CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218590Orig1s000

PRODUCT QUALITY REVIEW(S)

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Office of Pharmaceutical Quality

New Drug Application (NDA)
Integrated Quality Assessment Template

NDA Executive Summary

1. Application/Product Information

NDA Number	218590		
Applicant Name	Purdue Pharma L.P.		
Drug Product Name	Nalmefene Hydrochloride Injection, Auto-Injector		
Dosage Form	Solution		
Proposed Strength(s)	1.5 mg/ 0.5mL		
NDA Classification	Type 5 – New Formulation or New Manufacturer		
Route of Administration	Intramuscular		
Maximum Daily Dose	(b) (4)		
Rx/OTC Dispensed	Rx		
Proposed Indication	Emergency treatment of known/suspected opioid overdose induced by natural/synthetic opioids in adults and pediatric patients aged 12 years and older.		
Drug Product Description	(b) (4), disposable auto-injector that houses a prefilled syringe (PFS) containing a clear, colorless to light yellow solution of nalmefene hydrochloride		
Co-packaged product information	N/A		
Device information	(b) (4)		
Storage Temperature/ Conditions	20-25 ºC		
Review Team	**Discipline**	**Primary**	**Secondary**

	Drug Substance	Zhixing Shan	Katie Duncan
	Drug Product/ Labeling	Jizhou Wang	Valerie Amspacher/Julia Pinto
	Manufacturing	Sugandha Saboo	Cassie Abellard
	Biopharmaceutics	N/A	N/A
	Microbiology	George Arhin	Bethanie Lee
	Other (specify)	N/A	N/A
	RBPM	Teicher Agosto	
	ATL	Valerie Amspacher	
Consults	CDRH - Michael Lancina (primary reviewer) and Shruti Mistry (secondary reviewer)		

2. Final Overall Recommendation - Approval with QPA(s)

3. Action Letter Information

a. Expiration Dating: The proposed shelf life of 24 months is acceptable when stored at 20°C to 25°C (68°F to 77°F) (Controlled Room Temperature).

b. Additional Comments for Action

We have the following PMC's for the action letter:

1.We note that only three (3) non-volatile, but no volatile or semi-volatile extractables (b) (4) were observed in the extractables studies, while multiple semi-volatile extractables are noted (b) (4) It is unusual to see these extractables (b) (4). Therefore, your extractables studies may not be appropriately designed to produce a complete extractables profile to guide leachables studies.

In order to obtain a complete extractables profile, re-run the extractables studies in 5% IPA, 50% IPA, pH 3 and 9 buffer solutions and reflux the samples in each media for 12-24 hours to achieve an equilibrium. We recommend that you size the components or materials (for example, by cutting the samples to smaller pieces, or grinding them) to increase the surface area and extraction stoichiometry before extraction. Ensure all the limits of quantitation (LOQs) of the reference standards are at or lower than

the analytical evaluation threshold (AET). In addition, at least a confident level of structural identification should be achieved if a confirmation level is not possible as defined in USP <1663>.

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

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

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

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The CMC recommendation for this NDA is approval with post-marketing commitments. This is based on reviews by drug substance, drug product, process and 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 with QPAs**
Quality Labeling	-	**Adequate**
Manufacturing	-	**Adequate**
Biopharmaceutics	-	**N/A**
Microbiology	-	**Adequate**

Environmental Assessment: Review & EI Statement - Adequate
QPA for EA(s): Yes

5. Life-Cycle Considerations
Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 1; eCTD 0001	7 Feb 2024	All, original submission
Supporting document 3; eCTD 0003	12 Mar 2024	Process facilities
Supporting document 4; eCTD 0004	19 Mar 2024	Drug product
Supporting document 5; eCTD 0006	19 Apr 2024	Process facilities
Supporting document 7; eCTD 0007	8 May 2024	Process facilities
Supporting document 8; eCTD 0008	15 May 2024	Microbiology
Supporting document 9; eCTD 0009	16 May 2024	Process facilities
Supporting document 10; eCTD 0010	7 Jun 2024	Drug product
Supporting document 11; eCTD 0011	12 Jun 2024	Drug product

Supporting document 13; eCTD 0013	17 Jun 2024	Drug substance

Valerie Amspacher

Digitally signed by Valerie Amspacher
Date: 7/09/2024 11:38:40AM
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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide (OPQ-ALL-WI-0006)

NDA Number	218590
Assessment Cycle Number	1
Drug Product Name	Nalmefene Hydrochloride Injection, Auto-Injector, 1.5 mg/0.5 mL

Assessment Recommendation: Inadequate

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Inadequate	N/A
Patient Information	Inadequate	N/A
Instruction for Use (IFU)	adequate	
Container Labels	Inadequate	**N/A**
Carton Labeling	Inadequate	**N/A**

Brief Description of Outstanding Issues:

See comments in Section 4 below.

Submissions being reviewed:

Document(s) Assessed	Date Received
New/NDA submission (SN1)	2/7/2024
Amendment (SN10)	6/7/2024

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(copy of proposed text)

[1] Labeling Review Tool (LRT) (March 2022), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights[2] [21 CFR 201.57(a)(2)]		
Established name(s)[3]	Inadequate	(b) (4) should be removed from the drug name. The name should be: TRADENAME® (nalmefene injection), for intramuscular or subcutaneous use, in current PI. *See comment in Section 4 below.*
Route(s) of administration	Adequate	intramuscular and subcutaneous use
Controlled drug substance symbol (if applicable)	N/A	N/A
Initial U.S. Approval [§201.57(a)(3)]	Adequate	1995
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s)[4] and strength(s) in metric system[5]	Adequate	Injection: 1.5 mg nalmefene base/0.5 mL
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).[6]	Adequate	1.5 mg nalmefene base/0.5 mL.

[2] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018)
[3] Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).
[4] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline
[5] Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>
[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7]	N/A	N/A
For injectable drug products for parenteral 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.[8]	Inadequate	*Need to include "single-dose"* See Comment in Section 4 below.

Assessment: *Inadequate*

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

(b) (4)

[redacted]

[7] Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)
[8] Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>
[9] See § 201.57(c)(3); draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023); Labeling Review Tool (March 2022, page 25)

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product).	N/A	N/A
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	N/A	
For parenteral products: include statement: *"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*[11]	Adequate	Adequate

[10] Draft Guidance: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments

[11] §201.57(c)(3)(iv)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.[12] Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	N/A
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	N/A
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs."	N/A	N/A

Assessment: *Inadequate*

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[13]

(*copy of proposed text*)

(b) (4)

[12] USP General Notices 2.30 Legal Recognition

[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Injection: 1.5 mg/0.5 mL nalmefene (base) solution in a pre-filled auto-injector.
Strength(s) in metric system	Adequate	1.5 mg/0.5 mL nalmefene (base) solution
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	Inadequate	1.5 mg/0.5 mL nalmefene (base) solution Should include: Each 0.5 mL solution contains 1.5 mg nalmefene (equivalent to 1.7 mg nalmefene hydrochloride). *See comments in Section 4 below*
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable.	Inadequate	*See comments in Section 4 below.*
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	N/A
For injectable drug products for parenteral administration, use appropriate package type term (e.g., **single-dose**, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>).	Inadequate	Inadequate

Assessment: *Inadequate*

1.2.3 Section 11 (DESCRIPTION)[14]

(*copy of proposed text*)

(b) (4)

[redacted]

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		

[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Proprietary and established name(s)[15] [§ 201.57(c)(12)(i)(A)].	Adequate	TRADENAME® (nalmefene hydrochloride injection)
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	TRADENAME® (nalmefene hydrochloride injection) (b) (4) is a pre-filled, single-dose device
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].	Adequate	deliver a dose of 1.5 mg nalmefene (provided as nalmefene hydrochloride) in 0.5 mL. .
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid brand names. [§201.57(c)(12)(i)(C)].	Adequate	magnesium chloride, hydrochloric acid to adjust pH, and water for injection
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	Adequate	Adequate

[15] Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

[16] Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
statement of effect. [§ 201.100(b)(5)(iii)].		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	N/A
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	Adequate	
Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)].	Adequate	**an opioid antagonist**
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	Molecular Formula: C21H25NO3•HCl Molecular Weight: 375.9, CAS# 58895-64-0 Chemical Name: 17-(Cyclopropylmethyl)-4,5α-epoxy-6-methylenemorphinan-3,14-diol, hydrochloride salt
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	N/A

[17] Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in FDA's Labeling Resources for Human Prescription Drugs for the most recent EPC list.

[18] Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Adequate	Adequate
For oral prescription drug products, include gluten statement[19] (if applicable).	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity").	N/A	N/A
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	N/A

Assessment: *Inadequate*

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)[20]

(*copy of proposed text*)

(b) (4)

[redacted]

[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)
[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	Auto-Injector
Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety. No equivalency statement.	Adequate	single-dose auto-injector device delivers 1.5 mg of nalmefene in 0.5 mL
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	single-dose auto-injector device
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Inadequate	*See comments in Section 4 below*
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	N/A

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For injectable drug products for parenteral 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 (see USP <659>).	Adequate	
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.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)]	Adequate	Do not freeze or refrigerate. Store in a clean dry place. Protect from light.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Adequate	Store at controlled room temperature 20°C to 25°C (68°F to 77°F), with excursions permitted between 15°C and 30°C (59°F and 86°F).
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*	N/A	N/A

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
statements such as "latex-free."[21]		
Include information about child-resistant packaging[22] (if chosen by manufacturer).	N/A	

Assessment: *Inadequate*

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 review 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.

N/A

1.2.6 Manufacturing Information After Section 17 (for drug products)[23]

(b) (4)

Assessment: *Adequate*

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

[21] Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)
[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)
[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[24]	Adequate	TRADENAME (b) (4)
Special preparation instructions (if applicable).	Adequate	(b) (4)
Storage and handling information (if applicable).	Adequate	(b) (4)

[24] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
		(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differ from the dosage form.	N/A	
Active ingredient(s) (if applicable).	Adequate	nalmefene (b) (4)
Alphabetical listing of inactive ingredients (if applicable).	Inadequate	*Need to include the quantity of MgCl2. See comments in Section 4 below*
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	(b) (4)

Assessment: *Inadequate*

Title: NDA IQA Template CHAPTER IV-LABELING

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name[26], (font size and prominence) [§ 201.10(g)(2)].	Inadequate	Yes	(b) (4) [redacted] should be removed from the drug name. The name should be: TRADENAME® (nalmefene injection), for intramuscular or subcutaneous use.

[26] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
			See Commment in Section 4 below.
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[27]	Adequate	Yes	1.5 mg/0.5 mL
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	For intramuscular or subcutaneous use only.
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	Adequate	Yes	Each 0.5 mL solution contains 1.5 mg nalmefene (equivalent to 1.7 mg nalmefene hydrochloride)
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[28]	Adequate	Yes	0.5 mL
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Yes	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	Yes	
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Yes	
Storage conditions. If applicable, include a space on the carton labeling for the	Adequate	Yes	

[27] Express as " XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)

[28] § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
user to write the beyond-use-date (BUD).			
For injectable drug products for parenteral 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, and these products require a "Not for direct infusion" statement. (See USP <659>).	Adequate	yes	
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	Inadequate		Name of all inactive ingredients have bee listed without the quantity for $MgCl_2$. *See Commment in Section 4 below.*
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A		

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Linear Bar code [§ 201.25(c)(2)].[29]	Adequate	Yes	
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	Yes	
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Yes	
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	N/A	Yes	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Yes	
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Yes	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Yes	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by	N/A	Yes	

[29] See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.[30]			
And others if space is available.	Adequate	Yes	

Assessment of Carton Labels and Container Labeling: *Adequate*

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

With respect to PI:

1. Revise the drug name to: TRADENAME® (nalmefene injection), for intramuscular or subcutaneous use.

2. Section 2 (DOSAGE AND ADMINISTRATION), include a salt equivalency statement "Each 0.5 mL solution contains 1.5 mg nalmefene (equivalent to 1.7 mg nalmefene hydrochloride).

3. In Section 3 (DOSAGE FORMS AND STRENGTHS),
   a. Include a description of identifying characteristics of the dosage form, such as color and clarity of the solution in accordance with 21 CFR 201.57(c)(4)(ii).
   b. Include single-dose as an appropriate package type term.

4. In Section 11 (DESCRIPTION),
   a. include a Sterility statement.
   b. include a salt equivalency statement "Each 0.5 mL solution contains 1.5 mg nalmefene (equivalent to 1.7 mg nalmefene hydrochloride).

[30] USP General Notices 3.20 Indicating Conformance

5. In Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) of Prescribing Information Labeling,
    a. include a description of identifying characteristics of the dosage form, such as color and clarity of the solution in accordance with 21 CFR 201.57(c)(17)(iii).
    b. include a salt equivalency statement "Each 0.5 mL solution contains 1.5 mg nalmefene (equivalent to 1.7 mg nalmefene hydrochloride).
    c. Add a statement "Protect from light and keep the auto-injector in carton until use."

With respect to CCL:

6. Revise the drug name to: TRADENAME® (nalmefene injection), for intramuscular or subcutaneous use.
7. List inactive ingredients by the USP/NF names in alphabetical order and include the amount to of the excipient $MgCl_2$ on the side panel.
8. Add a statement "Protect from light and keep the auto-injector in carton until use."

Primary Labeling Assessor Name and Date: Jizhou Wang, PhD. 06/6/2024

Secondary Assessor Name and Date (and Secondary Summary, as needed): Julia Pinto, PhD.

Jizhou Wang

Digitally signed by Jizhou Wang
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Julia Pinto

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Date: 7/03/2024 12:49:01PM
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U.S. FOOD & DRUG ADMINISTRATION

MICROBIOLOGY

Product Information	
NDA Number	218590
Assessment Cycle Number	1
Drug Product Name / Strength	Nalmefene Hydrochloride Injection, Auto-Injector, (b) (4) (0.5 mL fill)
Route of Administration	Intramuscular and subcutaneous injection
Applicant Name	Purdue Pharma L.P.
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: **Adequate**

Theme:

☐ N/A	☒ Depyrogenation Validation Data
☒ Product Sterility Assurance	☒ Product Release and/or Stability Specifications
☒ Media Fill Data	☒ Validation for Product Release and/or Stability Test Method
☒ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: N/A

Assessment Summary: The submission **is recommended** for approval on the basis of sterility assurance.

List Submissions Being Assessed (table):

Submit	Received	Review Request	Assigned to Reviewer
February 7, 2024 (eCTD sequence # 0001)	February 7, 2024	N/A	February 9, 2024
May 15, 2024 (eCTD sequence # 0008)	May 15, 2024	N/A	May 16, 2024

May 15, 2024 submission is response to Agency April 25, 2024 Information Request

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

Concise Description of Outstanding Issues: N/A.

Supporting Documents:

- DMF [redacted] LOA dated 06/23/2023. Reviewed in Microbiology [redacted] dated 8/4/2022. Adequate.
- DMF [redacted]. LOA dated 05/11/2022. Reviewed in Microbiology [redacted] dated 6/8/2023. Adequate.

Select Number of Approved Comparability Protocols: 0

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –**
  The drug product, Nalmefene Hydrochloride Injection is a sterile, nonpyrogenic, clear, colorless to light yellow solution [redacted] (0.5 mL fill) in a 1 mL single-dose prefilled syringe enclosed/housed in a [redacted], disposable auto-injector.

- **Drug product composition** –

Ingredient	Quantity per 0.5 mL fill)	Function
Nalmefene Hydrochloride, in-house	1.5 mg	Active Pharmaceutical Ingredient
Magnesium Chloride Hexahydrate, USP	[redacted]	
Hydrochloric Acid, NF	q.s.	pH adjusting agent
Water for Injection, USP/EP	[redacted]	

- **Description of container closure system –**

  A. Primary packaging:

Description	Manufacturer
[redacted]	

B. Secondary packaging: Pre-assembled, (b) (4), disposable drug delivery auto-Injector.

Overall container/closure assembly (primary + secondary packaging)

(b) (4)

Reviewer's Assessment: Adequate

(b) (4)

Valerie Amspacher

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/s/

VALERIE R AMSPACHER
07/09/2024 01:38:58 PM