CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217470Orig1s000

PRODUCT QUALITY REVIEW(S)

Table of Contents

NDA Executive Summary NDA 217470 Assessment 1

1. Application/Product Information

NDA Number.	217470		
Applicant Name	Opiant Pharmaceuticals, Inc.		
Drug Product Name	Nalmefene nasal spray		
Dosage Form.	Spray, metered		
Proposed Strength(s)	2.7 mg in 100 microliters		
Route of Administration	Nasal		
Maximum Daily Dose	5.4 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Complete or partial reversal of opioid drug effects, including respiratory depression, induced by either natural or synthetic opioids.		
Drug Product Description	clear and colorless to light yellow solution, which is filled into unit dose 400 microliter (b) (4) glass vials closed with a black (b) (4) rubber stopper and then assembled into the Aptar Unidose Nasal Spray (UDS) device		
Co-packaged product information	N/A		
Device information:	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 microliters per actuation.		
Storage Temperature/ Conditions	°C Appears this way on original		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Katie Duncan	Gaetan Ladouceur
	Drug Product/ Labeling	Renish Delvadia	Valerie Amspacher

	Manufacturing	Raeann Wu	Cassandra Abellard
	Biopharmaceutics	N/A	N/A
	Microbiology	Ryan Blower	Erika Pfeiler
	Other (specify):	N/A	N/A
	RBPM	Anika Lalmansingh	
	ATL	Valerie Amspacher	
Consults	CDRH: Porsche Bennett		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: The provided data supports an expiry period of 28 months when stored at controlled room temperature 15°C to 25°C (59°F to 77°F).

b. Additional Comments for Action

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

CMC recommends approval for this application based on reviews by drug substance, drug product, process/facilities and microbiology.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance - Adequate
Drug Product - Adequate
Quality Labeling - Adequate
Manufacturing - Adequate

Biopharmaceutics - Adequate
Microbiology - Adequate

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

Valerie Amspacher

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate with comments; comments for PI are included in the OND working label and reproduced in the review below.

NDA 217470 (nalmefene nasal spray)

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	"Tradename"	Applicant will update to TRADENAME, if proprietary name is granted.
Established name(s)	(nalmefene) nasal spray	Acceptable
Route(s) of administration	N/A	Included in established name.
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Proposed "(b) (4) [redacted]	Change to "Nasal spray: 2.7 mg of nalmefene (b) (4) [redacted] comment included in OND label.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

Reference ID: 5166639

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	n/a

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Reference ID: 5166639

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section **Proposed:** (b) (4) . Change to "Nasal Spray: 2.7 mg nalmefene per device. Each unit-dose nasal spray device delivers a single spray containing 2.7 mg of nalmefene."		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Yes	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2.3 Section 11 (DESCRIPTION)

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Reference ID: 5166639

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section **Track change version**  		
Proprietary and established name(s)	Established name not included	See Track change version above
Dosage form(s) and route(s) of administration	Yes	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Yes	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Yes	

For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	N.A	
Pharmacological/ therapeutic class	Yes	
Chemical name, structural formula, molecular weight	Yes	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Yes	See Track change version above for pH.

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	None	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Reference ID: 5166639

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section **Tracked change version** (b) (4) 		
Available dosage form(s)	Yes	See Track change version above
Strength(s) in metric system	Yes	
Available units (e.g., bottles of 100 tablets)	Yes	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	

Reference ID: 5166639

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Included	See Track change version above
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.		See Track change version above
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”	N/A	
Include information about child-resistant packaging	N/A	

Reference ID: 5166639

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for: Opiant Pharmaceuticals Santa Monica, CA 90401	Acceptable

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling

Patient information (Tracked change version from OND working label (section pertaining to CMC)

(b) (4)

[redacted]

3.0 CARTON AND CONTAINER LABELING

3.1 Blister Label

(Copy/paste or refer to a representative example of a proposed container)

3.2 Carton Labeling

(Copy/paste or refer to a representative example of a proposed carton labeling)

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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Yes	
Dosage strength	Yes	Change from (b) (4) [redacted] to "Each unit-dose nasal spray device delivers 2.7 mg nalmefene in 0.1 mL solution" on cartoon and blister labels"
Route of administration	Yes	
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Yes	
Net contents (e.g. tablet count)	States on cartoon "two unit-dose devices"	
"Rx only" displayed on the principal display	Yes (on blister and package)	
NDC number	Yes (on cartoon, blister and device)	
Lot number and expiration date	Yes (on cartoon and blister)	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Yes (on cartoon and blister)	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	

Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	States “for use in the nose only” on cartoon, blister and device.	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Yes	

Item	Information Provided in the NDA	Assessor’s Comments about Carton Labeling
Name of manufacturer/distributor	Yes	
Medication Guide (if applicable)	Yes	
No text on Ferrule and Cap overseal	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available		

Assessment of Carton and Container Labeling: ***Adequate with a comment***

1. Make the following change on the proposed cartoon and blister labels: Replace “ (b) (4) with “Each unit-dose nasal spray device delivers 2.7 mg nalmefene in 0.1 mL solution”

Reference ID: 5166639

Overall Assessment and Recommendation:

Adequate with changes

Primary Labeling Assessor Name and Date: Renishkumar Delvadia, 04/26/2023

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Reference ID: 5166639

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	217470
Assessment Cycle Number	01
Drug Product Name/ Strength	nalmefene/ 2.7 mg/100µl
Route of Administration	Nasal Spray
Applicant Name	Opiant Pharmaceuticals Inc.
Therapeutic Classification/ OND Division	CDER/OND/ON/DAAP
Manufacturing Site	(b) (4)
Method of Sterilization	N/A; non-sterile

Assessment Recommendation: **Adequate**

Assessment Summary: The application is adequate from the standpoint of product quality microbiology.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0002 SD 2	08/30/2022
0017 SD 17	02/08/2023

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

Remarks: The drug product is a non-sterile clear and colorless to light yellow nasal spray indicated for the treatment of opioid overdose as an easy-to-administer nasal spray that comes in a 400 µL (b) (4) glass vials closed with a black (b) (4) rubber stopper and then assembled into the Aptar Unidose Nasal Spray device. (b) (4)

Concise Description of Outstanding Issues: N/A

Supporting Documents: N/A

S DRUG SUBSTANCE

The manufacturing process for the drug substance is not reviewed because the drug substance is non-sterile.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –** Section 3.2.P.1. The drug product is a multi-dose non-sterile nasal spray that contains 30 mg/mL Nalmefene.

- **Drug product composition –** Section 3.2.P.1

Ingredient	Quantity per mL	Quantity / 100 µl Spray Volume[a]	Function
Nalmefene hydrochloride[b]	30 mg	3.0 mg[c]	API
Sodium chloride	(b) (4)	(b) (4)	(b) (4)
Dodecylmaltoside (DDM)			Permeation Enhancer
Disodium edetate dihydrate			(b) (4)
Benzalkonium chloride[d]			
Purified Water			
(b) (4)			

[c] 3.0 mg nalmefene hydrochloride is equivalent to 2.7 mg nalmefene free base
[d] (b) (4) Benzalkonium chloride solution is used.

- **Description of container closure system –** Section 3.2.P.7

	Component	Description	Manufacturer
	Rubber Stopper	(b) (4)	(b) (4)
	Container / Vial		
Aptar Unidose Nasal Spray device	Container Holder		Aptar Pharma
	Actuator		

		(b) (4)	

Assessment: Adequate
The applicant provided an adequate description of the drug product composition and container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

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Erika Pfeiler

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