, where t = time and $x\%$ = probability of meeting requirement(s). For example,

R(24 months) = 99.99%. As an example of a reliability requirement, a failure of the device to activate/spray occurs when one or more functional failure modes result in the spray failing to initiate or failing to complete drug delivery when or as intended. Failure to activate/spray is one of the primary design input requirements that should be assessed for reliability. Other design input requirements may also be important to evaluate. The reliability requirement(s) should be objective and relate to the ability of a population of devices to function as intended after pre-conditioning to elements outlined within (iv), below. Verify the reliability requirement(s) with a high degree of statistical confidence (e.g., 95% confidence).

- ii) Provide rationale and justification supporting the clinical acceptability of the established reliability requirement(s) pass/fail criteria.
- iii) Collect data to support the reliability requirement(s) specified in (a) above. For reliability specification(s) that may require an unreasonably large quantity of samples to be tested as a simple one-time verification test, it is recommended that you develop a fault-tree analysis to support the established reliability specification(s). For example, for a specification surrounding a failure to activate/spray the basic events leading to these faults should be documented through a fault tree analysis and the probability data for each basic event should be included in the fault tree. Include an assessment of common cause failures, and the analysis should also consider whether or not assumptions of independence of events are supportable. If other tools are used to develop the reliability model, the submission should include an explanation of how the tool is used and its validity for supporting the reliability specification(s). Additionally, the basic events should be linked to appropriate design and/or manufacturing controls. Data linked to the fault tree basic events may be in the form of additional verification testing on finished products, verification testing on subcomponents/ subassemblies of the finished product, validation of manufacturing processes, etc. and should be conducted with a high degree of statistical confidence.
- iv) Devices assessed within reliability testing should be preconditioned to worst-case, reasonably foreseeable conditions. We have 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. Base your assessment of the preconditioning parameters on your own failure analyses (e.g., fault tree analysis) in order to assure that the scope of preconditions and their boundary values are adequately correct and complete.

- (1) Shipping
- (2) Aging
- (3) Storage orientation and conditions
- (4) Vibration handling
- (5) Shock handling (e.g., resistance to random impacts, such as being dropped).

- b) Devices assessed within reliability analyses should be activated under worst-case reasonably foreseeable conditions. We have conceived the following recommended circumstances of activation; however, provide rationale supporting the final circumstances of activation chosen.
- i) Activation orientation
 - ii) Environmental temperature
- c) Your reliability report should document the manufacturing controls implemented and explain how they are adequate to assure that the reliability specification for the released product is achieved and how they are being monitored on an ongoing basis to assure continuity of the reliability specifications. In particular, describe the following in your report:
- i) Describe the acceptance activities, including the specific product attributes that are evaluated, evaluation methods, and acceptability criteria. Describe the in-process control and release test sampling plan in detail to ensure that the reliability specification is maintained for each released lot. It is noted that these controls may be part of the data collection methods utilized for satisfying (a) above.
 - ii) Describe corrective and preventive action activities to assure that, among other possible sources of information, root cause analysis is conducted on failures occurring during lot release testing. Establish the action limits for significant increases in rejections of the product and its components due to particular incoming inspection, in-process control, or release test failures. The activities triggered by the exceeding an action limit should include, at a minimum, a root-cause investigation and an associated risk analysis of the failure. Update the process failure mode analysis with any newly discovered failure modes. If a newly discovered failure mode could reasonably decrease

released product reliability, then new lots should not be released until the failure mode has been adequately mitigated.

Human Factors

We understand that you are planning to use nalmeferene nasal spray to treat known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. However, you have not submitted a comprehensive risk analysis or your plans for a Human Factors (HF) validation study.

We recommend you conduct a comprehensive use-related risk analysis if you have not already completed one. The comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis) the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures.

If models of the same or similar combination products exist, your use-related risk analysis should incorporate applicable information on known use-related problems with those products. Useful information can be obtained from your own experience as well as from public sources such as literature, adverse event reports, and product safety communications (see draft guidance for industry *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development*).

Additionally, if models of the same or similar combination products exist, it may be useful to conduct comparative analyses such as a labeling comparison, a comparative task analysis, and a physical comparison between your proposed product and the comparator for the purposes of identifying what differences exist between the user interfaces and where the same or similar risks may apply to your proposed product.

Based on the aforementioned information and data, you should determine whether you need to perform a human factors (HF) validation study. If you determine that an HF validation study is not needed for your product, submit your risk analysis, comparative analyses, and justification for not conducting the HF validation study to the IND for our review. The Agency will notify you if we concur with your determination.

Type C Written Responses: 11/03/2021

Question 2a: Opiant is providing the proposed reliability study protocol, (b) (4)
(b) (4) The study is intended to demonstrate the reliability of the nalmeferene hydrochloride nasal spray that utilizes the Aptar unit dose device. Does the Agency agree with the design of the proposed reliability study as presented in the meeting package? Does the Agency agree with the proposed sample size?

FDA Response:

The important aspects of the reliability plan are the fault tree analysis, identification of essential performance requirements (EPR), and the total product lifecycle plan for maintaining product reliability. While your draft plan makes mention of a fault tree analysis and EPR, it does not include the fault tree, justification for included EPR, or a plan for maintaining total product lifecycle reliability. We recommend you update the reliability plan to address these items. Additionally, we recommend that the fault tree address successful spray as the top level goal and we recommend you modify the pump delivery specification to (b) (4) %.

Question 2b: Does the Agency agree with the proposed shipping and pre-conditioning scenarios?

FDA Response:

We have the following comments on your proposed shipping and preconditioning strategy:

- a. You have not addressed the need to sequentially precondition test samples prior to device performance testing. Since the product is intended for non-medically trained lay users, and the exposure of conditions is likely to be varied and sequential, we believe verifying performance of sequentially conditioned samples is warranted. You should consider the appropriate sequencing and test points and describe your rationale in your application.
- b. Your preconditioning plan should add product age as a precondition.
- c. Product orientation should be addressed in the device performance tests after preconditioning.
- d. Your test plan incorporates standards that are not FDA recognized. Your application should describe the appropriateness of these standards to demonstrate acceptable performance of the device.
- e. Drop testing should also be conducted on unpackaged devices.

Question 2c: Does the Agency agree with the proposed critical performance characteristics which will be determined at (b) (4)?

FDA Response:

You should provide data to support that (b) (4) is the optimal test distance.

Question 2d: Does the Agency agree that the critical performance characteristics and level of confidence are:

Successful activation: (b) (4) %
Delivered dose: (b) (4) %
Droplet size distribution including D50, D10, D90, % (b) (4)
Spray pattern including Dmax, Ovality: (b) (4) %
Actuation force: (b) (4) %

FDA Response:

We recommend that the fault tree analysis support (b) (4) % reliability for successful spray. The verification testing data reliability for successful activation, delivered dose, droplet size, spray pattern and actuation force data are adequate.

Question 2e: Does the Agency agree with the proposed sample size and specifications of the additional device characterization testing covering orientation performed in an upright position (0°) and at an incline (45°, 135° & 180°), plume geometry, photostability and temperature cycling.

FDA Response:

It appears that you are pooling the test samples for each endpoint. In order to do this, we recommend that you provide characterization studies confirming that orientation does not impact reliability of device performance, particularly on aged product.

We agree with use of ISO 16269, Statistical Interpretation of Data, Part 6 – Determination of Statistical Tolerance Intervals. The acceptability of individual test data will be a review issue.

Type B Meeting: March 30, 2022; 4:00 p.m. – 5:00 p.m. ET (TCON)

ADDITIONAL COMMENTS

Center for Devices and Radiological Health (CDRH)

1. We remind you of the agreement between the Division and Opiant to conduct biocompatibility testing for irritation and sensitization endpoints on the final finished device prior to submission of your NDA.

As noted in the Full Clinical Hold Letter issued on January 27, 2020.

(b) (4)

For additional details, refer to both the Full Clinical Hold Letter as well as the Type A Meeting Minutes issued on April 17, 2020.

Opiant's Pre-meeting comments:

The agreement to conduct (b) (4) prior to submission of the NDA was in relation to the (b) (4) device which is no longer being used. Opiant is now using the Aptar Unidose device which is currently used in several approved pharmaceutical products, including Narcan Nasal Spray. Opiant will have right of reference to the Aptar device DMF which contains the relative biocompatibility studies, and which will be included in the NDA. No further discussion is needed.

Discussion: No further discussion

3.2.1. Related Files

3.3. Indications for Use

Combination Product	Indications for Use
(b) (4) (nalmeferene) nasal spray	For the complete or partial reversal of opioid drug effects, including respiratory depression, induced by either natural or synthetic opioids; In the emergency treatment of known or suspected opioid overdose; Not a substitute for emergency medical care
Nasal Spray	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	Module(s)
0001-0029	1.1.2 FDA 356h
	1.4.1 Letter of Authorization
	1.4.2 Statement Right to Reference
	1.4.4 Cross reference
	1.6 Meetings
	1.14.1 Draft Labeling
	2.3.P- Manufacture
	2.3.P-Control of Drug Product
	2.3.P- Container Closure System
	2.3.P- Stability Drug Product

	2.3.P- Pharmaceutical Development
	3.2.P.2- Container Closure System
	3.2.P.8.1 Stability Summary and Conclusion
	3.2.P.8.2 Post-approval protocol and stability commitment
	3.2.P.8.3 Stability Data
0034	1.11.1 Quality Information Amendment
	3.2.P.2.3 Manufacturing Process Development
0034	3.2.P.2.4 Drug Product
0001	3.2.S.4.1 Specification
0001	3.2.P.7 Container Closure System
0001	3.2.P.3.4 Controls of Critical Steps and Intermediates 2.7mg
0001	3.2.P.5.1 Specifications 2.7mg

Note: Information taken verbatim from the submission has been included in *italics*.

4. DEVICE DESCRIPTION

4.1. Device Description

Nalmefene nasal spray is an aqueous solution in a single use container. The solution is clear and colorless to light yellow, which is filled into unit dose 400 µL (b) (4) glass vials closed with a black (b) (4) rubber stopper and then assembled into the Aptar Unidose Nasal Spray (UDS™) device. The device is a (b) (4) dispenser delivering a spray containing a unit dose of the active ingredient. Each delivered dose contains 2.7 mg nalmefene dispensed in a volume of 100 µL per actuation.

The primary container closure is a 400 µL (b) (4) glass vial closed with a black (b) (4) rubber stopper into which (b) (4) µL of the drug product solution is filled. The primary container closure is then assembled into the Aptar Unit Dose nasal Spray (UDS™) device, which consists of an actuator and container holder. After assembly, the UDS device is secondary packaged into individual single use blisters composed of (b) (4) (b) (4). After a single actuation, the unit dose system is then considered depleted and discarded. Two UDS devices are packaged in a carton. Detailed information on the primary and secondary container closure system is provided in Module 2, Section 2.3.P.7.

The proposed shelf life is 28 months.

Table 1: Primary Packaging Components

Component	Material	Component Manufacturer	DMF #
Rubber stopper			(b) (4)
Container / Vial			
Container Holder			
Actuator			

Figure 1: Unidose Device Description



4.2. Steps for Using the Device

1. Remove device from packaging
2. Hold nasal spray with two fingers, with thumb on actuator (plunger)
3. Tilt patient neck and head back
4. Insert nozzle into nostril
5. Push the plunger up until the plunger cannot compress anymore
6. Administer subsequent nasal spray doses as needed

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments The device constituent part of the combination product is the Aptar device that is commonly used among approved nasal spray combination products. The device description is adequate.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

5. FILING REVIEW

CDRH performed Filing Review	☒
CDRH was not consulted prior to the Filing Date; therefore, CDRH did not perform a Filing Review	☐

5.1. Filing Review Checklist

Filing Review Checklist			
Description	Present		
	Yes	No	N/A
Description of Device Constituent -2.3.P.7 Container closure system, sequence 001	X		
Device Constituent Labeling -1.14.1 Draft labeling (Device label, -1.14.1.3 Instructions for use	X		
Letters of Authorization -1.4.1 Letter of authorization for DMF (b) (4) -1.4.2 Statement right to reference for DMFs (b) (4)	X		
Essential Performance Requirements defined by the application Sponsor -2.3.P Control of Drug Product, Sequence 002	X		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor -2.3.P Drug Product- control of drug product, sequence 002 (Refer to IR1 dated 04/24/23 sent by CDER)	X		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	X		
Risk Analysis supplied in the NDA / BLA by the application Sponsor (Refer to IR2 dated 04/28/23)		X	

Traceability between Design Requirements, Risk Control Measures and V&V Activities (Refer to IRs 1 and 2 dated 05/03/23)			X	
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	X		
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)	X		
	Reliability (Refer to IR1 dated 04/28/23) -2.3.P.2 pharmaceutical development.	X		
	Biocompatibility -Papatya consulted: IR sent out and response determined to be sufficient for fileability. The sponsor plans to leverage biocompatibility data from a referenced DMF.	X		
	Sterility -Deferred to CDER			X
	Software			X
	Cybersecurity			X
	Electrical Safety			X
	EMC/RF Wireless			X
	MR Compatibility			X
	Human Factors -Deferred to DMEPA			X
	Shelf Life, Aging and Transportation -Stability 2.3.P Stability, sequence 002. Accelerated (40°C/75%RH) 0, 1, 6 months, upright and inverted on 3 lots each. -Transportation 2.3.P.2 Pharmaceutical development, sequence 002	X		
	Clinical Validation	X		
	Human Factors Validation -Deferred to DMEPA			X
	Description of Device Manufacturing Process -2.3.P Control of Drug Product, Sequence 002	X		
Quality Systems/ Manufacturing Controls Check	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	X		
	CAPA Procedure (Refer to IR3 dated 04/28/23)		X	
	Control Strategy provided for EPRs -In-process controls (2.3.P-Manufacture- Drug Product, sequence 002)	X		

Reviewer Comment

The documentation submitted is adequate for filing. Adequacy of data/information will be determined during review.

5.2. Facilities Information

Firm Name:	(b) (4)
Address:	
FEI:	
Responsibilities:	

Release and Stability Testing
<u>Inspectional History</u> An analysis of the firm's inspection history over the recent years: ☒ Inspection was conducted (b) (4) The inspection covered drug CGMP and was classified as NAI. ☐ An analysis of the firm's inspection history over the recent years showed that it has never been inspected. ☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product
<u>Inspection Recommendation:</u> ☒ An inspection <u>is not required</u> because the most recent inspection was a surveillance cGMP inspection that was categorized as NAI. The inspection conducted (b) (4) (b) (4) A summary of the (b) (4) inspection is as follows (per OSAR): (b) (4)

Table 1: Manufacturer Information

Facility	Responsibility
(b) (4)	Manufacturing and Device Assembly Primary, Secondary and Tertiary Packaging Labeling Release and Stability Testing
	Tertiary Packaging

5.3. Quality System Documentation Triage Checklist

Was the last inspection of the finished combination product manufacturing site, or other site, OAI for drug or device observations?	☐ Yes ☒ No ☐ UNK
Is the device constituent a PMA or class III device?	☐ Yes ☒ No ☐ UNK
Is the final combination product meant for emergency use?	☒ Yes ☐ No ☐ UNK
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	☒ Yes ☐ No ☐ UNK
Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	☐ Yes ☒ No ☐ UNK
Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	☒ Yes ☐ No ☐ UNK
Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	☐ Yes ☒ No ☐ UNK
cGMP Risk:	
☐ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.	
☒ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.	

Reviewer Comment

The combination product is considered high risk as it is intended to be indicated for emergency use for one-opportunity situations.

5.4. Filing Review Conclusion

FILING REVIEW CONCLUSION	
Acceptable for Filing: ☒ Yes ☐ No (Convert to a RTF Memo) ☐ N/A	
Facilities Inspection Recommendation:	
☐ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance	

ICC2300074 ICC2201077
NDA217470, (b) (4) (nalmeferene) nasal spray
Opiant pharmaceuticals, Inc.

☒ No Inspection ☐ N/A

Site(s) needing inspection:

Reviewer Comments

No inspection is recommended at this time as the firm had an inspection in (b) (4) that was categorized as NAI for a combination product that has the same device constituent part as the proposed combination product for this submission. The firm did not provide adequate biocompatibility information, refer to information request 1 dated

Refuse to File Deficiencies: ☐ Yes ☒ No ☐ N/A

74-Day Letter Deficiencies: ☐ Yes ☒ No ☐ N/A

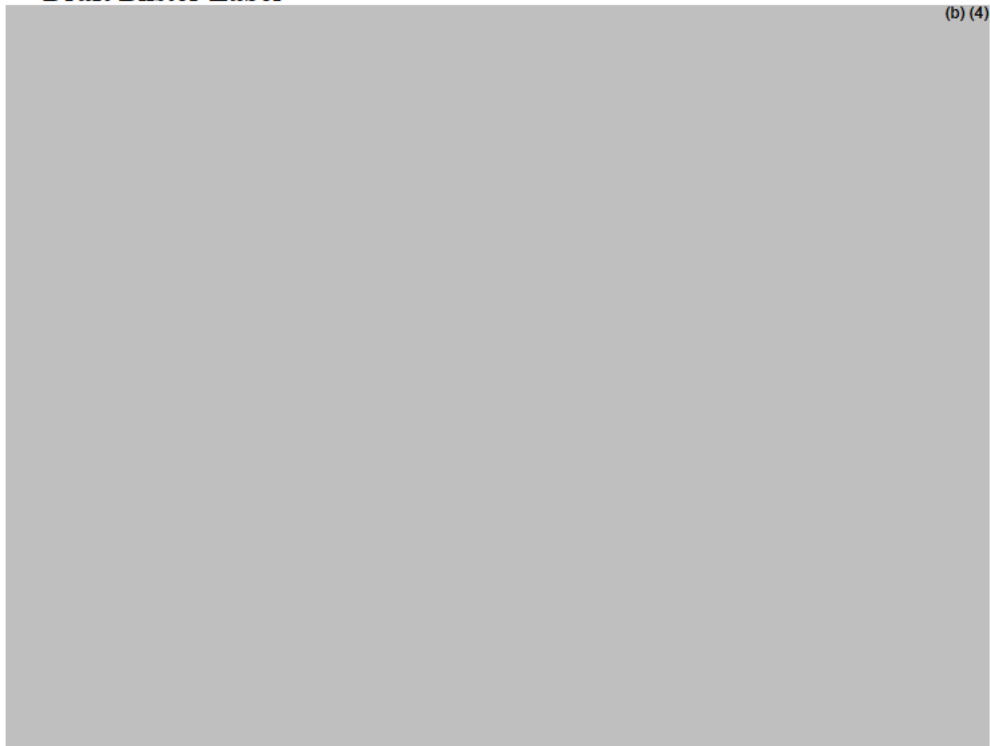
	Date Sent: 1/10/2023	Date/Sequence Received: 1/11/2023
Information Request #1	(b) (4)	
Sponsor Response		

	(b) (4)
Reviewer Comments	The biocompatibility data has been located in the referenced DMF; therefore, the firm's response is adequate.
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

6. LABELING

6.1. General Labeling Review

Draft Blister Label



Draft Carton Label

(b) (4)

Draft Device Label

(b) (4)

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		

Warnings	X		X
Contraindications			
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors			X- Deferred to DMEPA
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
<u>MRI</u> Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

Reviewer Comments

The packaging information, instructions for use, carton label, device label, and blister label were all reviewed. All labeling is adequate.

6.2. Device Specific Labeling Review

Device Specific Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation (Section V- Labeling considerations, pg. 37/45)			
Instructions for Use Label, Blister Label, and PI Label:			
• Product Title	X		
• Established name of the drug product	X		
• Amounts of the drug substance delivered from the pump nasal actuator or	X		
Number of medication sprays per container	X		
Net content	X		
Usual dosage	X		
Excipients (established names)	X		
Route of administration	X		
Recommended storage conditions including any warning statements regarding temperature or light exposure	X		
Manufacturer's and/or distributor's name and address	X		
"Rx Only" or "• Only" statement	X		
Lot number	X		
Expiration date	X		
Use period once drug product is removed from protective packaging (if applicable)			X
Instructions regarding shaking of suspension drug products			X
Description section of the package insert	X		
How supplied section of the package insert	X		
Patient package insert	X		

Reviewer Comments

The packaging information, instructions for use, carton label, device label, and blister label were all reviewed. All labeling according to the nasal spray guidance is adequate.

6.3. Clinical Labeling Review

The following Clinical Labeling Review was completed by ☐ Insert Consultant Name ; The full memo is located in Appendix B. ☒ The Lead Reviewer Below is a summary of the review & recommendation: The packaging information, instructions for use, carton label, device label, and blister label were all reviewed. All labeling aligns with the nasal spray guidance and therefore adequate.

6.4. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments The carton and device label as well as the instructions for use and PI were assessed by the lead reviewer and determined to be adequate as it relates to device labeling and alignment with the nasal spray and emergency use guidances.		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

7. DESIGN CONTROL [SUMMARY](#)

7.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g., FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		
Version history demonstrates risk management throughout design / development activities			X
Design Inputs/Outputs	Yes	No	N/A
Design requirements / specifications document present (essential performance requirements included)	X		
Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial	X		
Bioequivalence Study utilized to-be-marketed device			X
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e., emergency use combination product may require separate reliability study)	X		
Traceability demonstrated for specifications to performance data	X		

Reviewer Comments
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7.2. Design Inputs and Outputs

Essential Performance Requirements

The device specifications are in 3.2.P- Control of drug product.

Design Inputs (Essential Performance Requirement)	Design Outputs (Specification)
Pump Delivery	(b) (4)
Spray Content Uniformity (SCU)	
Spray Pattern	
Droplet Size Distribution	
Activation Force	

Reviewer Comments
(b) (4)

(b) (4)

	Date Sent: 4/24/2023	Date/Sequence Received: 4/25/2023
Information Request #1 (Issued by CDER Drug Product Reviewer)		
Sponsor Response		

(b) (4)

Reviewer Comments	(b) (4)
Response Adequate:	☒ Yes ☐ No, See IR # Sent on 4/27/2023

7.3. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
IEC 60601-1-2:2014	NA
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Y
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	NA
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	NA
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y
Applying Human Factors and Usability Engineering to Medical Devices	Y

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
Guidance for Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation	Y	Y
Technical Considerations for Demonstrating Reliability of Emergency-Use Injectors Submitted under a BLA, NDA or ANDA: Guidance for Industry and Food and Drug Administration Staff	Y	Y

7.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

8. RISK ANALYSIS

8.1. Risk Management Plan

(b) (4)

Reviewer Comments

The firm's risk approach appears adequate.

(b) (4)

8.2. Hazard Analysis and Risk Summary Report

The harms and severity of a given hazard appear to be appropriate.
Module 3.2.P.2.3.

Reviewer Comments

The harms and severity of a given hazard appear to be appropriate as the device is indicated for emergency use.

(b) (4)

8.3. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION

Filing Deficiencies:

☐ Yes ☒ No ☐ N/A

Mid-Cycle Deficiencies:

☐ Yes ☒ No ☐ N/A

Final Deficiencies:

☐ Yes ☒ No ☐ N/A

[Reviewer Comments](#)

CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No

	Date Sent: 4/28/2023	Date/Sequence Received: 5/1/2023
Information Request #2		
Sponsor Response		

(b) (4)

	(b) (4)
Reviewer Comments	The firm updated the device risk analysis (b) (4) and is determined to be adequate.
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

9. DESIGN VERIFICATION REVIEW

9.1. Performance/Engineering Verification

9.1.1. Essential Performance Requirement Evaluation

Stability data can be found in sequence 0002, module 3.2.P.8.3-stability data.

Design Verification/Reliability data can be found in sequence 0002, module 2.3.P.2- pharmaceutical development and 3.2.9.2 Container closure system (section 3).

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method <u>Acceptable</u> (Y/N)	<u>Validation</u> (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Pump Delivery	(b) (4)	Yes (b) (4)	Yes To-be-marketed combination product utilized in clinical study. CDER drug product reviewers confirmed appropriateness of specification	Yes 3 registrations batches up to 12 months at the long-term (25°C/60%RH), 0, 6, 12 months, both Upright and inverted orientation 3 registration batches tested at 16 months, inverted only, 25°C/60%RH 3 registration batched, 6 months at the accelerated (40°C/75%RH) storage conditions, 0, 1, 6 months both upright and inverted orientations - According to ICH Q1E - All data met specification	Yes Per ASTM D4169-16, Distribution Cycle 2
Spray Content Uniformity (SCU)	(b) (4)	(b) (4)	Yes To-be-marketed combination product utilized in clinical study. CDER	Yes 3 registrations batches up to 12 months at the long-term (25°C/60%RH), 0, 6, 12 months, both Upright and inverted orientation	Note: SCU was not considered for design verification (post shipping)/reliability; however, SCU was tested on stability at

	(b) (4)	(b) (4)	drug product reviewers confirmed appropriateness of specification	3 registration batches tested at 16 months, inverted only, 25°C/60%RH 3 registration batches, 6 months at the accelerated (40°C/75%RH) storage conditions, 0, 1, 6 months both upright and inverted orientations - According to ICH Q1E All data met specification	T=0 and accelerated equivalent to the proposed shelf life.
Spray Pattern	(b) (4)	Yes (b) (4)	Yes (b) (4) To-be-marketed combination product utilized in clinical study. CDER drug product reviewers confirmed appropriateness of specification	Yes 3 registrations batches up to 12 months at the long-term (25°C/60%RH), 0, 6, 12 months, both Upright and inverted orientation 3 registration batches tested at 16 months, inverted only, 25°C/60%RH 3 registration batches, 6 months at the accelerated (40°C/75%RH) storage conditions, 0, 1, 6 months both upright and inverted orientations - According to ICH Q1E All data met specification	Yes Per ASTM D4169-16, Distribution Cycle 2
Droplet Size Distribution	(b) (4)	Yes (b) (4)	Yes (b) (4) To-be-marketed combination product utilized	Yes 3 registrations batches up to 12 months at the long-term (25°C/60%RH), 0, 6, 12 months,	Yes Per ASTM D4169-16, Distribution Cycle 2

	(b) (4)	(b) (4)	in clinical study. CDER drug product reviewers confirmed appropriateness of specification	both Upright and inverted orientation 3 registration batches tested at 16 months, inverted only, 25°C/60%RH 3 registration batches, 6 months at the accelerated (40°C/75%RH) storage conditions, 0, 1, 6 months both upright and inverted orientations - According to ICH Q1E All data met specification	
Activation Force	(b) (4)	Yes (b) (4)	Yes To-be-marketed combination product utilized in clinical study. CDER drug product reviewers confirmed appropriateness of specification	Yes 3 registrations batches up to 12 months at the long-term (25°C/60%RH), 0, 6, 12 months, both Upright and inverted orientation 3 registration batches tested at 16 months, inverted only, 25°C/60%RH 3 registration batches, 6 months at the accelerated (40°C/75%RH) storage conditions, 0, 1, 6 months both upright and inverted orientations - According to ICH Q1E All data met specification	Yes Per ASTM D4169-16, Distribution Cycle 2

STABILITY TESTING

Stability data have been generated on three registration batches of Nalmefene Nasal Spray in accordance with ICH guideline Q1A(R2) at long-term (25°C/60%RH) and accelerated (40°C/75%RH) storage conditions. Given the stability at the 25°C/60%RH and 40°C/75%RH conditions did not result in any notable change, the testing at 30°C/65%RH is not reported. Accelerated stability studies are complete; studies under long-term storage conditions are ongoing.

Based on the available 16 months long term stability data which demonstrated acceptable results with little or no change and with no observable trend over time and six (6) months accelerated stability data which demonstrated no significant change, a shelf life of 28 months is proposed in accordance with ICH Q1E for the drug product in the commercial container closure system.

POST-APPROVAL STABILITY

Stability will be generated at long-term conditions (25°C/60%RH) at 0, 3, 6, 12, 18, 24 and 36 months, and accelerated conditions (40°C/75%RH) at 0, 3 and 6 months, in the inverted orientation which is considered the worst-case condition. Yearly thereafter, a minimum of one (1) commercial production batch will be added to the long term stability program, if manufactured, and tested at intervals of 0, 6, 12, 24 and 36 months.

DESIGN VERIFICATION TESTING POST SEQUENTIAL CONDITIONING (named reliability testing)

(b) (4)

9.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments Design verification testing post shipping and aging was adequate; however, the firm’s reliability data was not adequate and the fault tree analysis was inadequate. Refer to IR 1 below dated 04/28/23 for details regarding inadequacy of reliability.		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		

	Date Sent: 4/28/2023	Date/Sequence Received: 5/5/2023
Information Request #1	(b) (4)	

	(b) (4)
Reviewer Comments	The firm referenced their interaction with FDA 03 November 2021 and feedback provided to the firm with regards to their reliability protocol. The firm's approach aligns with their protocol submitted to FDA in 2021. Refer to section 3.2 above for an excerpt of key device reliability feedback FDA issued to the firm. (b) (4) The overall reliability of the proposed combination product is adequate.
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

Discipline: Consultant:	Date Sent: 5/3/2023	Date/Sequence Received: 5/5/2023
Information Request #1	(b) (4)	
Sponsor Response		
Reviewer Comments	The firm's tracematrix included as Appendix 1 (b) (4) The response is tracematrix is adequate.	
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

9.3. Discipline Specific Sub-Consulted Review Summary

- ☐ No Additional Discipline Specific Sub-Consults were requested
- ☒ The following additional Discipline Specific Sub-Consults were requested:

<u>Discipline</u> -Specific Design Verification / Validation adequately addressed						
Discipline	Consult needed			Consultant	Section	Adequately Addressed (Y/N/NA)
	Yes	No	N/A			
Engineering (Materials, Mechanical, General)		X				Y
Biocompatibility	X			Papatya Kaner	9.3	Y
Sterility			X			Deferred to CDER
Software / Cybersecurity			X			NA
Electrical Safety / EMC			X			NA
Human Factors			X		11	Deferred to DMEPA
Clinical			X			Deferred to CDER

CDRH sent Deficiencies or Interactive Review Questions to the Sponsor	☒ Yes ☐ No
---	---

Discipline: Consultant:	Date Sent: 1/10/2023	Date/Sequence Received: 1/11/2023
Information Request #1	(b) (4)	
Sponsor Response		
Reviewer Comments	The firm adequately provided the information and data to access the safety of the Aptar device. The device biocompatibility testing is determined to be adequate.	
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

9.3.1. Insert Discipline Review

The following biocompatibility review was completed by Papatya Kaner. The full memo is located in **Appendix B**. Below is a summary of the **recommendation**:

Opiant Pharmaceuticals, Inc. has developed (b) (4) (nalmefene) nasal spray for the complete or partial reversal of opioid drug effects including respiratory depression, induced by either natural or synthetic opioids. It will be used in the emergency treatment of known or suspected opioid overdose. Submission indicates that the Aptar UDS device, a single-use, single dose, disposable nasal spray delivery system consisting of the actuator and container holder, will be used as the primary closure system and method for dispensing the drug product. The Aptar UDS device's biocompatibility data is incorporated by cross-reference to DMF (b) (4). The referenced DMF included cytotoxicity, sensitization and irritation testing to demonstrate the biological safety of the actuator and container holder components. Since the drug will be absorbed systematically via nose for the treatment, we also needed acute systemic toxicity endpoint for the biocompatibility assessment of the actuator. However, the drug will be used in the emergency treatment of known or suspected opioid overdose and not on a regular basis; hence the nasal spray's actuator will only have limited contact with the nasal mucosa. In addition, the Aptar device has a history of safe use with other drugs such as the following NDAs: Narcan Nasal Spray (NDA# 016636), (b) (4)

Hence, we determined that the biocompatibility assessment of the Aptar UDS device is appropriate for use as the (b) (4) (nalmefene) nasal spray.

10. CLINICAL VALIDATION REVIEW

10.1. Review of Clinical Studies Clinical Studies

- ☐ There is no device related clinical studies for review
☒ There are clinical studies for review

This information was obtained from the following **documents**:

Study Name	PK-001
Study Type	A Two-Period, Two-Treatment, Randomized Crossover Study of the Pharmacokinetics of Nalmefene by Intranasal and Intramuscular Administration in Healthy Volunteers (Study OPNT003-PK-001)
Objectives/Endpoints and brief description of protocol	Study OPNT003-PK-001 was an open-label, randomized, 2-period, 2-treatment, 2-sequence, crossover study in 68 healthy volunteers. Subjects were randomly assigned to one of the 2 possible sequences for each period. Each subject received 2 treatments during the 2 dosing periods: IN dose of 3 mg nalmefene hydrochloride and IM dose of 1.0 mg nalmefene, with a 4- day washout period between doses. The study design and pharmacokinetic (PK) results were provided in Module 2, Section 2.7.2.2.1
Drug/Device Studied	Final-to-be-marketed formulation and device (Aptar)
Number and Type of Subjects	66/68 subjects received nalmefene hydrochloride 3 mg IN 68/68 subjects received nalmefene 1 mg IM
Results	A total of 96 treatment-emergent AEs (TEAEs) were reported by 48 subjects over the course of the study: 73 AEs were reported by 45 (68.2%) subjects following Treatment A (IN) and 23 AEs were reported by 13 (19.1%) subjects following Treatment B (IM). Overall, the investigational product was well-tolerated when administered as a 3 mg IN spray in healthy subjects under fasted conditions. All AEs were mild in severity, there were no severe or serious AEs and no unusual or

	unexpected AEs related to the investigational product. No AEs led to a subject discontinuation, and there were no clinically significant events based on clinical laboratory results, vital signs, 12-lead ECGs, adverse events, or physical examinations.
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Study Name	PK-002								
Study Type	An Open-Label, Three-Period, Three-Treatment, Six-Sequence, Randomized Crossover Study of the Pharmacokinetics of Intranasal Nalmefene in Healthy Volunteers using Three Dosing Regimens (Study OPNT003-PK-002)								
Objectives/Endpoints and brief description of protocol	Study OPNT003-PK-002 was an open-label, randomized, 6-sequence, 3-treatment, 3-period crossover study in which 24 healthy subjects received 3 separate administrations of IN nalmefene hydrochloride. As described in Module 2, Section 2.7.2.2.2, subjects were randomly assigned to 1 of 6 sequences (4 subjects per sequence). Each subject received one of the 3 treatments in each of the 3 treatment periods as shown in Table 1. Table 1: Identity of Study Treatments <table> <tr> <th>Treatment</th><th>Dose</th></tr> <tr> <td>Treatment 1 (T1)</td><td>3 mg (one 0.1 mL spray of 30 mg/mL nalmefene hydrochloride in one nostril)</td></tr> <tr> <td>Treatment 2 (T2)</td><td>6 mg (one 0.1 mL sprays of 30 mg/mL nalmefene hydrochloride in each nostril)</td></tr> <tr> <td>Treatment 3 (T3)</td><td>6 mg (two 0.1 mL sprays of 30 mg/mL nalmefene hydrochloride in one nostril)</td></tr> </table>	Treatment	Dose	Treatment 1 (T1)	3 mg (one 0.1 mL spray of 30 mg/mL nalmefene hydrochloride in one nostril)	Treatment 2 (T2)	6 mg (one 0.1 mL sprays of 30 mg/mL nalmefene hydrochloride in each nostril)	Treatment 3 (T3)	6 mg (two 0.1 mL sprays of 30 mg/mL nalmefene hydrochloride in one nostril)
Treatment	Dose								
Treatment 1 (T1)	3 mg (one 0.1 mL spray of 30 mg/mL nalmefene hydrochloride in one nostril)								
Treatment 2 (T2)	6 mg (one 0.1 mL sprays of 30 mg/mL nalmefene hydrochloride in each nostril)								
Treatment 3 (T3)	6 mg (two 0.1 mL sprays of 30 mg/mL nalmefene hydrochloride in one nostril)								
Drug/Device Studied	Final-to-be-marketed formulation and device (Aptar)								
Number and Type of Subjects	23/24 subjects received nalmefene hydrochloride 3 mg IN, one 0.1 mL spray in one nostril 23/24 subjects received nalmefene hydrochloride 6 mg IN, one 0.1 mL spray in each nostril. 24/24 subjects received nalmefene hydrochloride 6 mg IN, two 0.1 mL sprays in one nostril. Twenty-three of 24 subjects enrolled were administered all scheduled doses of nalmefene hydrochloride nasal spray. Dosing in the 3 study periods was separated by a 6-day washout period. The total dose administered to each subject who completed all study periods was 15 mg of nalmefene hydrochloride.								
Results	Overall, the investigational product was well-tolerated when administered as a 3 mg and 6 mg dose in healthy subjects under fasted conditions. A total of 68 TEAEs were reported by 22 subjects over the course of the study: 20 AEs were reported by 10 (43.5%) subjects following Treatment 1, 24 AEs were reported by 14 (60.9%) subjects following Treatment 2, and 24 AEs were reported by 14 (58.3%) subjects following Treatment 3. There were no serious AEs (SAEs) or AEs that led to a subject withdrawal or death. No clinically significant abnormalities in ECGs, physical examinations, or nasal examinations were observed. There were no clinically significant findings in NRS data. There were no AEs related to clinically significant out-of-range vital signs or clinical laboratory assessments. All AEs were mild in severity, and there were no severe or serious AEs and no unusual or unexpected AEs related to the investigational product. No AEs led to a subject discontinuation, and there were no clinically significant events.								

Study Name	OOD-001
Study Type	A Two-Part Open-Label Study of the Pharmacodynamic Effects of Intranasal Nalmefene Compared to Intranasal Naloxone in Healthy Volunteers Under Steady- State Opioid Agonism (Study OPNT003-OOD-001)
Objectives/Endpoints and brief description of protocol	Study OPNT003-OOD-001 was a Phase 1, open-label, 2-part study. As described in Module 2, Section 2.7.2.2.3.1, the Part 1 and Part 1 extension were a pilot study to determine the relationship between remifentanyl dose on suppression of CO₂-induced increases in minute ventilation in up to 16 healthy volunteers with prior opioid exposure. Part 2 was a 2-period, 2-treatment, crossover study to evaluate the pharmacodynamic (PD) effects of IN nalmefene compared to IN naloxone to reverse remifentanyl-induced suppression of CO₂-induced increases in minute ventilation, in at least 46 healthy volunteers with prior opioid exposure. In Part 1 and Part 1 extension, each subject received 4 mg IN naloxone hydrochloride, on Dose Day 1 and Dose Day 2, with a 4-day washout period between doses. In Part 2, each subject received 3 mg IN nalmefene hydrochloride or 4 mg IN naloxone hydrochloride in a randomized 2-period crossover manner, with a 4-day washout period between doses.
Drug/Device Studied	Final-to-be-marketed formulation and device (Aptar)
Number and Type of Subjects	Part 1: • 7/7 subjects received naloxone hydrochloride 4 mg IN Part 1 Extension: • 8/8 subjects received naloxone hydrochloride 4 mg IN Part 2: • 61/69 subjects received nalmefene hydrochloride 3 mg IN • 60/69 subjects received naloxone hydrochloride 4 mg IN
Results	In Part 2 of the study where the subjects received IN nalmefene hydrochloride and IN naloxone, A total of 131 TEAEs were reported by 52 (86.7%) subjects after administration of naloxone hydrochloride, and 172 TEAEs were reported by 56 (91.8%) subjects after administration of nalmefene hydrochloride. These TEAEs occurred with subjects who were also being administered a hypercapnic gas mixture and an infusion of remifentanyl. Overall, a total of 9 (13.0%) subjects receiving either naloxone hydrochloride or nalmefene hydrochloride, discontinued the study drug due to an AE. Among them, 5 (8.3%) subjects receiving naloxone hydrochloride reported 4 TEAEs of hypercapnia and 1 TEAE of hypoxia, while 4 (6.6%) subjects receiving nalmefene hydrochloride reported 2 TEAEs of headache and 2 TEAEs of hypercapnia, all with outcome recovered/resolved. subjects receiving nalmefene hydrochloride reported 2 TEAEs of headache and 2 TEAEs of hypercapnia, all with outcome recovered/resolved. Overall, the most common TEAEs were headache (reported by 48 [69.6%] subjects receiving either naloxone hydrochloride or nalmefene hydrochloride), nausea (39 [56.5%] subjects receiving either naloxone hydrochloride or nalmefene hydrochloride), and dizziness (21 [30.4%] subjects receiving either naloxone hydrochloride or nalmefene hydrochloride).

	Overall, nervous system and gastrointestinal disorders were most frequently reported among subjects receiving naloxone hydrochloride and nalmefene hydrochloride, reported by 55 (79.7%) and 46 (66.7%) subjects, respectively. All events had outcome recovered/resolved. No deaths or SAEs occurred in this study. Treatment with naloxone hydrochloride and nalmefene hydrochloride was safe and well tolerated. The safety profiles of naloxone hydrochloride and nalmefene hydrochloride were similar.
Device Related Comments for all 3 studies (OPNT003-PK-001, OPNT003-PK-002, and OPNT003-OD-001)	There were no device-related comments included in the study summary.
Reviewer Conclusion for all 3 studies (OPNT003-PK-001, OPNT003-PK-002, and OPNT003-OD-001)	There does not appear to be any device related comments, particularly adverse events for any of the 3 studies.

Table 4: Overall Summary of Adverse Events - Pooled Population

	Nalmefene hydrochloride IN				Comparators	
	3 mg one nostril ¹ (N=150)	6 mg 1 spray in each nostril ² (N=23)	6 mg 2 sprays in one nostril ³ (N=24)	6 mg Combined ⁴ (N=24)	Nalmefene 1 mg IM (N=68)	Naloxone Hydrochloride 4 mg IN ¹ (N=75)
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
No. (%) of Subjects with at Least 1 TEAE	111 (74.0%)	14 (60.9%)	14 (58.3%)	20 (83.3%)	13 (19.1%)	60 (80.0%)
No. (%) of Subjects with at Least 1 SAE	0	0	0	0	0	0
No. (%) of Subjects with TEAE Leading to Discontinuation	2 (1.3%)	0	0	0	0	1 (1.3%)
No. (%) of Subjects with Treatment-Related TEAE	107 (71.3%)	14 (60.9%)	13 (54.2%)	20 (83.3%)	8 (11.8%)	55 (73.3%)
No. (%) of Subjects Who Died	0	0	0	0	0	0

Abbreviations: AE = adverse event, N = number of unique subjects, n(%) = percent of subjects, SAE = serious adverse event, TEAE = treatment emergent adverse event

¹ Subjects in the OPNT003-OD-001 study received hypercapnic gas mixture and remifentanyl infusion in addition to 3 mg nalmefene hydrochloride and 4 mg naloxone hydrochloride.

² 6 mg nalmefene hydrochloride IN (3 mg in each nostril)

³ 6 mg nalmefene hydrochloride IN (3 mg twice in one nostril)

⁴ 6 mg nalmefene hydrochloride IN dose includes subjects that received two 3 mg doses one in each nostril and 3 mg doses twice in one nostril

Source: ISS, Table 9

Reviewer Comment

There were not any unexplained discrepancies in that PK data; and therefore, clinical determined the studies to be acceptable. Note that the device used in the clinical trials is the Aptar nasal spray device approved for use as the device constituent part of several other approved combination products.

CDER clinical reviewers, Srikanth Nallani and Tanya Brescia-Oddo were consulted via email to confirm adequacy of clinical studies.

10.2. Clinical Validation Review Conclusion

CLINICAL VALIDATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments		
CDRH sent Clinical Validation Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

11. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐
Human factors review deferred to DMEPA	☒

12.FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☐
CDRH Facilities Inspection Review was not conducted	☒

12.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☒
CDRH Quality Systems Documentation Review was not conducted	☐

12.2.1. Description of the Device Manufacturing Process

Summary of Manufacturing Process / Production Flow

The Sponsor provided the following summary of the manufacturing process of the combination product, including the drug product/biologic and device constituent parts:

2 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Device Manufacturing Process Conclusion		
The Sponsor provided adequate information for the summary of the manufacturing process / production flow.	☒ Yes	☐ No

12.2.2. cGMP Review

Does Sponsor have all elements of their GMP compliance approach included in submission:

What Quality System did the Sponsor choose:

- ☐ [Device](#) QSR-based
☒ Drug cGMP-Based Streamline –
☐ Stream-line Both ([no streamlined approach](#))

21 CFR 820.20
Summary of
Management
Responsibility

21 CFR 820.30
Summary of
Design Controls

21 CFR 820.50
Summary of
Purchasing
Controls

(b) (4)

(b) (4)

21 CFR 820.100
Summary of
Corrective and
Preventive
Actions

Reviewer Comments

(b) (4)

(b) (4)

GMP Compliance Summary Conclusion

The Sponsor provided adequate summary information about the GMP compliance activities

☒ Yes

☐ No

12.2.3. Corrective and Preventive Action Review

(b) (4)

CAPA Conclusion		
The Sponsor provided adequate information for corrective and preventive actions.	☒ Yes	☐ No

12.3. Control Strategy Review

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g., emergency-use)*

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N/NA)
Pump Delivery, Spray Pattern, Droplet Size Distribution, and Activation Force	(b) (4)	Y

	(b) (4)	
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Reviewer Comments

(b) (4)

Therefore, the overall control strategy for the proposed combination product appears adequate.

Control Strategy Conclusion

The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.

☒ Yes

☐ No

12.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments The firm's quality systems are adequate.		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		

	Date Sent: 4/28/2023	Date/Sequence Received: 5/1/2023
Information Request #3	(b) (4)	
Sponsor Response		

		(b) (4)

	Date Sent: 5/3/2023	Date/Sequence Received: 5/5/2023
Information Request #2	(b) (4)	
Sponsor Response		
Reviewer Comments		

	(b) (4) Therefore, the overall control strategy for the proposed combination product appears adequate.
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

<<END OF REVIEW>>

13.APPENDIX A (INFORMATION REQUESTS)

(b) (4)

14. APPENDIX B (CONSULTANT MEMOS)

14.1. Biocompatibility Review Memo – Papatya Kaner

Date	5/2/2023		
To:	Porsche Bennett, CDRH Device Reviewer		
Requesting Center/Office	CDER/OND	Clinical Review Division	DROII
From	Papatya Kaner OPEQ/OHT3/DHT3C/THT3C3		
Through (Team)	Courtney Evans Team Lead, Injection Team OPEQ/OHT3/DHT3C/THT3C1		
Through (Division) *Optional	CPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C/THT3C1		
Subject	NDA 217470, (b) (4) (nalmeferene) nasal spray ICC2201077 ICCR00886193		
Recommendation	Recommendation Date: 4/24/2023 ☐ Device Constituents Parts of the Combination Product <u>are reasonably safe</u> for use in the proposed clinical study ☒ Device Constituents Parts of the Combination Product <u>are reasonably safe</u> for use in the proposed clinical study, CDRH has non-hold comments below ☐ Device Constituents Parts of the Combination Product are <u>not safe</u> for use in the proposed clinical study, CDRH has CLINICAL HOLD comments		

Review Summary:

Opiant Pharmaceuticals, Inc. has developed (b) (4) (nalmeferene) nasal spray for the complete or partial reversal of opioid drug effects including respiratory depression, induced by either natural or synthetic opioids. It will be used in the emergency treatment of known or suspected opioid overdose. Submission indicates that the Aptar UDS device, a single-use, single dose, disposable nasal spray delivery system consisting of the actuator and container holder, will be used as the primary closure system and method for dispensing the drug product. The Aptar UDS device's biocompatibility data is incorporated by cross-reference to DMF (b) (4). The referenced DMF included cytotoxicity, sensitization and irritation testing to demonstrate the biological safety of the actuator and container holder components. Since the drug will be absorbed systematically via nose for the treatment, we also needed acute systemic toxicity endpoint for the biocompatibility assessment of the actuator. However, the drug will be used in the emergency treatment of known or suspected opioid overdose and not on a regular basis; hence the nasal spray's actuator will only have limited contact with the nasal mucosa. In addition, the Aptar device has a history of safe use with other drugs such as the following NDAs: Narcan Nasal Spray (NDA# 016636), (b) (4)

Hence, we determined that the biocompatibility assessment of the Aptar UDS device is appropriate for use as the (b) (4) (nalmeferene) nasal spray.

Digital Signature Concurrence Table (Doc ID: 04504.03.05)	
For each of the specific issues identified in the recommended requests to the applicant above, I and/or if applicable contributing consulting reviewer(s) (and or supervisors), have provided a statement of basis for the request(s); and either cited as part of it an available, applicable, and relevant final rule, statute, final guidance, or FDA-recognized consensus standard, or confirmed to the best of my ability that there is no final rule, statute, final guidance, or FDA-recognized consensus standard available, applicable, and relevant to the request(s).	
Reviewer Sign-Off	

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: 5/10/2023

TO: Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Office of Neuroscience (ON)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 217470

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) conducted an inspection for the site in February 2023. The inspection was conducted under the following submission: (b) (4)

OSIS determined that data from the reviewed study was reliable.

OSIS notes that the site was formerly located at 700 East 3838 South, Suite 200, Salt Lake City, UT, and operations have since moved to the address listed in the table below.

Site

Facility Type	Facility Name	Facility Address
Clinical	PRA Health Sciences/ICON	1255 East 3900 South, Salt Lake City, UT

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/

JAMES J LUMALCURI
05/10/2023 10:29:20 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Division of Pediatrics and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

Division of Pediatrics and Maternal Health Review

Date: May 9, 2023 **Date of Consult Request:** December 14, 2022

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health, Division of Pediatrics and Maternal Health (DPMH)

Through Tamara Johnson, M.D., MS, Team Leader, Maternal Health, DPMH

To: Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

NDA Number: 217470

Drug: (b) (4) (nalmeфene) nasal spray

Applicant: Opiant Pharmaceuticals, Inc.

Indication: Indicated for the emergency treatment of known or suspected opioid overdose in adults and pediatric patients aged 12 years and older, as manifested by respiratory and/or central nervous system depression. (b) (4) nasal spray is intended for immediate administration as emergency therapy in settings where opioids may be present. (b) (4) nasal spray is not a substitute for emergency medical care.

Subject: Labeling review as per Pregnancy and Lactation Labeling Rule (PLLR).

Materials Reviewed

- Applicant's rolling submission of May 27, 2022, August 30, 2022, and November 22, 2022

- Division's Consult request of December 14, 2022, DARRTS Reference ID: 5093957

INTRODUCTION

On May 27, 2022, the applicant, Opiant Pharmaceuticals, Inc. (Opiant), submitted a rolling new NDA 217470 for (b) (4) (nalmeferene) nasal spray, for the emergency treatment of known or suspected opioid overdose in adults and pediatric patients aged 12 years and older, as manifested by respiratory and/or central nervous system depression. (b) (4) nasal spray is intended for immediate administration as emergency therapy in settings where opioids may be present. (b) (4) nasal spray is not a substitute for emergency medical care. This NDA was submitted under the 505(b)(2) pathway with drug relied upon REVEX, (nalmeferene hydrochloride) NDA 020459 for intravenous, intramuscular, and subcutaneous administration. The proposed labeling is in PLR and PLLR format. DAAP has requested DPMH to ensure that the labeling complies with the PLLR content and format.

BACKGROUND

The opioid epidemic continues to grip the United States, with over 550,000 opioid overdose deaths since 1999 (CDC–2021)^{1,2}. Recent studies provide evidence that individuals who survive a nonfatal opioid overdose are at higher risk of a subsequent overdose both within 30 days and over the next 12 months following the initial event. For example, in a retrospective study of over 4100 patients who survived an overdose, ~15% of patients had a repeat overdose, with 29% occurring within the first 30 days.³ Respiratory depression is responsible for opioid-induced deaths as well as the short- and long-term morbidities linked to a non-fatal overdose including brain injuries produced by hypoxia and in more severe cases, anoxia.^{4,5} The opioid receptor antagonist naloxone has been approved by the Food and Drug Administration (FDA) since 1971 to treat opioid overdose, originally as a needle-and-syringe injection and more recently as a nasal spray and intramuscular (IM) auto-injector. REVEX (nalmeferene hydrochloride injection) for complete or partial reversal of opioid drug effects, including respiratory depression, induced by either natural or synthetic opioids and in the management of known or suspected opioid overdose was approved on April 17, 1995. REVEX was withdrawn from the US market in 2008 for reasons other than safety or effectiveness (Federal Register-2017).

REVEX (nalmeferene) Drug Characteristics⁶

Half Life	11.4 Hours
Molecular Weight	375.9 Daltons
Protein bound	45%. In vitro determination of the distribution of nalmeferene in human blood demonstrated that nalmeferene distributed 67% (CV 8.7%) into red blood cells and 39% (CV 6.4%) into plasma.

¹ Center of Disease Control. Data tables for NCHS Data Brief, no 428. Hyattsville, MD: National Center for Health Statistics. 2021:1-3

² Center for Disease Control. Health Alert Network. Increase in Fatal Drug Overdose Across the United States Driven by Synthetic Opioids Before and During the Covid 19 Pandemic. December 2020.

³ Suffoletto B., Ziegler A. Risk and protective factors for repeated overdose after opioid overdose survival. Drug and Alcohol Dependence. 2020;209:107890

⁴ Skolnick P. Treatment of overdose in the synthetic opioid era. Opiant Pharmaceuticals, 233 Wilshire Blvd., Suite 280, Santa Monica, CA 90401, United States of America

⁵ Boyer EW. Management of Opioid Analgesic Overdose. N Engl J Med Drug Therapy. 2012;367:146-55.

⁶ Nalmeferene nasal spray applicant's proposed labeling and edited by Clinical Pharmacology

Dosage	One spray delivered by intranasal administration, which delivers 2.7 mg of nalmefene.
Treatment duration	Seek emergency medical assistance as soon as possible after intranasal administration of the first dose of nasal spray. If the patient responds to nasal spray and relapses back into respiratory depression before emergency assistance arrives, administer an additional dose in the opposite nostril using a new nasal spray and continue surveillance of the patient. If the desired response is not obtained after 2 to 5 minutes, administer an additional dose of nasal spray device.
Mechanism of action	Nalmefene is an antagonist at opioid (b) (4)

REVIEW

Pregnancy

Non-clinical Data

The applicant did not conduct any non-clinical studies but relied on those for Revex for injection. In animal reproduction studies, no embryotoxic effects on embryo-fetal development were observed in rats and rabbits treated with nalmefene at exposures at least 6 times (rats) and up to 20 times (rabbits) the exposure at two human nasal doses of 5.4 mg.

Clinical Data

As per applicant, studies in the nalmefene nasal spray clinical program include: 1) the two-period, two treatment, randomized crossover study of the pharmacokinetics of nalmefene by intranasal (IN) and IM administration in healthy volunteers, 2) the six-sequence, three-treatment, three-period randomized crossover study of the pharmacokinetics of nalmefene by IN administration in healthy volunteers comparing a single dose to two doses in each nostril and one nostril, and 3) the two-part open-label study of the pharmacodynamic effects of IN nalmefene compared to IN naloxone in healthy volunteers under steady state. No efficacy studies using intranasal nalmefene formulations have been reported in the peer reviewed literature. NDA 217470 relies on the previous findings of safety and efficacy for the reference listed drug REVEX (nalmefene hydrochloride injection) NDA 020459. The safety of nasal spray has not been studied in pregnant women. There were no pregnancies during the drug development program. Nalmefene may precipitate opioid withdrawal in the pregnant woman and fetus.

Applicant states, "Nalmefene Nasal Spray is being submitted via the 505(b)(2) regulatory pathway and relies on the previous findings of safety and efficacy for the reference listed drug REVEX (nalmefene hydrochloride injection) NDA 020459."

Applicant's Review of Literature

Opiant conducted a published literature search of the active ingredient nalmefene as it pertains to the use in pregnant women. The databases used include:

- FDA's Adverse Event Reporting System (FAERS) Public Dashboard
- PubMed including the MEDLINE database

The search from the FDA's Adverse Event Reporting System (FAERS) Public Dashboard using the defined search terms, including: nalmefene and pregnancy, pregnant, stillbirth, miscarriage, congenital anomalies and preterm birth returned no records that were related to pregnancy.

There were no publications identified in search from the PubMed database using the same defined search terms.

DPMH Review of Literature

DPMH searched PubMed, Reprotox⁷ and GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk for use of nalmefene during pregnancy. Reprotox states:

- Nalmefene hydrochloride injection has no effect in cases in which opioids are not responsible for sedation and hypoventilation. Only use in patients when the likelihood of an opioid overdose is high, based on history of opioid overdose or the clinical presentation of respiratory depression with concurrent pupillary constriction.
- Nalmefene hydrochloride may cause acute withdrawal symptoms in patients who have some degree of tolerance to and dependence on opioids. Observe these patients for symptoms of withdrawal following the initial and subsequent injections of nalmefene hydrochloride.
- Do not administer more nalmefene hydrochloride than is required to restore the respiratory rate to normal, minimizing the likelihood of cardiovascular stress and precipitated withdrawal syndrome

No additional studies have been identified in PubMed.

The American College of Obstetrics & Gynecology⁸ notes the following about naloxone, another opioid antagonist, and opioid withdrawal in pregnant women: "Although induced withdrawal may possibly contribute to fetal stress, naloxone should be used in pregnant women in the case of maternal overdose in order to save the woman's life."

Reviewer Comment

Although induced opioid withdrawal may contribute to fetal stress, nalmefene should be used in pregnant women with known or suspected opioid overdose in order to save the woman's life. Additionally, the optimal method for fetal assessment during patient stabilization is unknown, and there are no data to support an approved protocol for fetal assessment and monitoring for opioid withdrawal. Therefore, DPMH does not recommend language about monitoring the fetus for potential nalmefene-precipitating opioid withdrawal. Because nalmefene is used in life-threatening situations, it should not be withheld in pregnant women due to lack of data to support monitoring for fetal opioid withdrawal.

Summary

There are no available data on nalmefene use in pregnant women to evaluate for a drug-associated risk of major birth defects or miscarriage. In animal reproduction studies, no embryotoxic effects on embryo-fetal development were observed in rats and rabbits treated with nalmefene at exposures at least 6 times (rats)

⁷ Reprotox is a data base on the reproductive effects of chemicals, medications, physical agents, and biologics. Reprotox contains summaries on the effects of medications, chemicals, biologics, and physical agents on pregnancy, reproduction, lactation, and development. It covers male and female fertility, pregnancy, lactation, and neonatal development and clinical, experimental animal, and in vitro studies

⁸ Committee on Obstetric Practice. Opioid Use and Opioid Use Disorder in Pregnancy. ACOG Number 711. August 2017.

and up to 20 times (rabbits) the exposure at two human nasal doses of 5.4 mg. Life-sustaining therapy for the pregnant woman should not be withheld due to lack of existing data for potential effects of nalmefene on the fetus.

Lactation

Non-Clinical Data

The applicant did not conduct any non-clinical studies but relied on those conducted for Revex for injection. Those studies demonstrated nalmefene and its metabolites are present in rat milk.

Clinical Review of Data

There is no data on the presence of nalmefene and its metabolites in human milk, the effects of on the breastfed child, or the effects on milk production. No studies were conducted in lactating women.

Applicant's Review of Literature

Opiant conducted a published literature search of the active ingredient nalmefene as it pertains to the use in lactating women. The databases used include:

- FDA's Adverse Event Reporting System (FAERS) Public Dashboard
- PubMed including the MEDLINE database

The search from the FDA's Adverse Event Reporting System (FAERS) Public Dashboard using the defined search terms, including: nalmefene and lactation, lactating, breastfed, breastfeeding, returned no records that were relevant.

There were no publications identified in search from the PubMed database using the same defined search terms as above.

DPMH Review of the Literature

Review by this reviewer of PubMed Reprotox/Micromedex, GG Briggs & RF Freeman in Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk and Halesmeds.com identified no entries.

Summary

There are no available human data on the presence of nalmefene in human milk, the effects on the breastfed infant, or the effects on milk production. There is reasonable expectation that breast-feeding an infant will not take place when a mother has experienced a life-threatening situation such as opioid overdose-induced respiratory and CNS depression.

DPMH has previously not recommended inclusion of the standard risk/benefit statement for naloxone products since the indication is for emergent treatment of opioid overdose and a similar approach is also recommended for this product.

Females and Males of Reproductive Potential

Non-Clinical Data

Nalmefene did not have mutagenic activity in the Ames test with five bacterial strains or the mouse lymphoma assay. Clastogenic activity was not observed in the mouse micronucleus test or in the cytogenic bone marrow assay in rats. Oral administration of nalmefene up to 1200 mg/m²/day did not affect fertility in rats at exposures at least 6 times the exposure corresponding to a human dose of 5.4 mg (two nalmefene nasal sprays) on an AUC basis.

Clinical Data

No information is provided by the applicant regarding the use of nalmefene in females and males of reproductive potential.

Applicant's Review of Literature

Opiant conducted a published literature search of the active ingredient nalmefene as it pertains to the use in females and males of reproductive potential. The databases used include:

- FDA's Adverse Event Reporting System (FAERS) Public Dashboard
- PubMed including the MEDLINE database

The search from the FDA's Adverse Event Reporting System (FAERS) Public Dashboard using the defined search terms, including: nalmefene and fertility, returned no relevant records.

There were no publications identified in search from the PubMed database using the same defined search terms as above.

DPMH Review of the Literature

Review of published literature by this reviewer of PubMed, Reprotox/Micromedex, GG Briggs & RF Freeman in Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk identified no entries.

Summary

No relevant published information was identified by either the applicant or this reviewer for nalmefene use in patients of reproductive potential. Nalmefene is not genotoxic, does not have any reported effects on fertility, and (based on animal studies) is not teratogenic. Therefore, there is no need for pregnancy testing or contraception recommendations in labeling. Labeling subsection 8.3 Females and Males of Reproductive Potential will be omitted.

CONCLUSION

Animal reproduction studies with nalmefene did not reveal any evidence of teratogenicity. In animal reproduction studies, no embryotoxic effects on embryo-fetal development were observed in rats and rabbits treated with nalmefene at exposures at least 6 times (rats) and up to 20 times (rabbits) the exposure at two human nasal doses of 5.4 mg. There are no human data with nalmefene use during pregnancy to determine a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Life-sustaining therapy for the pregnant woman should not be withheld due to lack of data on the potential effects of nalmefene on the fetus.

There is no data on the presence of nalmefene and its metabolites in human milk, the effects of on the breastfed child, or the effects on milk production. Nalmefene and its metabolites are present in rat milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk.

Nalmefene is not clastogenic or genotoxic. There are no data on fertility effects of nalmefene in patients of reproductive potential.

DPMH does not recommend a Post Marketing Requirement (PMR) for a descriptive pregnancy safety study or a clinical lactation milk-only study to collect safety data because such studies will be difficult to conduct in this patient population. The information collected will be highly confounded with other medications used in the critical care setting. This is one time use of the drug in a life-threatening situation.

DPMH LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of nalmefene labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Life-sustaining therapy for opioid overdose should not be withheld (*see Clinical Considerations*). There are no available data on nalmefene use in pregnant women to evaluate for a drug-associated risk of major birth defects or miscarriage. In animal reproduction studies, no embryotoxic effects on embryo-fetal development were observed in rats and rabbits treated with nalmefene at exposures at least 6 times (rats) and up to 20 times (rabbits) the exposure at two human nasal doses of 5.4 mg (*see Data*).

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

An opioid overdose is a medical emergency and can be fatal for the pregnant woman and fetus if left untreated. Treatment with TRADENAME for opioid overdose should not be withheld because of potential concerns regarding the effects of TRADENAME on the fetus.

Data

Animal Data

Reproduction studies have been performed in rats (up to 1200 mg/m²/day) and rabbits (up to 2400 mg/m²/day) by oral administration of nalmefene and in rabbits by intravenous administration up to 96 mg/m²/day. No effects on embryo-fetal development were observed at exposures at least 6 times (rats) and up to 20 times (rabbits) the exposure corresponding to a human dose of 5.4 mg (two nalmefene nasal sprays) on an AUC basis. The treatment in rats did not affect offspring survival.

8.2 Lactation

Risk Summary

There is no data on the presence of nalmefene and its metabolites in human milk, the effects of nalmefene on the breastfed child, or the effects on milk production. Nalmefene and its metabolites are present in rat milk (*see Data*). When a drug is present in animal milk, it is likely that the drug will be present in human milk.

Data

Nalmefene and its metabolites were secreted into rat milk, reaching concentrations approximately three times those in plasma at one hour and decreasing to about half the corresponding plasma concentrations by 24 hours following bolus administration. The concentration of nalmefene in animal milk does not necessarily predict the concentration of drug in human milk.

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/

CHRISTOS MASTROYANNIS
05/09/2023 03:10:33 PM

TAMARA N JOHNSON
05/10/2023 09:54:41 AM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: May 6, 2023

To: Tanya Brescia-Oddo, Clinical Reviewer
Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Sandy Truong, Regulatory Project Manager, DAAP

Lisa Basham, Associate Director for Labeling, DAAP

From: L. Sheneé Toombs, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for TRADENAME® (nalmeferene) nasal spray

NDA: NDA 217470

In response to DAAP's consult request dated January 12, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), Quick Start Guide (QSG), and carton and container labeling for the original NDA submission for TRADENAME® (nalmeferene) nasal spray.

PI/PPI/IFU/QSG:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on April 21, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI/IFU/QSG, and comments were sent under separate cover on May 5, 2023.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on April 12, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Sheneé Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

46 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/

LATOYA S TOOMBS
05/06/2023 12:08:26 AM

HUMAN FACTORS STUDY REPORT REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 5, 2023
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 217470
Product Type:	Combination Product
Product Name, Dosage Form, and Strength:	Opvee ¹ (nalmefene) nasal spray, 2.7 mg
Device Constituent:	Nasal Spray
Rx or OTC:	Rx
Applicant/Sponsor Name:	Opiant Pharmaceuticals Inc. (Opiant)
Submission Date:	November 22, 2022; January 5, 2023; March 13, 2023; March 20, 2023; April 26, 2023
TTT ID #:	2022-2888
DMEPA 1 Safety Evaluator:	Avani Bhalodia, PharmD, BCPS
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director for Human Factors:	Jason Flint, MBA, PMP

¹ The proposed proprietary name for this NDA, Opvee was found conditionally acceptable on April 24, 2023.

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study results report submitted under NDA 217470 for Opvee (nalmeferene) nasal spray, 2.7 mg.

1.1 PRODUCT DESCRIPTION

Table 1. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	Opioid antagonist
Active Ingredient (Drug or Biologic)	nalmefene
Indication	is indicated - for the complete or partial reversal of opioid drug effects, including respiratory depression, induced by either natural or synthetic opioids. - in the emergency treatment of known or suspected opioid overdose.
Route of Administration	intranasal
Dosage Form	nasal spray
Strength	2.7 mg
Dose and Frequency	The recommended initial dose of Opvee nasal spray in adults and children over 12 years is one spray delivered by intranasal administration, which delivers 2.7 mg of nalmefene. The requirement for repeat doses of Opvee nasal spray (2.7 mg) depends upon the amount, type, and route of administration of the opioid being antagonized. If the desired response is not obtained after 2 to 5 minutes, administer an additional dose of Opvee using a new Opvee nasal spray. If there is still no response and additional doses are available, administer additional doses of Opvee nasal spray every 2 to 5 minutes using a new Opvee nasal spray with each dose until emergency assistance arrives.
How Supplied	Opvee nasal spray is supplied in 2.7 mg doses. Each carton of Opvee nasal spray contains two packs. Each pack contains a single dose.
Storage	Store Opvee nasal spray below 77° F (25° C). Excursions permitted up to 104°F (40°C). Do not freeze.

	Do not open individual blister packs or test nasal spray devices before use.
Container Closure/Device Constituent	(b) (4)
Intended Users	Lay users (adults and adolescents' users), first responders
Intended Use Environment	Public, domestic, and emergency environments

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

- On October 22, 2021, the Applicant submitted their HF validation study protocol under IND 136851 for Opvee (nalmefene hydrochloride) nasal spray, 3 mg². We reviewed the protocol and provided recommendations.³
- On May 24, 2022, the Applicant submitted clarifying questions in response to recommendations that we made during a previous HF protocol review.³ We reviewed the questions and provided responses.⁴
- On November 22, 2022, the Applicant submitted a new drug application (NDA) for Opvee (nalmefene) nasal spray, 2.7 mg under NDA 217470. This submission included HF validation study results report, which is the subject of this review.

² Per the Agency's recommendation in Meeting Minutes dated April 28, 2022, the Applicant changed the strength expression from 3 mg which is the expression of the nalmefene hydrochloride salt to 2.7 mg, which is the expression of the nalmefene base, to align with USP Salt Policy "Monograph Naming Policy for Salt Drug Substances in Drug Products and Compounded Preparations" and FDA guidance "Naming of Drug Products Containing Salt Drug Substances".

³ Barlow M. HF Protocol Review for (b) (4) (IND 136851). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 DEC 17. RCM No.: 2021-2066.

⁴ Oguntimein M. HF Protocol Clarifying Questions Review for (b) (4) (IND 136851). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 JUN 27. RCM No.: 2021-2066-1.

1.3 MATERIALS REVIEWED

We considered the materials listed in Table 2 for this review.

Table 2. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	Section 1.1
Background Information Previous HF Reviews (DMEPA)	A
Background Information on Human Factors Engineering (HFE) Process	B
Human Factors Validation Study Report	C
Information Requests Issued During the Review	D
Labels and Labeling	E

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed, and our analysis to determine if the results indicate that the user interface supports the safe and effective use of the proposed product.

2.1 SUMMARY OF STUDY DESIGN

Table 3 presents a summary of the HF validation study design. See Appendix C for more details on the study design.

Table 3. Study Methodology for Human Factors (HF) Validation Study	
Study Design Elements	Details
Participants	• 26 General population adults with no experience in using single dose nasal devices, ages 18 and older • 25 General population adolescents with no experience in using single dose nasal devices, ages 10–17 • 15 First responders (e.g., police, EMT, paramedic, firefighter)
Training	Study participants did not receive training.
Test Environment & Materials	The use environment was in a non-clinical setting. The demonstration room included a simulated overdose victim on the floor, represented by an adult-sized mannequin. The exterior carton with placebo nasal spray devices, along with the Quick Start Guide (QSG) and Patient Information Leaflet (PIL) were available to the user. Background noise simulated a crowd of

	people talking, similar to what might be expected if a crowd formed around a victim. Lighting was ambient.
Sequence of Study	Simulated use Debriefing of use errors/use difficulties/close calls Knowledge-based task questions Debriefing of errors Qualitative questions (post-use interview)

2.2 DISCUSSION

During the course of our review of the HF validation study, we noted that the Applicant did not implement our recommendation to conduct the knowledge-based task questions via open-ended questions. Specifically, study included multiple choice and yes/no questions. Although the knowledge-based task questions were not open-ended, we acknowledge the knowledge-based task associated with the critical task was also assessed in simulated use scenario. Knowledge-based task questions are typically designed to focus on tasks that cannot be assessed through direct observation during simulated use. As such, in this particular instance, given the critical task was also assessed in simulated use scenario, we have no comments regarding the knowledge-based task questions.

3 RESULTS AND ANALYSES

We have carefully reviewed each observed event, the applicant's URRAs, the participants' subjective feedback, the applicant's RCA, and the Applicant's comments and proposed mitigations below.

Table 4. Focused Analysis of Use Errors, Use Difficulties and Close Calls and DMEPA's Recommendations

Legend: UE = use error; CC = close call; UD = use difficulty; URRRA = use-related risk analysis; RCA = root cause analysis Participants ID: AL: General Population Adults, Ages 18 and Older; AD: General Population Adolescents, Ages 10-17; FR: First Responders (Police, EMT, Firefighter, Paramedic)								
Information Supplied by Applicant		DMEPA’s Findings and Recommendations						
Task: Call 911: Put person on their side <table><tr><td>Errors:</td><td>Participant Type:</td></tr><tr><td>UE (n=33)</td><td>AL = 12, AD = 14, FR = 7</td></tr><tr><td>CC (n=4)</td><td>AL = 1, AD = 3</td></tr></table> Observed error(s): Participants did not put person on their side. Risk associated with Task Errors (Per Applicant URRRA): if this task is omitted or performed incorrectly there is risk of aspiration pneumonitis. Relevant RCA/Subjective Feedback/Observation: - Cognition: participants did not see instruction, one participant suggested to bold this task in the instructions for use (IFU), one participant indicated that they assumed all of the instruction in step 4 of the quick start guide (QSG) was to call 911 because QSG says call 911 and the participant assumed that was the only instruction in step 4 and didn’t continue reading. - Behavior: participants used their own experience to not put the person on their side. For example, one participant assumed you don’t move a person that is unresponsive from an overdose. (b) (4)		Errors:	Participant Type:	UE (n=33)	AL = 12, AD = 14, FR = 7	CC (n=4)	AL = 1, AD = 3	
Errors:	Participant Type:							
UE (n=33)	AL = 12, AD = 14, FR = 7							
CC (n=4)	AL = 1, AD = 3							
Applicant Comment and Proposed Mitigations: none								
		Our review of the IFU indicates that, step 9 includes instructions and figure to put person on their side. However, based on subjective feedback (participants did not see the instruction, one participant suggested to bold this task), and our overall assessment, we find that the step 9 can be improved to be more prominent. We provide our recommendation in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.						

	Additionally, our review of the QSG indicates that, step 4 includes instructions and figure to put person on their side. However, based on subjective feedback (one participant assumed all of the instruction in step 4 was to call 911 because QSG says call 911 and participant assumed that "Call 911" was the only instruction in step 4 and didn't continue reading), and our overall assessment, we find that the step 4 title can be improved to be inclusive of all the tasks users should perform within that step. We provide our recommendation in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing for Agency review.						
Task: Give a Dose in the Nose: Press the plunger firmly to give the dose <table border="1"> <tr> <td>Errors:</td><td>Participant Type:</td></tr> <tr> <td>UE (n=5)</td><td>AL = 3, AD = 1, FR = 1</td></tr> <tr> <td>CC (n=2)</td><td>AD = 2</td></tr> </table>	Errors:	Participant Type:	UE (n=5)	AL = 3, AD = 1, FR = 1	CC (n=2)	AD = 2	We considered one close call as a use error because the participant sprayed the first dose in the air instead of administering it to the patient.
Errors:	Participant Type:						
UE (n=5)	AL = 3, AD = 1, FR = 1						
CC (n=2)	AD = 2						
Observed error(s): Participants did not press the plunger hard enough. One participant pressed the plunger before insertion into nostril. Risk associated with Task Errors (Per Applicant URR): if this task is omitted or performed incorrectly there is risk of • Respiratory/central nervous system depression, coma • Slowed respiratory rate, miotic pupils, lethargy • Death Relevant RCA/Subjective Feedback/Observation: • Behavior: participants used their own experience to perform this task; some participants did not read the instructions entirely. For example, a few participants did not press the plunger firmly because they either thought it was like a 'dummy' device and they looked for a basin to possibly squirt the liquid into since this was a test or because they were not familiar with the device. These participants were able to correctly dispense a dose using the second device. • One participant assumed the medication would be administered via mouth because they thought it was a medication that you just inhaled it. Another participant pressed plunger before inserting in nostril because they didn't think it would dispense with that little pressure. • Behavior: one participant did not initially administer the first dose because they did not hold the device correctly; however, after reading the instructions again, they self-corrected and correctly administered a dose. One participant							

accidentally sprayed the first dose in the air but used the second dose to administer dose correctly.							
Applicant Comment and Proposed Mitigations: none	Our review of the user interface and labels and labeling indicates that the IFU and QSG contains instructions and/or images to support this task. Additionally, we note the majority of the participants experiencing use errors did not read the IFU and QSG. Based on our review of the user interface, subjective feedback, and RCA, we did not identify areas of improvement and have no recommendations at this time.						
Task: Give Second Dose: If the person does not wake up, get another (b) (4) nasal spray and give another dose in the nose <table border="1" data-bbox="321 488 722 581"> <tr> <td>Errors:</td><td>Participant Type:</td></tr> <tr> <td>UE (n=6)</td><td>AL = 3, AD = 3</td></tr> <tr> <td>CC (n=2)</td><td>AD = 1, FR = 1</td></tr> </table> Observed error(s): Participants did not give second dose. Risk associated with Task Errors (Per Applicant URRRA): if this task is omitted or performed incorrectly there is risk of • Respiratory/central nervous system depression, coma • Slowed respiratory rate, miotic pupils, lethargy • Death Relevant RCA/Subjective Feedback/Observation: • Cognition: participant did not understand instructions in the IFU to use new device for second dose. One participant did not think second dose needed to be given because person was still unresponsive, but then self-corrected and gave second dose. • Behavior: participants were unable to perform this step as they used both devices to give first dose. One participant used their own intuition and overrode instructions to give second dose. The participant thought two doses would be too much and could cause harm and would rather wait for 911 to help instead. One participant initially tried to use first used device for second dose but self-corrected and used second device.	Errors:	Participant Type:	UE (n=6)	AL = 3, AD = 3	CC (n=2)	AD = 1, FR = 1	
Errors:	Participant Type:						
UE (n=6)	AL = 3, AD = 3						
CC (n=2)	AD = 1, FR = 1						
Applicant Comment and Proposed Mitigations: none	Our review of the user interface and labels and labeling indicates that the IFU and QSG contains instructions and/or images to support this task. However, based on subjective feedback (one participant did not understand the instruction to use “another” device to mean to use a “new” device), and our overall assessment, we find that the IFU Step 10 and QSG Step 5 can be improved for clarity. We provide our recommendations in Table A to address this concern. We have determined that this change can be						

	implemented without submitting additional HF validation testing for Agency review.
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3.1 ANALYSIS OF OTHER CRITICAL AND NON-CRITICAL TASK ERRORS

The HF validation study showed use errors, use difficulties, and close calls with the tasks listed below in this section; however, based on our review of the available assessment of these use errors/use difficulties/close calls, the available participants' subjective feedback and the Applicant's root cause analysis, we determined the residual risk is acceptable. Specifically, users did not provide subjective feedback that indicated any potential issues with the user interface for the tasks identified. Based on our assessment, we find that the labeling mitigations in place include information that is prominently placed within the labels and labeling to address the tasks below. Subsequently, we did not identify further need for risk mitigation strategies at this time to address the use errors related to the following tasks and find the residual risks are acceptable:

- Check for Response
- Prepare: Holds device with fingers on both sides of nozzle and thumb on plunger
- Insert nozzle into the nose: there were one use error, two close calls and two use difficulties (however, we considered these two use difficulties as use errors because both participants did not complete the task. For example, one participant accidentally sprayed the first dose in the air as they inserted in the nose but pulled out before administering to look at the device and another participant called 911 again to be cautious) observed with this task. The root cause analysis indicated that these use error, close calls and use difficulties were due to participants using their own experience to perform this task or users not reading the instructions entirely (participants sprayed the first dose into the air, participant held device upside down and pointed towards the chin but self-corrected after reading instructions and gave dose correctly). Based on our review of the user interface, and the location and layout of the instructions for use and quick start guide, we did not identify any additional mitigations to address these use error, close calls and use difficulties and have no recommendations at this time.
- Call 911: There were 37 use errors, two close calls and two use difficulties observed with this task. The root cause analysis indicated that these use errors, close calls and use difficulties were due to behavior (the majority of the participants called 911 prior to administering the dose than instructed in the QSG, because of the belief that calling 911 immediately would be best due to the emergent nature of the event). These use errors do not appear to be based on the user interface, based on subjective feedback from the participants. Based on our review of the user interface, we did not identify any additional mitigations to address these use errors, close calls and use difficulties and have no recommendations at this time.
- Wait 2 to 5 minutes to see if the person wakes up: There were 31 use errors, one close call and one use difficulty observed with this task. The root cause analysis indicated that majority of these use errors, close call and use difficulty were due to behavior (participants used their own judgement to be quick because this was an emergency and administered the second dose earlier than 2 minutes). Including the number of people that completed this task in accordance with the QSG, majority of the participants administered the second dose in under 5 minutes. We reached out to the Division of

Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) clinical team to inquire about the risk if the user does not wait for 2 to 5 minutes before giving the second dose. The DAAP clinical team discussed with clinical pharmacology team and stated that, “2 back-to-back doses (without the 2-5 minute delay between doses) will not exceed the Cmax of previously approved doses of Revex (nalmefene) injection. Therefore, no new/unexpected AEs/reactions, as compared to the NDA review of AEs for Revex injection, are anticipated if 2 doses of Opvee are given in quick succession.” Based on this feedback and our review of the user interface, we did not identify any additional mitigations to address these use errors, close call and use difficulty and have no recommendations at this time.

- (Knowledge based assessment (KBA)) Store Opvee nasal spray at room temperature, below 77°F (25°C) and excursions permitted to 104°F (40°C).
- (KBA) According to the Patient Information, what is one example of a sign of an opioid overdose?
- (KBA) According to the Patient Information, is it okay or not okay for someone who is allergic to the ingredients to use this product?
- (KBA) Know that the dose has been delivered when the white plunger has been pushed all the way down until it stops.
- (KBA) Know how many doses are in each Opvee nasal spray.
- (KBA) After Opvee Nasal Spray has been used, put it back into its box and throw away the Opvee Nasal Spray away from children.

3.2 LABELS AND LABELING

Table A below includes the identified medication error issues with the submitted instructions for use (IFU) and Quick Start Guide (QSG) based on the HF study results, our rationale for concern, and the proposed recommendation to minimize the risk for medication error. Additionally, we note that the DMEPA 1 primary review team evaluated product specific labels and labeling under separate cover.⁵

⁵ Birkemeier, D. Label and Labeling Review for Nalmefene (NDA 217470). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 MAR 16. TTT ID #: 2022-2538.

Table A: Identified Issues and Recommendations for Opiant Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	Identified Issue	Rationale for Concern	Recommendation
Instructions for Use (IFU)			
1.	The instructions in Step 9 to put the person on their side is not prominent.	Per the use related risk analysis (URRA), if the user does not put person on their side there is risk of aspiration pneumonitis. The human factors (HF) validation study results identified subjective feedback that indicated that some participants did not see the instruction.	We recommend revising step 9 to bold the statement, "Put the person on their side (Recovery Position)".
2.	The instructions in Step 10 include the statement "(b) (4)" that can be improved for clarity.	Per the URRA, if the user does not give a second dose (if required), there is risk of respiratory/central nervous system depression, coma, slowed respiratory rate, miotic pupils, lethargy, and death. The HF validation study results identified subjective feedback that indicated that one participant did not interpret this statement to mean "get a new nasal spray" from the box.	Consider revising the statement "(b) (4)" to "Get a new (b) (4) Nasal Spray from the box."

Quick Start Guide (QSG)			
1.	Step 4's title is not inclusive of all the tasks users should perform within that step.	Per the URRRA, if the user does not put person on their side there is risk of aspiration pneumonitis. The HF validation study results identified subjective feedback that indicated a participant assumed all of the instructions in step 4 was to call 911 because the participant assumed that "Call 911" was the only instruction in step 4 and didn't continue reading.	We recommend revising step 4 title to be inclusive of all the tasks users should perform within that step.
2.	The instructions in Step 5 include the statement (b) (4) that can be improved for clarity.	Per the URRRA, if the user does not give a second dose (if required), there is risk of respiratory/central nervous system depression, coma, slowed respiratory rate, miotic pupils, lethargy, and death. The HF validation study results identified subjective feedback that indicated that one participant did not interpret this statement to mean "get a new nasal spray" from the box.	Consider revising the statement "(b) (4) (U) (4) to "Get a new Nasal Spray from the box."

4 CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study demonstrated several use errors, close calls, use difficulties with critical tasks that may result in harm. Based on our review of the available participants' subjective feedback, and root cause analysis, we identified additional risk mitigations to address the use errors. Above, we have provided recommendations in Table A for the Applicant. We ask that the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) convey Table A in its entirety to the Applicant. These changes can be implemented without submitting additional HF validation testing data for Agency review.

4.1 RECOMMENDATIONS FOR THE OPIANT PHARMACEUTICALS, INC.

Our evaluation of your human factors (HF) validation study indicates that there are additional mitigations that can be implemented to address use errors that occurred with critical task. We provide recommendations in Table A, and we recommend that you implement these recommendations and submit the revised label and labeling for our review. We have determined that in this instance, you may implement these revisions without submitting additional human factors validation data for Agency review.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. BACKGROUND INFORMATION

A.1 PREVIOUS HF REVIEWS

A.1.1 Methods

On December 30, 2022, we searched the L:drive and AIMS using the terms, IND 136851, NDA 217470, and (b) (4) to identify reviews previously performed by DMEPA.

A.1.2 Results

Our search identified two previous reviews^{3,4}, and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX B. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessible in the HF study results report. See Appendix C.

APPENDIX C. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:

<\\CDSESUB1\EVSPROD\nda217470\0004\m5\53-clin-stud-rep\535-rep-effic-safety-stud\emergency-treatment-of-known-or-suspected-opioid-overdose\5354-other-stud-rep\22037\22037.pdf>

APPENDIX D. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On January 3, 2023, we issued information request (IR) to:

- request their use-related risk analysis for their proposed product.
- clarify whether they implemented all of the Agency's recommendations and provide a table that includes the recommendations they implemented and the updated section in the HF validation study protocol within the study results report that reflects these implementations.
- request two (2) placebo only intend-to-market samples of their proposed product including the commercial layout of the Instructions for Use (IFU), quick start guide, container label, and carton labeling

The Applicant provided acceptable response on January 5, 2023, that can be accessible in EDR via: <\\CDSESUB1\EVSPROD\nda217470\0007\m5\53-clin-stud-rep\535-rep-effic-safety-stud\emergency-treatment-of-known-or-suspected-opioid-overdose\5354-other-stud-rep\fda-ir-4\fda-response-4.pdf>

On March 2, 2023, we issued IR to:

- request the full evaluation, subjective feedback, and root cause analysis for non-critical knowledge-based task errors.

- clarify whether the root causes described in Appendix 16.8 Detailed Root Cause Analysis pertain to use of the IFU or the QSG.

The Applicant provided acceptable response on March 13, 2023, that can be accessible in EDR via: <\\CDSESUB1\EVSPROD\nda217470\0022\m5\53-clin-stud-rep\535-rep-effic-safety-stud\emergency-treatment-of-known-or-suspected-opioid-overdose\5354-other-stud-rep\human-factor\hf-response.pdf>

On March 16, 2023, we issued IR to:

- clarify what side of the patient information leaflet (PIL) were the participants looking at when answering the knowledge-based questions for questions in which errors were observed
- request a complete evaluation, subjective feedback, and root cause analysis for all use errors, use difficulties and close calls that were observed in the study

The Applicant provided acceptable response on March 20, 2023, that can be accessible in EDR via: <\\CDSESUB1\EVSPROD\nda217470\0023\m5\53-clin-stud-rep\535-rep-effic-safety-stud\emergency-treatment-of-known-or-suspected-opioid-overdose\5354-other-stud-rep\human-factor-16-mar-2023\hf-ir-response.pdf>

On April 24, 2023, we issued IR to:

- request any additional information as to whether the moderator asked any other probing questions and participant's responses to the probing questions for the errors observed that had incomplete root cause description.
- request a revised use-related risk assessment with detailed descriptions of the clinical impact of potential use errors.

The Applicant provided acceptable response on April 26, 2023, that can be accessible in EDR via: <\\CDSESUB1\EVSPROD\nda217470\0033\m5\53-clin-stud-rep\535-rep-effic-safety-stud\emergency-treatment-of-known-or-suspected-opioid-overdose\5354-other-stud-rep\human-factor-24-april-2023\hf-response.pdf>

APPENDIX E. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁶ along with postmarket medication error data, we reviewed the following Opvee labels and labeling submitted by Opiant Pharmaceuticals, Inc. on November 22, 2022.

⁶ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Carton labeling
- Container label(s)
- Quick Start Guide (QSG)
- Prescribing information, Instructions for Use (Image not shown), available from EDR via: <\\CDSESUB1\EVSPROD\nda217470\0004\m1\us\prescribing-information-patient-info-ifu.docx>

E.2 Label and Labeling Images

Carton Labeling



Container/Blister Label(s)



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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: May 5, 2023

To: Sandy Truong, PharmD
Regulatory Project Manager
Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Jessica Chung, PharmD, MS
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

L. Sheneé Toombs, PharmD, CPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI),
Instructions for Use (IFU), and Quick Start Guide (QSG)

Drug Name (established name): TRADENAME (nalmeferene)

Dosage Form and Route: nasal spray, for intranasal use

Application Type/Number: NDA 217470

Applicant: Opiant Pharmaceuticals, Inc. c/o Pacific-Link Consulting

1 INTRODUCTION

On November 22, 2022, Opiant Pharmaceuticals, Inc. c/o Pacific Link-Consulting submitted for the Agency's review the final part of their rolling submission of a 505(b)(2) New Drug Application (NDA) 217470 for TRADENAME (nalmefene) nasal spray. The reference listed drug (RLD) for this submission is NDA 020459 for REVEX (nalmefene hydrochloride) injection. The proposed indications for TRADENAME (nalmefene) nasal spray are as follows:

- for the complete or partial reversal of opioid drug effects, including respiratory depression, induced by either natural or synthetic opioids.
- for the emergency treatment of known or suspected opioid overdose.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) on January 12, 2023, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI), Instructions for Use (IFU) and Quick Start Guide (QSG) for TRADENAME (nalmefene) nasal spray.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU and QSG was completed on March 16, 2023.

2 MATERIAL REVIEWED

- Draft TRADENAME (nalmefene) nasal spray PPI, IFU and QSG received on November 22, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 21, 2023.
- Draft TRADENAME (nalmefene) nasal spray Prescribing Information (PI) received on November 22, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 21, 2023. An updated PI was accessed from SharePoint on May 4, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU and QSG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more

accessible for patients with vision loss. We reformatted the PPI, IFU, and QSG document using the Arial font, size 10.

In our collaborative review of the PPI, IFU, and QSG we:

- simplified wording and clarified concepts where possible
- ensured that the PPI, IFU, and QSG are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI, IFU, and QSG are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI, IFU, and QSG meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI, IFU, and QSG are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI, IFU, and QSG are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI, IFU, and QSG.

Please let us know if you have any questions.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Rare Diseases, Pediatrics, Urologic,
and Reproductive Medicine
Division of Pediatrics and Maternal Health
Silver Spring, MD 20993

MEMORANDUM TO FILE

Date of Consult Request: December 14, 2022

From: Michelle L. Pollack PA-C, Regulatory Project Manager
Division of Regulatory Operations for Rare Diseases,
Pediatrics, Urologic, and Reproductive Medicine

Subject: Pediatric Labeling

NDA Number: NDA 217470

Drug: (b) (4) (Nalmefene) Nasal Spray

Applicant: Chiesi Farmaceutici S.p.A.

Indication(s): For the complete or partial reversal of opioid drug effects,
Including respiratory depression, induced by either natural
or synthetic opioids; In the emergency treatment of known
or suspected opioid overdose

The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) submitted a consult request to the Division of Pediatrics and Maternal Health (DPMH) for assistance with the review of pediatric and maternal health labeling language included in the Prescribing Information (PI) for the above referenced application. This memorandum is for the Pediatric Team portion of the consult.

The pediatric team participated in applicable team meetings to discuss the proposed labeling and provided labeling recommendations to DRDMG for subsequent negotiation with the applicant. This memorandum closes the pediatric portion of this consult request. A clinical review is being prepared to close out the maternal health portion of this consult request.

DPMH RPM- Michelle Pollack
DPMH Lead Consumer Safety Officer – George Greeley
DPMH Pediatric Reviewer- Sonaly McClymont

DPMH Pediatric Team Leader- Shetarra Walker
DPMH Deputy Division Director- John Alexander

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/s/

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 17, 2023
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 217470
Product Name, Dosage Form, and Strength:	Nalmefene nasal spray, 2.7 mg
Applicant/Sponsor Name:	Opiant Pharmaceuticals Inc. (Opiant)
TTT ID #:	2022-2538-1
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD, FISMP, NREMT
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label, blister tray labeling, and carton labeling received on April 12, 2023 for nalmefene. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container label, blister tray labeling, and carton labeling for nalmefene (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

We note that our previous recommendation for the quick start guide (QSG), which also relates to the QSG on the carton, will be conveyed to Opiant Pharmaceuticals Inc. at a later date in conjunction with Prescribing Information labeling negotiations.

The Applicant implemented all of our other container label, blister tray and carton labeling recommendations and we have no additional recommendations at this time.

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^a Birkemeier D. Label and Labeling Review for nalmefene (NDA 217470). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 MAR 16. TTT ID No.: 2022-2538.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 16, 2023
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 217470
Product Name and Strength:	Nalmefene nasal spray, 2.7 mg
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Opiant Pharmaceuticals Inc. (Opiant)
FDA Received Date:	May 27, 2022; November 22, 2022
TTT ID #:	2022-2538
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD, FISMP, NREMT
DMEPA 1 Team Leader:	Valerie Vaughan, PharmD

1 REASON FOR REVIEW

As part of the approval process for Nalmefene nasal spray, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the proposed nalmefene prescribing information (PI), container label, carton labeling, instructions for use (IFU) and quick start guide (QSG) for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

NDA 217470 is a 505(b)(2) NDA and the listed drug product is Revex, NDA 020459. Opiant originally submitted NDA 217470 on May 27, 2022, as part of a rolling review.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F
N/A=not applicable for this review	
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance	

3 CONCLUSION AND RECOMMENDATIONS

Our evaluation of the nalmefene instructions for use (IFU) did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time.

The proposed prescribing information (PI), container label, carton labeling, and quick start guide (QSG) may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Opiant Pharmaceuticals Inc.

Note that DMEPA 1 is evaluating the HF validation study results under separate cover and based on the outcome of that review additional label and labeling comments may be forthcoming.

4 RECOMMENDATIONS FOR DIVISION OF ANESTHESIOLOGY, ADDICTION MEDICINE, AND PAIN MEDICINE (DAAP)

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Issue			
1.	The Prescribing Information (PI) includes the proposed proprietary name, (b) (4)	The proposed proprietary name, (b) (4) was found unacceptable under OSE RCM# 2022-1044724825 on January 27, 2023, and a new proposed proprietary name is currently under review.	Replace all instances of the name “(b) (4)” with the placeholder, TRADENAME, until a propriety name is found conditionally acceptable.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	Section 2.1 contains a typo, “...allow the head to title back.”	Correcting the typo will help alleviate confusion.	Correct the statement to “...allow the head to tilt back.”
2.	The last bullet of Section 2.1 currently reads (b) (4)	The statement can be improved for clarity to state “recovery position”.	Revise the bullet to read “Place the patient in the recovery position (b) (4)”
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	As currently presented, the packaging type term is listed as “(b) (4)”.	The package type terminology is incorrect. Per USP <659> <i>Packaging and Storage Requirements</i> ,	Revise the package type term to read “unit-dose”. This recommendation is also applicable to <i>Dosage Forms</i>

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		the correct terminology for your product is “unit-dose”.	<i>and Strengths</i> in the highlights of prescribing information.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	As currently presented, the appropriate information to facilitate identification of the dosage form is not included.	Section 16 <i>How Supplied/Storage and Handling</i> should contain information suitable for product identification in accordance with 21 CFR 201.57(c)(17)(iii).	We recommend including identifying information in Section 16 <i>How Supplied/Storage and Handling</i> (e.g., add solution color and clarity information).
2.	Currently contains the phrase “(b) (4)” 	This statement can be improved for clarity.	We recommend revising this statement to read “Each unit-dose nasal spray device delivers 2.7 mg of nalmefene (equivalent to 3 mg of nalmefene hydrochloride) in 0.1 mL. Each carton contains two unit-dose nasal spray devices.”
3.	Currently the NDC # statement reads “NDC # 75095-003- (b) (4)” which appears to be associated with the individual device packs.	The product is intended to be dispensed as an intact carton containing two devices.	We recommend revising the NDC # statement to correspond to the NDC # contained on the carton labeling.
4.	As currently presented in Section 16.2 Storage and Handling, the packaging type term is listed as “(b) (4)”.	The package type terminology is incorrect. Per USP <659> <i>Packaging and Storage Requirements</i> , the correct terminology for your product is “unit-dose”.	Revise the package type term to read “unit-dose”. This recommendation is also applicable to <i>Dosage Forms and Strengths</i> in the highlights of prescribing information.

5 RECOMMENDATIONS FOR OPIANT PHARMACEUTICALS INC.

Table 3. Identified Issues and Recommendations for Opiant Pharmaceuticals Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Issue			
1.	The container label, carton labeling, blister tray labeling, IFU, and QSG include the proposed proprietary name, (b) (4)	The proposed proprietary name, (b) (4) was found unacceptable on January 27, 2023, and a new proposed proprietary name is currently under review.	Replace all instances of the name “(b) (4)” with the placeholder, TRADENAME, until a propriety name is found conditionally acceptable.
Container Label and Carton Labeling			
1.	As currently presented, the route of administration is listed as “(b) (4)”.	This statement can be improved to increase consistency with the IFU.	Revise this statement to read “For Use in the Nose Only”.
2.	The expiration date statement is missing.	Per 21 CFR 211.137, the expiration date is required on the immediate container and carton labeling.	Identify the location and format of the expiration date you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a forward slash be used to

Table 3. Identified Issues and Recommendations for Opiant Pharmaceuticals Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			separate the portions of the expiration date.
3.	The lot number statement is missing.	The lot number statement is required as per 21 CFR 201.10(i)(1).	Note the placement of the lot number statement.
Carton Labeling			
1.	As currently presented, the packaging type term is listed as (b) (4) ”.	The package type terminology is incorrect. Per USP <659> <i>Packaging and Storage Requirements</i> , the correct terminology for your product is “unit-dose”.	Revise the package type term to read “unit-dose”.
2.	As currently presented, the carton labeling contains the statement (b) (4) which does not include the package type term. Additionally, there is no space between the numerical strength and unit of measure. Additionally, the numerical strength “3.0” is presented with a trailing zero.	Per USP <659> <i>Packaging and Storage Requirements</i> , the correct package type terminology for your product is “unit-dose”. Additionally, the lack of space between the numerical strength and unit of measure decreases readability. Additionally, trailing zeros can lead to tenfold dosing errors when the decimal point goes unnoticed.	Revise the statement to include the package type term. For example, “Each unit-dose nasal spray device (b) (4) ...” Additionally, to improve the readability of the statement, place adequate space between the numerical dose and unit of measure and remove the trailing zero (i.e., 2.7 mg, 3 mg, 0.1 mL).
3.	We note the fifth panel from the right of the carton labeling states, (b) (4) ”.	We note that the carton contains the instructions for use, however the blister trays (“(b) (4)”) contain a copy of the quick start	Revise this statement to read “Each carton contains Instructions for Use”.

Table 3. Identified Issues and Recommendations for Opiant Pharmaceuticals Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4)	guide, not the instructions for use.	
Blister Tray (Pack) Labeling			
1.	As currently presented, the route of administration is listed as “(b) (4)”.	This statement can be improved to increase consistency with the IFU.	Revise this statement to read “For Use in the Nose Only”.
2.	As currently presented, the blister tray labeling contains the statement (b) (4). Additionally, this statement does not include the package type term. Additionally, there is no space between the numerical strength and unit of measure. Additionally, the numerical strength “3.0” is presented with a trailing zero.	The phrase “nasal spray unit” can be improved to maintain consistency. Additionally, per USP <659> <i>Packaging and Storage Requirements</i> , the correct package type terminology for your product is “unit-dose”. Additionally, the lack of space between the numerical strength and unit of measure impairs readability. Additionally, trailing zeros can lead to tenfold dosing errors when the decimal point goes unnoticed.	Revise the statement to change the phrase “(b) (4)” to “nasal spray device” and to include the package type term. For example, “Each unit-dose nasal spray device (b) (4) ...” To improve the readability of the statement, place adequate space between the numerical dose and unit of measure and remove the trailing zero (i.e., 2.7 mg, 3 mg, 0.1 mL).

Table 3. Identified Issues and Recommendations for Opiant Pharmaceuticals Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Quick Start Guide (QSG)			
1.	Step 4 currently depicts the person in the recovery position, and the text states (b) (4)	The recovery position is a common first aid practice that is performed when a person is unconscious but breathing and has no other life-threatening conditions. The recovery position helps to keep the airway clear and open and ensures that any vomit or fluid will not create a choking hazard. The textual description can be improved for clarity to state “recovery position”.	We recommend revising the textual statement “(b) (4) to “(b) (4) the person on their side (recovery position).” Note these changes are also applicable to the QSG depicted on the carton labeling.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table presents relevant product information for nalmefene that Opiant Pharmaceuticals Inc. submitted on November 22, 2022, and the listed drug (LD).

Table 4. Relevant Product Information for Listed Drug and nalmefene		
Product Name	Revex (discontinued)	nalmefene
Application Type and Number	NDA 020459	NDA 217470
Initial Approval Date	April 17, 1995	N/A
Active Ingredient	Nalmefene hydrochloride	Nalmefene
Indication	Complete or partial reversal of opioid drug effects, including respiratory depression, induced by either natural or synthetic opioids.	
Route of Administration	Intranasal	Intravenous, intramuscular, subcutaneous
Dosage Form	Nasal spray	Injection ampule
Strength	2.7 mg	100 mcg/mL 2 mg/2 mL (1 mg/mL)
Dose and Frequency	Initial dosing in adults and children over 12 years in one spray (2.7 mg) delivered by intranasal administration. If the desired response is not obtained after 2 to 5 minutes, administer an additional dose using a new nasal spray device. If there is still no response and additional doses are available, administer additional doses every 2 to 5 minutes using a new nasal spray device with each nose. If the patient responds and relapsed back into respiratory depression, administer an additional dose using a new nasal spray device.	Recommended initial dose for non-opioid dependent patients is 0.5 mg/70 kg. If needed, this may be followed by a second dose of 1 mg/70 kg 2 to 5 minutes later. If a total dose of 1.5 mg/70 kg has been administered without clinical response, additional doses is unlikely to have an effect. Patients should not be given more Revex than is required to restore the respiratory rate to normal, this minimizing the likelihood of cardiovascular stress and precipitated withdrawal syndrome. If there is a reasonable suspicion of opioid dependency, a challenge dose of 0.1 mg/70 kg should be administered initially. If there

		is no evidence of withdrawal within 2 minutes, the recommended dosing should be followed.
How Supplied	One carton containing two packs, each pack containing one nasal spray device. Each nasal spray device delivers one 2.7 mg dose of nalmefene.	• Ampule containing 1 mL of 100 mcg/mL nalmefene base (Blue Label) Box of 10 • Ampule containing 2 mL of 1 mg/mL nalmefene base (Green Label) Box of 10
Storage	Store below 77°F (25°C). Excursions permitted up to 104°F (40°C). Do not freeze.	Store at controlled room temperature

APPENDIX F. LABELS AND LABELING

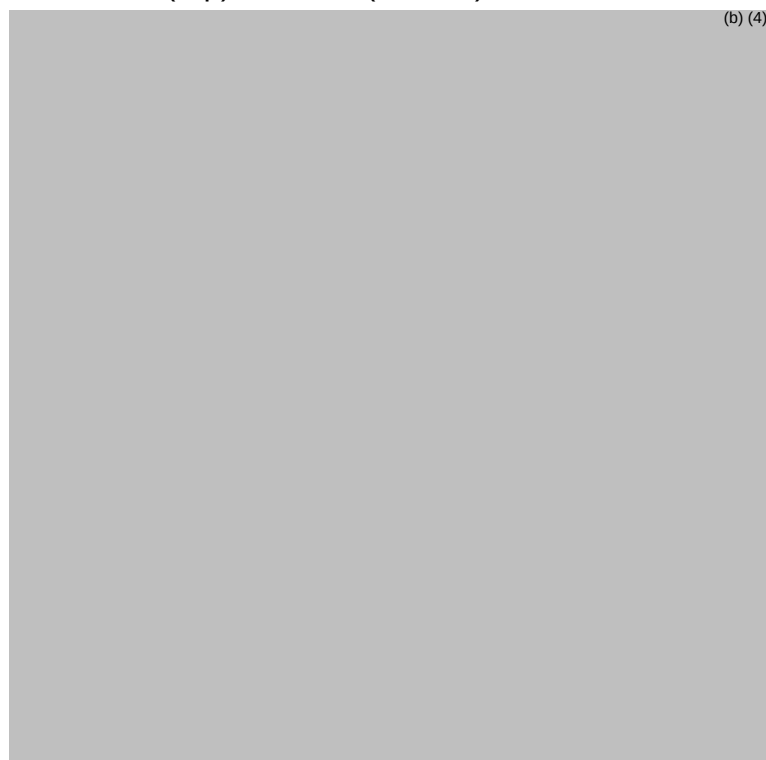
F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following nalmefene labels and labeling submitted by Opiant Pharmaceuticals Inc. submitted on November 22, 2022.

- Container Label
- Blister Tray Labeling
- Carton Labeling
- Quick Start Guide
- Instructions for Use (IFU) (Image not shown) (available in the PI)
- Prescribing Information (PI) (Image not shown) available from <\\CDSESUB1\EVSPROD\nda217470\0004\m1\us\draft-annot-labeling-text.pdf>

F.2 Label and Labeling Images

Container Label – Device Front (top) and Back (bottom)



^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

5 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/

DAMON A BIRKEMEIER
03/16/2023 06:35:44 AM

VALERIE S VAUGHAN
03/16/2023 01:27:25 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 2/3/2023

TO: Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Office of Neuroscience (ON)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct on-site inspections**

RE: NDA 217470

The Office of Study Integrity and Surveillance (OSIS) determined that inspections are not needed for the sites listed below. The rationale for this decision is noted below.

Rationale

Worldwide, San Antonio: The Office of Regulatory Affairs (ORA) conducted an inspection for the clinical site in September 2022. The inspection was conducted under the following submission: NDA (b) (4).

OSIS concluded that data from the reviewed studies were reliable.

(b) (4) OSIS conducted a Remote Regulatory Assessment (RRA) for the analytical site in (b) (4). The RRA was conducted under the following submission: NDA (b) (4).

OSIS concluded that data from the reviewed studies were reliable.

OSIS notes that this site is permanently closed.

(b) (4): OSIS conducted an RRA for the analytical site in (b) (4). The RRA was conducted under the following submission: NDA (b) (4).

OSIS concluded that data from the reviewed studies were reliable.

Sites

Facility Type	Facility Name	Facility Address
Clinical	Worldwide Clinical Trials (WCT) Early Phase Services, LLC.	2455 Northeast Loop 410, Suite 150, San Antonio, TX
Analytical	(b) (4)	
Analytical		

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/s/

WENDY NG
02/03/2023 02:55:57 PM