

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215487Orig1s000

PRODUCT QUALITY REVIEW(S)



Title:	NDA IQA Template Title Page-EXEC SUMMARY		
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Template Revision: 03

NDA Executive Summary

1. Application/Product Information

NDA Number	215487		
Applicant Name	Summit Biosciences Inc.		
Drug Product Name	Naloxone HCl Nasal Spray		
Dosage Form	Solution, metered		
Proposed Strength(s)	10 mg		
NDA Classification	Type 5 – New Formulation or New Manufacturer		
Route of Administration	Nasal		
Maximum Daily Dose	20 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Opioid Overdose		
Drug Product Description	A unit dose device containing a vial held tightly within a vial holder. The vial is a clear, glass vial containing (b) (4) rubber stopper/plunger.		
Co-packaged product information	N/A		
Device information	(b) (4) unit dose sprayer		
Storage Temperature/ Conditions	2-25 °C		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Katie Duncan	Donna Christner
	<i>Drug Product/ Labeling</i>	Renish Delvadia	Valerie Amspacher
	<i>Manufacturing</i>	Vicky He	Shu-Wei Yang

	<i>Biopharmaceutics</i>	N/A	N/A
	<i>Microbiology</i>	Renee Marcisisin-Rogers	Elizabeth Bearr
	<i>Other (specify)</i>	N/A	N/A
	<i>RBPM</i>	Teicher Agosto	
	<i>ATL</i>	Valerie Amspacher	
Consults			

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. **Expiration Dating:** The provided data supports an expiry period of 36 months at 2°C to 25°C (36°F to 77°F). Excursions permitted up to 104 °F (40 °C). Do not freeze or expose to excessive heat above 104°F (40°C). Protect from light.

b. **Additional Comments for Action**

4. Basis for Recommendation:

a. **Summary of Rationale for Recommendation:**

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

The provided data supports an expiry period of 36 months at 2°C to 25°C (36°F to 77°F). Excursions permitted up to 104 °F (40 °C). Do not freeze or expose to excessive heat above 104°F (40°C). Protect from light.

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

Recommendation by Subdiscipline:

Drug Substance - Adequate
Drug Product - Adequate
Quality Labeling - Pending
Manufacturing - Adequate
Biopharmaceutics - N/A
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:

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 1; eCTD 0001	24 Mar 2023	All, original submission
Supporting document 4; eCTD 0004	10 May 2023	Facilities
Supporting document 5; eCTD 0005	22 May 2023	Facilities
Supporting document 7; eCTD 0007	16 Jun 2023	Microbiology
Supporting document 8; eCTD 0008	22 Jun 2023	Drug product
Supporting document 12; eCTD 0012	20 Jul 2023	Microbiology
Supporting document 15; eCTD 0015	4 Aug 2023	Microbiology
Supporting document 16; eCTD 0016	8 Aug 2023	Process
Supporting document 17; eCTD 0017	14 Aug 2023	Drug product
Supporting document 18; eCTD 0018	23 Aug 2023	Facilities
Supporting document 19; eCTD 0019	8 Sep 2023	Microbiology
Supporting document 20; eCTD 0020	12 Sep 2023	Process
Supporting document 22; eCTD 0022	29 Sep 2023	Drug product
Supporting document 24; eCTD 0024	12 Oct 2023	Drug product



Valerie
Ampacher

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CHAPTER IV: LABELING

NDA 215487 Naloxone Nasal Spray, 10 mg

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate, with comments directly added to the working PI, PPI, IFU.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	TRADENAME (naloxone hydrochloride) nasal	Add tradename when finalized
Established name(s)	hydrochloride) nasal	Yes
Route(s) of administration	spray	Yes
Dosage Forms and Strengths Heading in Highlights		
Proposed "Nasal spray: 10 mg of naloxone hydrochloride in (b) (4) mL"		
Summary of the dosage form(s) and strength(s) in metric system.	Yes	Change (b) (4) mL" to "0.11 mL" to accurately reflect the dispensed volume.
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	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

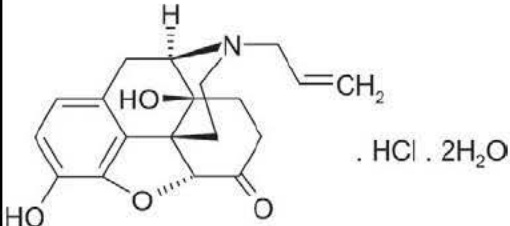
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted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

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Proposed "TRADENAME Nasal Spray is supplied as a single-dose intranasal spray containing 10 mg of naloxone hydrochloride in (b) (4) mL. Change to: "Nasal Spray: 10 mg of naloxone hydrochloride in 0.11 mL in a single dose nasal spray."		
Available dosage form(s)	Nasal Spray	Adequate
Strength(s) in metric system	Yes	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Salt policy exemption per Policy per FDA Guidance. Strength is based on naloxone hydrochloride amount.	Adequate; The name of the salt is necessary to maintain consistency with other approved Naloxone nasal spray products
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)

APPEARS THIS WAY ON ORIGINAL

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section Proposed: TRADENAME (naloxone hydrochloride) Nasal Spray is a pre-filled, single dose intranasal spray. Chemically, naloxone hydrochloride is the hydrochloride salt of 17-Allyl-4,5α-epoxy- 3,14-dihydroxymorphinan-6-one hydrochloride with the following structure:  <chem>C=CCN1[C@H]2CC[C@@]1(O)C3=C(C=C4C(=O)CC[C@]4(O)C5=CC=C(O)C=C35)O2</chem> . HCl . 2H₂O Naloxone hydrochloride, an opioid antagonist, occurs as a white, to slightly off-white powder or almost white crystalline powder and contains two molecules of water of hydration. It is freely soluble in water, in dilute acids, and in strong alkali; slightly soluble in ethanol. Each TRADENAME Nasal Spray (b)(4) 10 mg (b)(4) of naloxone hydrochloride (equivalent to 9 mg of naloxone) in a (b)(4) mL aqueous solution. Inactive ingredients include glycerin, trisodium citrate dihydrate, hydrochloric acid and sodium hydroxide to adjust pH, and purified water. The pH range is (b)(4)		
Proprietary and established name(s)	Yes	
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.	Salt policy exemption per Policy per FDA Guidance. Strength is based on naloxone hydrochloride amount.	Adequate; The name of the salt is necessary to maintain consistency with other approved Naloxone nasal spray products. Equivalency statement for naloxone base is included.
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		Applicant is asked to add molecular formula and molecular weight
If radioactive, statement of important nuclear characteristics.		
Other important chemical or physical properties (such as pKa or pH)		Applicant is asked to revise the pH range to reflect the currently proposed drug product specification. Applicant is asked to add pKa value. Change (b) (4) to "delivers 10 mg". Change (b) (4) mL" to "0.11 mL".

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.,	No such statements.	Adequate

“synthesized and developed by Drug Company X,” “structurally unique molecular entity”		

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Proposed: TRADENAME Nasal Spray 10 mg is supplied as a carton containing two (2) blister packages (NDC 43674-003-02) each with a single spray device. TRADENAME Nasal Spray is not made with natural rubber latex.		
Store TRADENAME Nasal Spray in the blister and cartons provided.		
Store (b) (4) Excursions permitted up to 104°F (40°C). Do not freeze or expose to excessive heat above 104°F (40°C). Protect from light.		
TRADENAME Nasal Spray (b) (4) If this happens, the device will not spray. If TRADENAME Nasal Spray is frozen and is needed in an emergency, do NOT wait for TRADENAME Nasal Spray to thaw. Get emergency medical help right away. (b) (4)		
Available dosage form(s)	Yes	
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	Yes	
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	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
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.)	"Do not freeze or expose to excessive heat above 104°F (40°C). Protect from light." "Store TRADENAME Nasal Spray in the blister and cartons provided."	Adequate.
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.	(b) (4) Excursions permitted up to 104°F (40°C)." "Do not freeze or expose to excessive heat above 104°F (40°C)."	Change to "Store between 2°C to 25°C (36°F to 77°F). Excursions permitted up to 40°C (104°F)." to reflect the available long-term stability data. Change to "Do not freeze or expose to excessive heat above 40°C (104°F)."

Additional	The label claims ████████████████████ (b) (4) ████████████████████ ████████████████████ ████████████████████ If this happens, the device will not spray. If TRADENAME Nasal Spray is frozen and is needed in an emergency, do NOT wait for TRADENAME Nasal Spray to thaw. Get emergency medical help right away. ██████████ (b) (4) ████████████████████ ████████████████████ ████████████████████ ████████████████████ ████████████████████ ████████████████████ ████████████████████ ████████████████████ ████████████████████	The data required to substantiate these statements has not been provided at the time of this review. Hence, these statements should be omitted from the label. Appropriateness of including these statements will be revisited once the necessary supporting data becomes available. Hence, change text to “TRADENAME Nasal Spray may freeze at cold temperatures. If this happens, the device will not spray. If TRADENAME Nasal Spray is frozen and is needed in an emergency, do NOT wait for TRADENAME Nasal Spray to thaw. Get emergency medical help right away”
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling
N/A

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 by: Summit Biosciences Inc., Lexington, KY 40511	Adequate

2.0 PATIENT LABELING

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

Patient information (PPI): Applicant will be asked to change storage conditions per the comment in PI section 16 in this review.

Quick Start Guide: No CMC section to review.

Instruction for use: Applicant will be asked to revise storage information for consistency with section 16 of the PI discussed in this review.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

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



Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	Yes	Change "TRADENAME" with the finalized name.
Dosage strength	Yes	Change the "0.11 mL" from "(b) (4) mL"
Route of administration	Yes	
If the active ingredient is a salt, include the equivalency statement per FDA Guidance		Add equivalency statement for naloxone base.
Net contents (e.g. tablet count)	Yes	
"Rx only" displayed on the principal display	Yes	
NDC number	Yes	
Lot number and expiration date	Only on the container label. There is a space allocated on blister and carton labels, but it is unclear if it is for lot number and expiration date information.	Add lot number and expiration date on blister and carton labels
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	(b) (4) Excursions permitted up to 104°F (40°C)." "Do not freeze or expose to excessive heat above 104°C (40°C)"	Change to "Store between 2°C to 25°C (36°F to 77°F). Excursions permitted up to 40°C (104°F)." Change to "Do not freeze or expose to excessive heat above 40°C (104°F)." on proposed blister and carton labels.
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.	N/A	
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	
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.	Salt policy exemption per Policy per FDA Guidance. Strength is based on naloxone hydrochloride amount.	Adequate; The name of the salt is necessary to maintain consistency with other approved Naloxone nasal spray products. Equivalency statement for naloxone base is included.
And others, if space is available	N/A	

Assessment of Carton and Container Labeling: Adequate with the following comment in the “ITEMS FOR ADDITIONAL ASSESSMENT.”

ITEMS FOR ADDITIONAL ASSESSMENT

Send the following comments to the Applicant

1. Include equivalency statement for naloxone base on the proposed blister and carton labels
2. Add lot number and expiration date on blister and carton labels.

Reference ID: 5271665

3. Change the delivered volume to “0.11 mL” from (b) (4) mL” on the proposed carton label.
4. Change (b) (4) ...” to “Each (b) (4) spray delivers...” on the proposed carton label.
5. Change (b) (4) Excursions permitted up to 104°F (40°C).” to “Store between 2°C to 25°C (36°F to 77°F). Excursions permitted up to 40°C (104°F).” on the proposed blister and carton labels.
6. Change “Do not freeze or expose to excessive heat above 104°C (40°C)” to “Do not freeze or expose to excessive heat above 40°C (104°F).” on proposed blister and carton labels.

Overall Assessment and Recommendation:

Adequate with comments.

Primary Labeling Assessor Name and Date: Renishkumar Delvadia

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



Renishkumar
Delvadia

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Julia
Pinto

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CHAPTER VII: MICROBIOLOGY

For more details about the items in this template, please see [Chapter VII \(Microbiology\) of the NDA IQA Guide](#)

Product Information	Indicated for opioid overdose
NDA Number	215487
Assessment Cycle Number	MR01
Drug Product Name/Strength	Naloxone HCl Nasal Spray, 10 mg
Route of Administration	Nasal
Applicant Name	Summit Biosciences Inc.
Therapeutic Classification/ OND Division	CDER/OND/ON/DAAP
Manufacturing Site	Summit Biosciences Inc., Coldstream Research Campus, 1513 Bull Lea Road, Lexington, KY 40511, FEI: 3007577023
Method of Sterilization	Non-sterile

Assessment Recommendation: Adequate

Assessment Summary: The drug product is administered as a nasal spray and is therefore not required to be sterile. Assessment of the product quality microbiology controls was performed.

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
eCTD sequence #0001	03/24/2023 (original)
eCTD sequence #0003	05/02/2023 (updated draft labeling)
eCTD sequence #0004	05/10/2023 (updated 3.2.P.3.1)
eCTD sequence #0007	06/16/2023 (IR response)
eCTD sequence #0008	06/22/2023 (IR response)
eCTD sequence #0012	07/20/2023 (IR response)
eCTD sequence #0015	08/04/2023 (IR response)
eCTD sequence #0019	09/08/2023 (IR response)

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

Remarks:

- An Information Request was sent to the applicant on 06/08/2023 and a response was received on 06/16/2023 and 06/22/2023.
- An Information Request was sent to the applicant on 07/10/2023 and a response was received on 07/20/2023.
- Information Requests were sent to the applicant on 07/25/2023 and 08/30/2023 and responses were received on 08/04/2023 and

09/08/2023, respectively. The original deficiencies are italicized below.

Concise Description of Outstanding Issues (list bullet points with key information and update as needed): N/A

Supporting Documents: N/A

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product:** (b) (4), and supplied as a single dose intranasal spray containing 10 mg of the API in a unit dose device (vial, plunger, vial holder, and actuator assembly).

- **Drug product composition:**

Component	Grade	Function	mg/dose*
Naloxone HCl (b) (4)	USP	API	(b) (4) (10.00)
Glycerin	USP	(b) (4)	(b) (4)
(b) (4)	USP	(b) (4)	(b) (4)
Hydrochloric acid	NF	pH adjustment	AR**
Sodium hydroxide	NF	pH adjustment	AR
Purified water	USP	(b) (4)	QS

**AR = as required to target pH (b) (4)

- **Description of container closure system:**

Component	Material type	Summit part #	Manufacturer
Vial	Clear, type (b) (4) glass vial (b) (4)	(b) (4)	(b) (4)
Plunger (rubber stopper)	(b) (4)	(b) (4)	(b) (4)
Container holder (vial holder)	(b) (4)	(b) (4)	(b) (4)
Actuator sub-assembly	(b) (4)	(b) (4)	(b) (4)

A diagram of the container closure system components and assembly is provided below.

Figure 1: Overview of Components and Assembly (Provided by

(b) (4)

(b) (4)



Assessment: Adequate

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

(b) (4)





Renee
Marcsisin

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Elizabeth
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