

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201656Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

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

Date: February 23, 2017

From: Hong Cai, Ph.D.
Drug Product Reviewer,
Branch V Division of New Drug Products II
Office of New Drug Products

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: CMC Labeling Review #1 of NDA 201656

Subject: Finalized Label/labeling of CMC Sections

At the time when Labeling Review of this application was completed (01/11/2017), this NDA was not recommended for approval due to unresolved CMC label/labeling issues. To resolve the outstanding label/labeling issues, the applicant submitted the amendments to the NDA on 02/08/2017, 02/09/2017, and 02/21/2017 that provide the revised package insert (PI), and container and carton labels. The revised labels/labeling were adequately addressed all CMC labeling issues (see the **Attachment-1 and Attachment-2**). Although the container and carton labels were adequate from CMC perspective at the time of the completion of CMC labeling review on January 11, 2017, subsequently, those labels were updated to address the comments from DMEPA. The attached container/carton labels in this addendum are deemed the finalized version. In addition, this addendum also addresses the typographic errors in the CMC comments in the previous labeling review dated 01/11/2017.

Regarding the PI submitted on 02/08/17, it is noted that the established name is shown as (b) (4) in the highlights section, which is not consistent with the recommended presentation of "(desmopressin acetate) nasal spray" in section #11 of PI and current updated Carton/Container labels submitted on 02/21/17. The corrected PI version, which was recommended by the review team, is attached (**Attachment-1**), and it is expected that the sponsor will accept the change of the parenthesis.

Recommendation:

The outstanding CMC label/labeling issues have been satisfactorily resolved. This application is now recommended for approval from the labeling perspective.

Hong Cai, Ph.D.
Drug Product Reviewer
Branch V, Division II, ONDP

Moo-Jhong Rhee, Ph.D.
Branch Chief
Branch V, Division II, ONDP

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



Moo Jhong
Rhee

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Hong
Cai

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Mark
Seggel

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Memorandum

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

Date: February 24, 2017

From: Mark R. Seggel, Ph.D.
Application Technical Lead
Office of New Drug Products
Branch V/DNDP II

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Office of New Drug Products
Branch V/DNDP II

To: OPQ IQA #1 of NDA 201656
for Noctiva (desmopressin acetate) nasal spray

Subject: Final Recommendation - APPROVAL

The OPQ Integrated Quality Assessment (IQA) #1, dated February 15, 2017, concluded that this 505(b)(2) NDA was Not Ready for Approval in its present form per 21 CFR 314.125(b)(8). Specifically, it was noted that labeling (package insert, container/carton) negotiations had not been completed, and in its present form, the labeling did not comply with the requirements under 21 CFR 201.

The NDA for this drug-device combination product was otherwise complete and adequate from the OPQ perspective.

The applicant has made revisions to the labeling (package insert, and container/carton labels). Hong Cai, Ph.D., ONDP drug product and labeling reviewer, now concludes that the labeling is acceptable from the CMC labeling perspective (see attached labeling review addendum).

Recommendation:

NDA 201656 for Noctiva (desmopressin acetate) nasal spray is now recommended for **Approval** from the OPQ perspective.

Application Technical Lead Signature:

Mark R. Seggel, Ph.D.
CMC Lead (acting)

Mark R.
Seggel -S

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Seggel -S
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ou=HHS, ou=FDA, ou=People,
cn=Mark R. Seggel -S,
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Recommendation: *As of this review, this 505(b)(2) NDA is Not Ready for Approval in its present form per 21 CFR 314.125(b)(8).*

NDA 201656

Review #1

Noctiva (desmopressin acetate) Nasal Spray

Drug Name/Dosage Form	Desmopressin Acetate Nasal Spray
Strength	<ul style="list-style-type: none"> • 0.83 mcg desmopressin acetate per 0.1 mL spray equivalent to 0.75 mcg desmopressin per 0.1ml spray. • 1.66 mcg desmopressin acetate per 0.1 mL spray equivalent to 1.5mcg desmopressin per 0.1ml spray.
Route of Administration	Nasal Spray
Rx/OTC Dispensed	Rx
Applicant	Serenity Pharmaceuticals, LLC
US agent, if applicable	-

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original 0000	02/04/16	All
0012 (labeling)	05/06/16	Drug Product
0014	06/02/16	Micro, CDRH-ODE
0015	06/17/16	Drug Product
0019	07/15/16	Drug Product; Micro; CDRH-ODE
0028	09/02/16	Drug Product; Micro; CDRH-ODE
0029 (labeling)	09/09/16	Drug Product
0030	09/12/16	Drug Product; CDRH-ODE
0032	09/19/16	CDRH-OC
0033 (in-use stability)	09/23/16	Drug Product
0035	10/03/16	Drug Product; CDRH-ODE
0037	10/14/16	Drug Product; CDRH-ODE
0038	10/21/16	Drug Product
0040	11/01/16	Drug Product
0046	11/17/16	Drug Product
0047 (labeling)	11/21/16	Drug Product
0048 (labeling)	12/02/16	Drug Product
0049 (labeling)	12/09/16	Drug Product
0050	01/10/17	CDRH-OC
0053	01/17/17	Drug Product

OPQ Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Ben Stevens	BII / DNDAPI / ONDP
Drug Product	Hong Cai	BV / DNDPII / ONDP
Process	Li Shan Hsieh	BVIII / DPAPII / OPF
Microbiology	Yarery Smith	BIII / DMA / OPF
Facility	Juandria Williams	BIII / DIA / OPF
Biopharmaceutics	Not Applicable	-
RBPM	Thao Vu	BI / DRBPM I / OPRO
Application Technical Lead	Mark Seggel	BV / DNDPII / ONDP
Laboratory (OTR)	Anjanette Smith, David Keire	DPA / OTR / OPQ
Environmental Analysis (EA)	Hong Cai	BV / DNDPII / ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (6)	Adequate	08/10/16	-
	Type III			-	-	See NDA review and CDRH reviews
	Type III			-	-	Sufficient information in NDA
	Type IV			Adequate	10/21/16	-

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Commercial IND, amendments, and associated reviews	IND 76667	IND for Desmopressin acetate nasal spray (SER120)
NDA and associated FDA approval	NDA 17922	Listed drug: DDAVP nasal spray (0.1 mg/mL)
Commercial IND	IND (b) (4)	(b) (4)
“Cyclopentadecanolide (CPD): 6-month Intranasal Administration Toxicity Study in Rats.”	-	

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
CDRH-ODE	Complete	Approval for device constituent design considerations	12/14/16	Kathleen Fitzgerald
CDRH-OC	Complete	Approval	02/06/17	Chris Brown

Executive Summary

I. Recommendations and Conclusion on Approvability

In its present form, Serenity Pharmaceuticals’ 505(b)(2) New Drug Application #201656, for Noctiva (desmopressin acetate nasal spray), a drug-device combination product, is not ready for approval. Labeling (package insert, container/carton) negotiations have not been completed, and in its present form the labeling does not comply with the requirements under 21 CFR 201(see the **Attachment II**). An addendum to this review will be completed upon receipt of labeling that is adequate from the CMC perspective.

Sufficient information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, potency and bioavailability of the drug product.

The drug substance and drug product manufacturing, packaging and testing facilities have acceptable CGMP status. CDRH-OC has determined that the applicant is in compliance with the applicable Quality System Requirements under 21 CFR 820, although post-approval inspections of two sites are recommended (see CDRH-OC consult review dated February 6, 2017).

CDRH-ODE has determined that the spray pump component of this drug-device combination product is suitable for the intended use. The device is suitable for preventing microbial contamination of the product in the absence of a preservative (see CDRH-ODE consult review dated December 14, 2016).

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	NOCTIVA is a vasopressin analog indicated for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least 2 times per night to void.
Duration of Treatment	Indefinite.
Maximum Daily Dose	1.66 micrograms desmopressin acetate (equivalent to 1.5 micrograms desmopressin), delivered in a single 0.1 mL spray at bedtime.
Alternative Methods of Administration	Not applicable.

Desmopressin is a synthetic 9-amino acid analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone which affects renal water conservation. Desmopressin differs from 8-arginine vasopressin in the stereochemistry of the arginine amino acid (D-isomer) and the cysteine amino acid in position 1 is deaminated.

Desmopressin acetate is the active ingredient in several FDA-approved drug products and their generic equivalents. It is available as a nasal spray, an injection, in rhinal tubes for intranasal application, and as an oral tablet. Desmopressin is indicated for patients with hemophilia A, Type I von Willebrand's Disease, central cranial diabetes insipidus, and primary nocturnal enuresis (tablets only). The nasal spray was previously used for the treatment of bed-wetting.

Noctiva is a low-dose desmopressin product supplied in a metered-dose nasal spray. Two strengths are proposed for marketing:

- 0.83 mcg desmopressin acetate per 0.1 mL spray equivalent to 0.75 mcg desmopressin per 0.1ml spray.
- 1.66 mcg desmopressin acetate per 0.1 mL spray equivalent to 1.5mcg desmopressin per 0.1ml spray.

Note that the two strengths [REDACTED] (b) (4). It is unknown if they are bioequivalent.

Unlike the approved desmopressin acetate nasal sprays which are formulated as true solutions, Noctiva is formulated as a sterile oil-in-water emulsion. In addition, Noctiva contains cyclopentadecanolide (CPD), a permeation enhancer. CPD is present in Testim (testosterone gel). However CPD has not previously been used in an approved nasal spray. The safety of CPD administered by the intranasal route was evaluated by Dr. Deepa Rao (see her review dated November 7, 2016).

The drug delivery system consists of an [REDACTED] (b) (4) mechanical multidose pump and a 3.5 mL amber glass bottle. The pump is designed to prevent ingress of microbial contamination. The metered dose pump was reviewed by CDRH.

Note that although the Noctiva is manufactured as a sterile product, nasal sprays are not typically required to be sterile and Noctiva is not labeled as sterile.

Noctiva may provide a useful treatment option for adult patients experiencing nocturia (defined as two or more nighttime voids each night interrupting sleep). Accurate and consistent dosing of the drug product is critical however. Under-dosing may result in lack of efficacy, while over-dosing could result in dangerously low blood sodium levels (hyponatremia).

B. Quality Assessment Overview

Drug Substance: Desmopressin acetate is the established name for 1-(3-Mercaptopropionic acid)-8-D-arginine-vasopressin monoacetate trihydrate. It is soluble in water and ethyl alcohol, and is hygroscopic. It is the subject of a USP monograph.

The chemistry, manufacturing and controls of desmopressin acetate drug substance are documented in (b) (4), Type II DMF (b) (4). The DMF was most recently reviewed by Dr. Ben Stevens and found adequate.

The information on the drug substance provided in the NDA and in the DMF is adequate to support approval of the NDA. The application is recommended for approval from the drug substance perspective (see IQA Chapter 1.)

Drug Product: Noctiva (desmopressin acetate) nasal spray) is a preservative-free oil-in-water emulsion formulation containing water for injection, cottonseed oil, polysorbate 20, sorbitan monolaurate, citrate buffer, (b) (4) and cyclopentadecanolide (CPD). Cyclopentadecanolide, also known as pentadecalactone, is a permeation enhancer included in the formulation to enhance absorption of desmopressin through the nasal mucosa.

The chemistry, manufacturing and controls for the cyclopentadecanolide used in the manufacture of Noctiva are adequately documented in (b) (4) Type IV DMF (b) (4).

Each bottle of Noctiva contains 3.8 mL of 16.6 mcg/mL or 8.3 mcg/mL desmopressin acetate nasal spray. The content is sufficient to provide up to 30 individual 0.1 mL doses in addition to the amount required for priming the device.

The drug product specification includes tests, and appropriate acceptance criteria, for identity, assay, CPD content, emulsion particle size distribution, spray content uniformity, pump delivery, spray droplet size, and spray pattern. The product is also tested for endotoxins and sterility. Note that a test for degradation products is not included in the specification. Potential levels of impurities in the maximum daily dose of 1.5 mcg desmopressin are not expected to present any safety concerns.

The long-term stability of Noctiva when stored upright at 2°C - 8°C for 24 months before opening has been established. Determination of an appropriate in-use period, i.e., the time after dispensing in which the product may be stored at room temperature by the patient, and the time that the product should be

discarded, was more problematic. The in-use stability protocol was poorly designed and the resulting data limited. Nevertheless, we conclude that the patient can store Noctiva nasal spray upright at room temperature 20°C to 25°C (68°F to 77°F) for 60 days after opening.

The drug delivery device requires five priming actuations before patient dosing to ensure that the full 0.1 mL spray is delivered. While the applicant performed a re-priming study and determined that re-priming of the pump was not necessary, the available data do not support this conclusion. If the pump has not been used in more than 3 days, the pump should be re-primed with two actuations. The labeling and instructions for use have been revised accordingly.

Leachables and extractables (L&E) testing of the drug contacting components of the nasal spray was conducted. While from the CMC perspective adequate information regarding the L&E testing, including the analytical methods, was eventually provided, assessment of the results was deferred to CDRH.

Overall, this NDA is recommended for approval from the drug product CMC perspective (see IQA Chapter II).

Analytical Methods Verification: Because of the low concentration of desmopressin in the emulsion formulations and the very low amount of desmopressin in each 0.1 mL spray actuation, and reported variability “due to analytical method variation, CDER/OPQ/OTR/Division of Pharmaceutical Analysis was consulted to perform laboratory verification of the RP-HPLC desmopressin assay and the RP-HPLC spray content uniformity assay.

DPA concluded that these methods are acceptable for control and regulatory purposes (see Methods Verification Report and Summary dated August 18, 2016 for details).

Environmental Assessment: A categorical exclusion from the environmental assessment requirements has been requested in accordance with 21 CFR 25.31(b). The estimated introduction concentration (EIC) is (b) (4) ppb, which is well below the 1 ppb threshold. No extraordinary circumstances are known to the applicant. The categorical exclusion is therefore granted (see IQA Chapter II for details).

Labeling: From the CMC perspective, the primary deficiencies associated with the package insert and container /carton labels are related to the expression of strength (free base versus salt) [see section C. Special Product Quality Labeling Recommendations, below for further discussion], the long-term and in-use storage statements, and the instructions for use (priming and re-priming). Recommendations have been conveyed to the applicant via the DBRUP project manager. See IQA Chapter IV for details. Proposed revisions were submitted by the applicant on February 8 and 9, 2017. The labeling is under review; an

addendum to this review will be completed when agreement is reached on all aspects of the labeling including labels.

Product Manufacturing Process: The drug product manufacturing process is currently based on (b) (4)

[REDACTED]

[REDACTED] (b) (4)

Facilities: Dr. Juandria Williams, OPF Division of Inspectional Assessment concludes that, “[t]here are no significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facilities’ inspectional history, relevant experience, and capabilities. The facilities are determined acceptable to support approval of NDA 201656.” However, it is recommended that the next routine inspections of Serenity Pharmaceuticals, LLC, New York, NY as the NDA applicant, and (b) (4) as the drug product manufacturer, cover medical device GMPs. See IQA Chapter VI and the CDRH-OC review dated February 6, 2017 for details.

Biopharmaceutics: The drug product consists of a liquid formulation for which no in vitro release testing is required. A biowaiver has not been requested. Therefore, a biopharmaceutics review is not needed for this NDA.

Product Quality Microbiology: Although Noctiva is manufactured as a sterile oil-in-water emulsion, it will not be not labeled and marketed as such. The approved

desmopressin acetate nasal sprays are not sterile products but do contain a preservative (b) (4).

Microbial contamination could result in degradation of desmopressin, a small synthetic peptide. To ensure that the product remains free of microbial contamination, it is packaged with the (b) (4) pump which is designed to prevent ingress of bacteria.

Although the subject drug product is manufactured under aseptic conditions, (b) (4). Since this is a non-sterile drug product, none of the sterilization processes or the aerosol challenge study were reviewed. Antimicrobial effectiveness testing (AET) is not applicable as the formulation does not have antimicrobial properties especially with respect to *P. aeruginosa*.

Therefore, the product quality microbiology review focused on container closure integrity testing (CCIT) and on sterility assurance testing (per USP<71>), both of which were found adequate. Dr. Yarey Smith, OPF microbiologist recommends approval of the NDA (see IQA Chapter VIII for details).

CDRH-ODE: The (b) (4) mechanical multidose pump constitutes the device component of this drug-device combination product.

The review encompassed device design, device functionality, biocompatibility, microbiology (sterility), and device stability materials provided in the NDA and (b) (4) Drug Master File # (b) (4), as well as materials submitted in response to information requests. Overall, the CDRH-ODE review team “determined that the device constituent parts of the combination product have been designed appropriately for the product’s intended use and essential performance requirements.” See the CDRH-ODE consult review dated December 14, 2016 for details.

C. Special Product Quality Labeling Recommendations

Based upon the recommendations from DMEPA, the USP Salt Nomenclature Policy is not being implemented with this drug product. Because there is numeric overlap in the strengths for Noctiva (1.5 microgram/spray) and Stimite (0.15 mg/spray), Serenity was asked to revise the product strengths to 0.83 mcg desmopressin acetate per 0.1 mL spray and 1.66 mcg desmopressin acetate per 0.1 mL spray, equivalent to 1.5 mcg desmopressin and 0.75 mcg desmopressin, respectively. Note that other approved desmopressin acetate nasal sprays (e.g., DDAVP) deliver 0.01 mg (10 mcg) per 0.1 mL spray.

D. Final Risk Assessment (see Attachment)**OVERALL ASSESSMENT AND SIGNATURES:***Application Technical Lead Name and Date:*

Mark R. Seggel, Ph.D.
CMC Lead (acting)

Mark R.
Seggel -S

Digitally signed by Mark R.
Seggel -S
DN: c=US, o=U.S.
Government, ou=HHS,
ou=FDA, ou=People,
cn=Mark R. Seggel -S,
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LABELING

R Regional Information

1.14 Labeling

Labeling & Package Insert

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1. **Package Insert**

(a) “Highlights” Section

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NOCTIVA™ safely and effectively. See full prescribing information for NOCTIVA.

NOCTIVA (desmopressin) nasal spray, for intranasal use
Initial U.S. Approval: 1978

DOSAGE FORMS AND STRENGTHS

Preservative-free nasal spray emulsion delivering (b) (4) mcg or (b) (4) desmopressin in each spray (3)

Item	Information Provided in NDA	Reviewer’s Comment and Recommendations
Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary name: Noctiva Established Name: (desmopressin) nasal spray	Not Satisfactory. The established name is not presented correctly. See detailed comments in Reviewer’s Assessment. Revise to “Noctiva (desmopressin acetate) nasal spray”
Dosage form, route of administration	NOCTIVA (desmopressin) nasal spray, for intranasal use	Satisfactory. Dosage form and route of administration is correctly presented.
Controlled drug substance symbol (if applicable)	NA	NA
Dosage Forms and Strengths (201.57(a)(8))	Preservative-free nasal spray (b) (4) in each spray (3)	Not Satisfactory. According to USP, nasal spray dosage form includes both solutions and emulsions. The delivered amount is not clear with the definition of “each spray”.



QUALITY ASSESSMENT



		Revise to Preservative-free nasal spray emulsion delivering 0.83 mcg of desmopressin acetate (equivalent to 0.75 mcg desmopressin) or 1.66 mcg of desmopressin acetate (equivalent to 1.5 mcg desmopressin) in each spray (0.1 mL) (3)
Whether the drug product is scored	NA	NA

(b) "Full Prescribing Information" Section

#3. Dosage Forms and Strengths

3 DOSAGE FORMS AND STRENGTHS

Preservative-free desmopressin nasal spray. Each spray delivers [redacted]. (3)

(b) (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Available dosage forms	Preservative-free desmopressin nasal spray.	<p>Not satisfactory. Established name is not correct. Dosage form, nasal spray, is correctly presented.</p> <p>Revise to Preservative-free desmopressin acetate nasal spray.</p>
Strengths: in metric system	Each spray delivers (b) (4)	<p>Not satisfactory. "Each spray" is not defined using the metric system.</p> <p>Revise to Each spray delivers 0.1 mL of NOCTIVA. Each spray contains 0.83 mcg or 1.66mcg of desmopressin acetate (equivalent to 0.75 mcg or 1.5 mcg of desmopressin) for the 0.83 mcg/0.1mL or 1.66 mcg/0.1 mL strength of desmopressin acetate.</p>
Active moiety expression of strength with equivalence statement (if applicable)	Each spray delivers (b) (4)	<p>Not satisfactory. The strength was expressed in active moiety but no metric units defined per spray. The recommended revision is clearly expressed the strength as the salt form of desmopressin acetate with the free base form desmopressin equivalency statement included.</p> <p>Revise to Each spray delivers 0.1 mL of NOCTIVA. Each spray contains 0.83 mcg or 1.66mcg of desmopressin acetate (equivalent to 0.75 mcg or 1.5 mcg of desmopressin) for the 0.83 mcg/0.1mL or 1.66 mcg/0.1 mL strength of desmopressin acetate.</p>



QUALITY ASSESSMENT

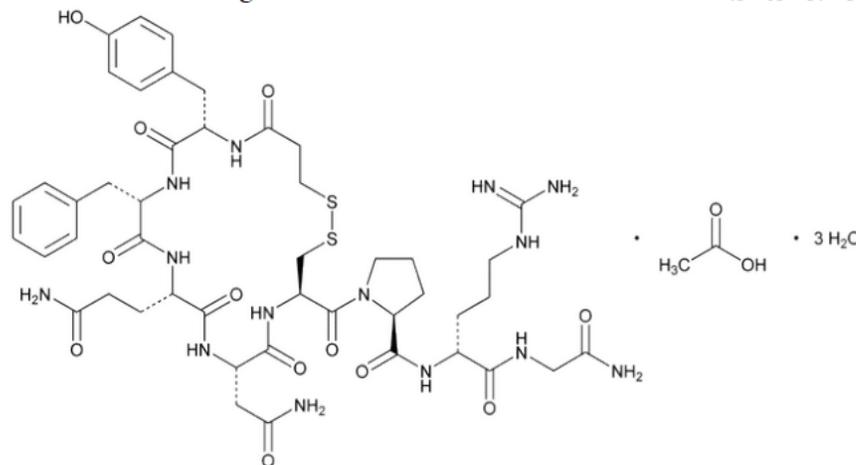


A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	NA	NA
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#11: Description

11 DESCRIPTION

Desmopressin is a synthetic analogue of (b) (4) 8-arginine vasopressin, an antidiuretic hormone (ADH). Its chemical name is 1-(3-mercaptopropionic acid)-8-D-arginine vasopressin monoacetate (salt) trihydrate, and its molecular weight is 1183.31. Its molecular formula is $C_{48}H_{68}N_{14}O_{14}S_2 \cdot 3H_2O$. Its chemical structure is:



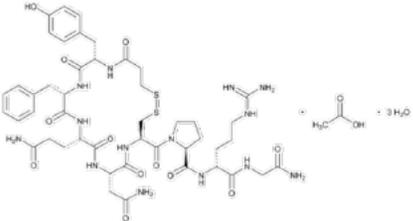
Desmopressin acetate is a white powder that is freely soluble in water. It is also soluble in alcohol and glacial acetic acid. **NOCTIVA** (desmopressin) is formulated for intranasal use as a milky white emulsion without preservatives at pH 5.5.

NOCTIVA is available as an emulsion at two dose strengths, 0.75 mcg and 1.5 mcg, for nasal administration. The dose strengths are expressed as desmopressin free base and are equivalent to 0.82 mcg and 1.64 mcg of desmopressin (b) (4) respectively. Both formulations also contain the following inactive ingredients: cyclopentadecanolide; cottonseed oil; sorbitan monolaurate; polysorbate 20; citric acid; sodium citrate; and water for injection.

After initial priming, each actuation of **NOCTIVA** 0.75 mcg (b) (4) mcg delivers a dose of 0.75 mcg and 1.5 mcg of desmopressin, respectively.

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name and established name	NOCTIVA (desmopressin)	Not satisfactory.

<p>Dosage form and route of administration</p>	<p>NOCTIVA (desmopressin) is formulated for intranasal use as a milky white emulsion without preservatives at pH 5.5.</p>	<p>Revise to “NOCTIVA (desmopressin acetate) nasal spray”</p> <p>Not satisfactory. The dosage form is not presented correctly. The dose strengths are not presented correctly. See the comments below.</p> <p>Revise to “NOCTIVA (desmopressin acetate) nasal spray is formulated for intranasal use as a milky white emulsion without preservatives at pH 5.5.”</p>
<p>Active moiety expression of strength with equivalence statement (if applicable)</p>	<p>NOCTIVA is available as an emulsion at two dose strengths, 0.75 mcg and 1.5 mcg, for nasal administration.</p> <p>The dose strengths are expressed as desmopressin free base and are equivalent to (b) (4) mcg and (b) (4) mcg of desmopressin acetate, respectively.</p> <p>After initial priming, each actuation of NOCTIVA 0.75 mcg and NOCTIVA 1.5 mcg delivers a dose of 0.75 mcg and 1.5 mcg of desmopressin, respectively.</p>	<p>Not Satisfactory. Only stated desmopressin amount as 0.75 mcg and 1.5mcg without specifying its volume. There is a minor calculation discrepancy at the second decimal place. The applicant has concurred to correct the equivalence calculations from (b) (4) to 0.83mcg and 1.66mcg of desmopressin acetate, respectively. (Response dated September 12, 2016).</p> <p>Revisions see above. “NOCTIVA is available as an oil-in-water emulsion at two dose strengths, 0.83 mcg and 1.66 mcg of desmopressin acetate per spray, for nasal administration. Each spray is 0.1 mL. The dose strengths are expressed as desmopressin acetate and are equivalent to 0.75 mcg and 1.5 mcg of desmopressin free base per spray, respectively.”</p> <p>“After initial priming, each actuation of NOCTIVA 0.83 mcg/0.1mL or 1.66 mcg/0.1mL delivers a dose of 0.83 mcg and 1.66 mcg of desmopressin acetate, respectively.”</p>
<p>Inactive ingredient information</p>	<p>Both formulations also contain the following</p>	<p>Not satisfactory.</p>

(quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	(b) (4)	Citric acid should be citric acid anhydrous; sodium citrate should be sodium citrate dihydrate Revise to “citric acid” to “citric acid anhydrous”; “sodium citrate” to “sodium citrate dihydrate”.
Statement of being sterile (if applicable)	N/A	NA
Pharmacological/ therapeutic class	(b) (4)	Not Satisfactory. The revision is based on the comment from Dr. Hylton Joffe and the review team on November 2, 2016 in the PI document. Revise to “Desmopressin acetate is a synthetic analogue of the endogenous pituitary hormone 8-arginine vasopressin, an antidiuretic hormone (ADH).”
Chemical name, structural formula, molecular weight	Its chemical name is 1-(3-mercaptopropionic acid)-8-D-arginine vasopressin monoacetate (salt) trihydrate, and its molecular weight is 1183.31. Its molecular formula is C ₄₈ H ₆₈ N ₁₄ O ₁₄ S ₂ ·3H ₂ O. Its chemical structure is: 	Satisfactory.
If radioactive, statement of important nuclear characteristics.	N/A	NA
Other important chemical or physical properties (such as pKa or pH)	Desmopressin acetate is a white powder that is freely soluble in water. It is also soluble in alcohol and glacial acetic acid.	Satisfactory.

#16: How Supplied/Storage and Handling

16.1 How Supplied

NOCTIVA (desmopressin) nasal spray is available in a 3.5 mL amber glass bottle (nominal volume) fitted with a nasal actuator, a cartridge pump, and a dip tube, delivering a dose of either [REDACTED] (b) (4) desmopressin per actuation.

(b) (4) NDC XXXX-XXXX-XX

(b) (4) NDC XXXX-XXXX-XX

16.2 Storage and Handling

(b) (4)

(b) (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Strength of dosage form	<p>NOCTIVA (desmopressin) nasal spray is available in a 3.5 mL amber glass bottle (nominal volume) fitted with a nasal actuator, a cartridge pump, and a dip tube, delivering a dose of either (b) (4) desmopressin per actuation.</p>	<p>Not Satisfactory. Established name is not correct. The amount per actuation is not defined.</p> <p>Revise to "NOCTIVA (desmopressin acetate) nasal spray"</p>
Available units (e.g., bottles of 100 tablets)	<p>NOCTIVA (desmopressin) nasal spray is available in a 3.5 mL amber glass bottle (nominal volume) fitted with a nasal actuator, a cartridge pump, and a dip tube, delivering a dose of either (b) (4) desmopressin per actuation.</p>	<p>Not Satisfactory. Available units are not provided.</p> <p>Revise to: "NOCTIVA (desmopressin acetate) nasal spray is available in a 3.5 mL amber glass bottle (nominal volume) fitted with a nasal actuator, a cartridge pump, and a dip tube, delivering a dose of either 0.83 mcg or 1.66 mcg of desmopressin acetate (equivalent to 0.75 mcg or 1.5 mcg of desmopressin) per spray (0.1mL). Each bottle contains a target amount of 3.8 g formulation with 30 effective doses in addition to the initial priming (5 actuations), the equivalent of 30 days' medication when used as one spray once a day."</p>
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	<p>(b) (4) (b) (4) NDC XXXX-XXXX-XX NDC XXXX-XXXX-XX</p>	<p>Not Satisfactory. The NDA# is displayed as the place holder initially, but updated on the submission on November 9, 2016. The strength is not specified in terms of the delivered amount, such as per actuation or mL.</p> <p>Revise to 0.83 mcg/0.1mL of desmopressin acetate NDC 0023-5227-35 1.66 mcg/0.1mL of desmopressin acetate NDC 0023-5670-35</p>
Special handling (e.g., protect from light)	<p>(b) (4)</p>	<p>Satisfactory.</p>
Storage conditions	<p>(b) (4)</p>	<p>Satisfactory.</p>

	<p>(b) (4)</p>	<p>The initial submission contains the direction for (b) (4) Based on the review team (labeling) comment to revise for consistency with the LRT: (b) (4)</p> <p>The applicant submitted a revised version on November 9, 2016 as following and is deemed satisfactory:</p> <ul style="list-style-type: none"> • Before opening, store upright in a refrigerator, 2°C to 8°C (36°F to 46°F); excursion permitted between 0°C and 15°C (32°F and 59°F) [See USP Controlled Cold Temperature]. • After opening , store upright at room temperature 20°C to 25°C (68°F to 77°F). • Discard NOCTIVA 60 days after opening.
<p>Manufacturer/distributor name (21 CFR 201.1(h)(5))</p>	<p>Not provided.</p>	<p>Satisfactory. No Manufacturer/distributor name displayed in the initial submission. But subsequently updated on November 9, 2016 based on the Agency comments.</p>

Reviewer's Assessment:

Serenity Pharmaceuticals submitted a NDA 201656: Desmopressin Acetate Nasal Spray (SER120) with two strengths of doses, 7.5ug/mL and 15ug/mL expressed as desmopressin free base. The drug product formulation is an oil-in-water emulsion. The proposed trade name is Noctiva. The drug is indicated for the treatment of nocturia in adults. It is administered by the intranasal route only with a single spray of 0.1mL daily.

ONDP recommends retaining the salt in the established name of the drug product as “(Desmopressin Acetate) Nasal Spray” despite USP monograph has a title, “Desmopressin Nasal Spray Solution”. According to USP Salt Policy, the drug product monograph title should use the name of the active moiety (desmopressin) instead of the name of the salt (desmopressin acetate) with the strength expressed according to the active moiety. However, FDA Guidance for Industry “Naming of Drug Products Containing Salt Drug Substances” (June 2015) allows to retain the salt in the established name if “The name of the salt is necessary to maintain consistency with other dosage forms of the same active ingredient (salt)”.

Desmopressin acetate as the active ingredient has a long human drug history with several dosages forms, such as tablet, injection, and nasal spray. Particularly, the name of the salt is necessary to maintain consistency with the already marketed nasal spray dosage forms of desmopressin acetate, i.e., DDAVP Nasal Spray (Desmopressin Acetate), 0.1 mg/mL (NDA 17922, Ferring); STIMATE (Desmopressin Acetate) Nasal Spray, 1.5 mg/mL (NDA20355, CSL Behring). Examples of the marketed DDAVP and STIMATE labels are attached. Further, according to USP general chapter <1151> for PHARMACEUTICAL DOSAGE FORMS, “A spray drug product is a dosage form that contains a drug substance in the liquid state as a solution or suspension and is intended for administration as a mist.” The formulation of the drug product, Noctiva (NDA201656), is an emulsion, and its proposed dosage form as nasal spray without a modifier, emulsion, is in line with USP <1151>.

(b) (4)

(b) (4)

Recommendation:

Regarding PI, the following deficiencies should be resolved before approval of this application.

A. Highlight Section

- a. Proprietary name and established name should be revised to,
 - “Noctiva (desmopressin acetate) nasal spray”.

- b. Dosage forms and Strengths section should be revised to,
Preservative-free nasal spray emulsion delivering 0.83 mcg of desmopressin acetate (equivalent to 0.75 mcg desmopressin) or 1.66 mcg of desmopressin acetate (equivalent to 1.5 mcg desmopressin) in each spray (0.1 mL) (3)

B. Full Prescribing Information

- a. **#3 Dosage Forms and Strengths** section should be revised to,
Each spray delivers contains 0.1 mL of NOCTIVA.
Each spray contains 0.83 mcg or 1.66mcg of desmopressin acetate (equivalent to 0.75 mcg or 1.5 mcg of desmopressin) for the 0.83 mcg/0.1mL or 1.66 mcg/0.1 mL strength of desmopressin acetate.

- b. In the **#11 Description** section,

- The established name should be revised to,
NOCTIVA (desmopressin acetate) nasal spray

- [REDACTED] (b) (4)

to

“Desmopressin acetate is a synthetic analogue of the endogenous pituitary hormone 8-arginine vasopressin, an antidiuretic hormone (ADH).”

- Regarding dosage form and route of administration:

- a. “[REDACTED]” (b) (4)

should be revised to

“NOCTIVA (desmopressin acetate) nasal spray is formulated for intranasal use as a milky white emulsion without preservatives at pH 5.5.”

- b. [REDACTED] (b) (4)

should be revised to

“NOCTIVA is available as an oil-in-water emulsion at two dose strengths, 0.83 mcg and 1.66 mcg of desmopressin acetate per spray, for nasal administration. Each spray is 0.1 mL. The dose strengths are expressed as desmopressin acetate and are equivalent to 0.75 mcg and 1.5 mcg of desmopressin free base per spray, respectively.”

c. [REDACTED] (b) (4)

should be revised to

“After initial priming, each actuation of NOCTIVA 0.83 mcg/0.1mL or 1.66 mcg/0.1mL delivers a dose of 0.83 mcg and 1.66 mcg of desmopressin acetate, respectively.”

d. Inactive ingredient information: [REDACTED] (b) (4) should be revised to “citric acid anhydrous”; [REDACTED] (b) (4)
[REDACTED] should be revised to “sodium citrate dihydrate”.

c. #16 How Supplied/Storage and Handling

1. The following statement,

[REDACTED] (b) (4)

should be revised to,

“NOCTIVA (desmopressin acetate) nasal spray is available in a 3.5 mL amber glass bottle (nominal volume) fitted with a nasal actuator, a cartridge pump, and a dip tube, delivering a dose of either 0.83 mcg or 1.66 mcg of desmopressin acetate (equivalent to 0.75 mcg or 1.5 mcg of desmopressin) per spray (0.1mL). Each bottle contains a target amount of 3.8 g formulation with

30 effective doses in addition to the initial priming (5 actuations), the equivalent of 30 days' medication when used as one spray once a day."

2. The dosage strength should be revised in the following statement to:

0.83 mcg/0.1mL of desmopressin acetate NDC 0023-5227-35

1.66 mcg/0.1mL of desmopressin acetate NDC 0023-5670-35"

The following Review of Container labels and Cartons are based on the submission by the applicant on September 9, 2016.

2. **Immediate Container Label**

0.75mcg container label:



0345201

1.5mcg container label:



0345201

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	(b) (4)	<p>Not Satisfactory. The established name is not correct.</p> <p>Revise to "Noctiva (desmopressin acetate) Nasal Spray"</p>
Dosage strength	(b) (4)	<p>Not Satisfactory. It did not express per the active ingredient as salt form.</p> <p>Revise to 0.83 mcg/0.1mL* or 1.66 mcg/0.1mL* * Each spray contains 0.1 mL.</p>
Net contents	Not stated.	<p>Not Satisfactory.</p> <p>State "Net content: 3.8g or 30 doses."</p>
"Rx only" displayed prominently on the main panel	Rx Only	Satisfactory.
NDC number (21 CFR 207.35(b)(3)(i))	NDC XXXX-XXXX-XX	<p>Satisfactory. There is a space holder and no actual NDC numbers displayed.</p>
Lot number and expiration date (21 CFR 201.17)	Lot: Exp:	<p>Satisfactory. There is a space holder</p>
Storage conditions	(b) (4)	<p>Not Satisfactory. Only stated patient storage condition. But it is acceptable due to the space available in the label.</p> <p>Revise to "•After opening , store upright at room temperature 20°C to 25°C (68°F to 77°F). •Discard NOCTIVA 60 days after opening."</p>
Bar code (21CFR 201.25)	Not specified.	Satisfactory.
Name of manufacturer/distributor	Manufactured by (b) (4)	Satisfactory.



QUALITY ASSESSMENT



	(b) (4)	
And others, if space is available		

Reviewer's Assessment:

- 1) The following needs to be resolved: The proposed presentation of the drug product identifying information of proprietary name, established name, strength, its active moiety and salt equivalency statement:

Noctiva

(desmopressin acetate) Nasal Spray, 0.83 mcg/0.1mL*

(b) (4)

* Each spray contains 0.1 mL.

Noctiva

(desmopressin acetate) Nasal Spray, 1.66 mcg/0.1mL*

(b) (4)

* Each spray contains 0.1 mL.

- 2) Strength should be revised to "0.83 mcg/0.1mL* or 1.66 mcg/mL* , * Each spray contains 0.1 mL".
- 3) Net content should be stated as "Net content: 3.8g or 30 doses."
- 4) Storage conditions*:
 - Before opening, store upright in a refrigerator, 2°C to 8°C (36°F to 46°F); excursion permitted between 0°C and 15°C (32°F and 59°F) [See USP Controlled Cold Temperature].
 - After opening , store upright at room temperature 20°C to 25°C (68°F to 77°F).
 - Discard NOCTIVA 60 days after opening.

(*The storage conditions can be abbreviated in the immediate container label, if space is limited.)

3. Carton Labeling

0.75 mcg carton labeling

Desmopressin Acetate Nasal Spray
NDA 201656

Serenity Pharmaceuticals, LLC
CONFIDENTIAL



(b) (4)

1.5 mcg carton labeling



QUALITY ASSESSMENT



Desmopressin Acetate Nasal Spray
NDA 201656

Serenity Pharmaceuticals, LLC
CONFIDENTIAL



(b) (4)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name, established name (font size, prominence)	Noctiva (b) (4)	Not Satisfactory. The established name is not correct. Revise to Noctiva (desmopressin acetate) Nasal Spray
Dosage strength	(b) (4)	Not Satisfactory. No volume defined for (b) (4) mcg. Revise to 0.83 mcg/0.1mL* or 1.66 mcg/0.1mL* *per spray is equal to 0.1mL
Net quantity of dosage form	Not displayed.	Not Satisfactory. "Net content: 3.8g or 30 doses." should be displayed.
"Rx only" displayed prominently on the main panel	Rx Only	Satisfactory.
Lot number and expiration date	LOT: EXP.:	Satisfactory.
Storage conditions	(b) (4)	Not Satisfactory. See comments in PI section review. Revise to: <ul style="list-style-type: none"> Before opening, store upright in a refrigerator, 2°C to 8°C (36°F to 46°F); excursion permitted between 0°C and 15°C (32°F and 59°F) [See USP Controlled Cold Temperature]. After opening, store upright at room temperature 20°C to 25°C (68°F to 77°F). Discard NOCTIVA 60 days after opening.
Bar code (21CFR 201.25)	Place holder demonstrated	Satisfactory. Only in a place holder, no specific number yet.



QUALITY ASSESSMENT



NDC number (21 CFR 207.35(b)(3)(i))	NDC XXXX-XXXX-XX	Satisfactory.
Manufacturer/distributor's name	(b) (4)	Satisfactory.
Quantitative ingredient information (injectables)	Inactive: (b) (4)	Not Satisfactory. Revise "citric acid" to "citric acid, anhydrous"; "sodium citrate" to "sodium citrate dehydrate"
Statement of being sterile (if applicable)	NA	Satisfactory.
"See package insert for dosage information"	Read Patient Instructions for Use carefully.	Satisfactory.
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	NA	NA

Reviewer's Assessment:

The following comments should be resolved:

1. (b) (4) should be revised to (desmopressin acetate) Nasal Spray,
2. Strength should be revised to be consistent with desmopressin acetate as 0.83 mcg/0.1mL* or 1.66 mcg/0.1mL*
* Each spray contains 0.1 mL.
3. "Net content: 3.8g or 30 doses." should be stated.
4. Storage condition should be revised to,
 - Before opening, store upright in a refrigerator, 2°C to 8°C (36°F to 46°F); excursion permitted between 0°C and 15°C (32°F and 59°F) [See USP Controlled Cold Temperature].
 - After opening, store upright at room temperature 20°C to 25°C (68°F to 77°F).
 - Discard NOCTIVA 60 days after opening.
5. (b) (4) should be revised "citric acid, anhydrous" and "sodium citrate dihydrate", respectively.

Overall Assessment and Recommendation:

Serenity Pharmaceuticals submitted a NDA 201656 with drug product Desmopressin Acetate Nasal Spray (SER120) for the treatment of nocturia in adults. This newly developed drug product SER120 is an oil-in-water emulsion with two strengths of doses, 7.5ug/mL and 15 ug/mL expressed as desmopressin free base. The proposed proprietary (trade) name is Noctiva. It is administered by the intranasal route only with a single spray of 0.1mL daily. The following materials related to labeling/label have been reviewed from CMC perspective:

1. Names and Dosage Forms and Strengths in the Highlights of Prescribing Information
2. #3 (Dosage Forms and Strengths), #11 Description and #16 (How Supplied/Storage and Handling) in the Full Prescribing Information
3. Container label and Carton Label for both strengths of the drug product

The applicant proposed desmopressin as the established name for drug product SER120 is not acceptable. After carefully examination of the relevant USP, FDA policies and the market history of desmopressin acetate as a human drug, the established name of the drug product for SER120 is recommended to be “(Desmopressin Acetate) Nasal Spray” despite USP monograph has a title, “Desmopressin Nasal Spray Solution”. Retaining the salt (acetate) in the established name is based on the exception rules according to FDA Guidance for Industry “Naming of Drug Products Containing Salt Drug Substances” (June 2015). Desmopressin acetate as the active ingredient has been approved with several dosages forms, e.g. tablet, injection, and nasal spray. To be consistent with the already approved nasal spray dosage forms of desmopressin acetate, i.e., DDAVP Nasal Spray (Desmopressin Acetate), 0.1 mg/mL (NDA 17922, Ferring); STIMATE (Desmopressin Acetate) Nasal Spray, 1.5 mg/mL (NDA20355, CSL Behring), the proposed drug is recommended to have the full salt name.

It is noted that the nasal spray defined as a dosage form formulated with either a solution or an emulsion according to USP general chapter <1151> for PHARMACEUTICAL DOSAGE FORMS.

As of this review, the deficiencies in the container and carton labels have been resolved satisfactorily via an amendment dated 12/9/16 (see the **Attachment**), however, the deficiencies in the PI as delineated below have not been satisfactorily resolved and therefore, this NDA is not recommended for approval from the ONDP perspective.

List of Deficiencies:**I. Regarding PI**

A. Highlight Section

- a. Proprietary name and established name should be revised to,
“Noctiva (desmopressin acetate) nasal spray”.
- b. Dosage forms and Strengths section should be revised to,
“Preservative-free nasal spray emulsion delivering 0.83 mcg of desmopressin acetate (equivalent to 0.75 mcg desmopressin) or 1.66 mcg of desmopressin acetate (equivalent to 1.5 mcg desmopressin) in each spray (0.1 mL) (3)”

B. Full Prescribing Information

- a. #3 Dosage Forms and Strengths section should be revised to,
“Each spray delivers contains 0.1 mL of NOCTIVA.”
“Each spray contains 0.83 mcg or 1.66mcg of desmopressin acetate (equivalent to 0.75 mcg or 1.5 mcg of desmopressin) for the 0.83 mcg/0.1mL or 1.66 mcg/0.1 mL strength of desmopressin acetate.”
- b. In the #11 Description section,
 - The established name should be revised to,
“NOCTIVA (desmopressin acetate) nasal spray”
 - (b) (4)
[REDACTED]to
“Desmopressin acetate is a synthetic analogue of the endogenous pituitary hormone 8-arginine vasopressin, an antidiuretic hormone (ADH).”
 - Regarding dosage form and route of administration:
(b) (4)
[REDACTED]
[REDACTED]
should be revised to

“NOCTIVA (desmopressin acetate) nasal spray is formulated for intranasal use as a milky white emulsion without preservatives at pH 5.5.”

(b) (4)

should be revised to

“NOCTIVA is available as an oil-in-water emulsion at two dose strengths, 0.83 mcg and 1.66 mcg of desmopressin acetate per spray, for nasal administration. Each spray is 0.1 mL. The dose strengths are expressed as desmopressin acetate and are equivalent to 0.75 mcg and 1.5 mcg of desmopressin free base per spray, respectively.”

(b) (4)

should be revised to

“After initial priming, each actuation of NOCTIVA 0.83 mcg/0.1mL or 1.66 mcg/0.1mL delivers a dose of 0.83 mcg and 1.66 mcg of desmopressin acetate, respectively.”

Inactive ingredient information: “(b) (4) should be revised to “citric acid anhydrous”; (b) (4) should be revised to “sodium citrate dihydrate”.

c. #16 How Supplied/Storage and Handling

1. The following statement,

should be revised to,

“NOCTIVA (desmopressin acetate) nasal spray is available in a 3.5 mL amber glass bottle (nominal volume) fitted with a nasal actuator, a cartridge pump, and a dip tube, delivering a dose of either 0.83 mcg or 1.66 mcg of desmopressin acetate (equivalent to 0.75 mcg or 1.5 mcg of desmopressin) per spray (0.1mL). Each bottle contains a target amount of 3.8 g formulation with 30 effective doses in addition to the initial priming (5 actuations), the equivalent of 30 days’ medication when used as one spray once a day.”

2. The dosage strength with NDC numbers should be revised as the following (NDC number is provided by the applicant):

“0.83 mcg/0.1mL of desmopressin acetate	NDC 0023-5227-35
1.66 mcg/0.1mL of desmopressin acetate	NDC 0023-5670-35”

II. *Regarding Container label (The following deficiencies have been satisfactorily resolved via an amendment dated 12/9/16)*

- 1) The following needs to be resolved: The proposed presentation of the drug product identifying information of proprietary name, established name, strength, its active moiety and salt equivalency statement:

Noctiva

(desmopressin acetate) Nasal Spray, 0.83 mcg/0.1mL*

(b) (4)

* Each spray contains 0.1 mL.

Noctiva

(desmopressin acetate) Nasal Spray, 1.66 mcg/0.1mL*

(b) (4)

* Each spray contains 0.1 mL.

2) Strength should be revised to “0.83 mcg/0.1mL* or 1.66 mcg/mL*, * per spray contains 0.1 mL”.

3) Net content should be stated as “Net content: 3.8g or 30 doses.”

5) Storage conditions*:

- Before opening, store upright in a refrigerator, 2°C to 8°C (36°F to 46°F); excursion permitted between 0°C and 15°C (32°F and 59°F) [See USP Controlled Cold Temperature].
- After opening, store upright at room temperature 20°C to 25°C (68°F to 77°F).
- Discard NOCTIVA 60 days after opening.

(*The storage conditions can be abbreviated in the immediate container label, if space is limited.).

III. Regarding Carton Label (The following deficiencies have been resolved satisfactorily via an amendment dated 12/9/16)

- 1) (b) (4) should be revised to (desmopressin acetate) Nasal Spray,
- 2) Strength should be revised to be consistent with desmopressin acetate as 0.83 mcg/0.1mL* or 1.66 mcg/0.1mL*
* Each spray contains 0.1 mL.
- 3) “Net content: 3.8g or 30 doses.” should be stated.
- 4) Storage condition should be revised to,
“Before opening, store upright in a refrigerator, 2°C to 8°C (36°F to 46°F); excursion permitted between 0°C and 15°C (32°F and 59°F) [See USP Controlled Cold Temperature]”.
“After opening, store upright at room temperature 20°C to 25°C (68°F to 77°F).”



QUALITY ASSESSMENT



"Discard NOCTIVA 60 days after opening."

5) " (b) (4) should be revised to "citric acid, anhydrous" and "sodium citrate dihydrate", respectively.

Primary Labeling Reviewer Name and Date:

Hong Cai, Ph.D.
Reviewer, Branch V
DNDP II/ONDP

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

I agree with Dr. Cai's assessment on the labeling and labels with the statement that this application is not ready for approval until the deficiencies in PI are resolved.

Moo-Jhong Rhee, Ph.D.
Chief, Branch V
DNDP II/ONDP

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Moo Jhong
Rhee

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MICROBIOLOGY

Product Background:

NDA: 201656

Drug Product Name

Proprietary: Noctiva

Non-proprietary: Desmopressin Nasal Spray (SER120)

Strength: 0.75 µg/mL and 1.5 µg/mL

Route of Administration: Intranasal

Applicant Name: Serenity Pharmaceuticals, LLC

Manufacturing Site:

(b) (4)

Method of Sterilization: N/A (drug product is marketed as non-sterile)

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

List Submissions being reviewed (table):

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
02/04/2016	02/04/2016	N/A	02/10/2016
06/02/2016*	06/02/2016	N/A	06/10/2016
09/23/2016*	09/23/2016	N/A	09/23/2016
10/14/2016*	10/14/2016	N/A	10/17/2016

*IR amendment

P.1 Description of the Composition of the Drug Product

P.2 Pharmaceutical Development

• Drug product composition –

The drug product is a multidose, non-sterile solution available at two dose strengths, 7.5 µg/mL and 15 µg/mL. The strength is expressed in terms of desmopressin free base concentration. The DP formulation does not contain any preservatives and is formulated as an oil-in-water emulsion packaged in an amber glass vial.

Ingredient	Content (mg per (b) (4) dose)	Function
Desmopressin	7.5	Active ingredient
Cyclopentadecanolide (CPD)		Permeation enhancer
Cottonseed oil		(b) (4)
Polysorbate 20		
Sorbitan monolaurate		
Citric acid, anhydrous		
Sodium citrate dihydrate		
(b) (4)		
Water for Injection (WFI)		

• **Description of container closure system –**

Configuration	Component	Description	Manufacturer
7.5 µg/mL and 15 µg/mL Configurations	Bottle		(b) (4)
	Pump		

The applicant stated that the (b) (4) is comprised of a unique nasal actuator, (b) (4) integrated safety feature which prevents the actuator from being removed. These components, together with the cartridge pump, create the packaging vehicle. The proposed (b) (4) system is made of numerous small parts. The applicant indicated that the internal engineering of the device is unique in that it is designed to maintain the filled vial free of microbial contamination (b) (4)

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity -

The applicant provides information regarding an aerosol challenge study (# 834289). The applicant indicated that the test articles demonstrated 100% no growth following an extreme bacterial aerosol challenge.

In addition, the applicant stated that validation of the integrity of the (b) (4) system that prevents microbial ingress was demonstrated in a tip seal integrity test and closure and ventilation test by (b) (4). In the tip seal integrity test, no bacterial growth was noted in any of the containers fitted with the (b) (4) devices after multiple challenges with *P aeruginosa* suspension over the course of 5 days. In the closure and ventilation integrity test, the applicant indicated that no bacterial growth was noted in the containers fitted with the (b) (4) devices following multiple challenges with *B. subtilis*. No data were provided in the original submission to support those statements.

The subject drug product is marketed as non-sterile; therefore, container closure integrity test (CCIT) is not required and the aerosol challenge study was not analyzed. Nevertheless, due to the non-preserved composition of this multi-dose drug product, the applicant was requested to

provide supporting information for the proposed in-use storage period, namely 60 days. However, since the results for the USP<51> test did not fully meet the acceptance criteria (See Section 2.A. Package Insert below), the applicant did not address the antimicrobial effectiveness test question and instead, on 09/23/2016 the applicant provided the report “Nine Weeks in-use study for Unidirectional valve efficacy of (b) (4) pump system” as an alternate CCIT method.

Test description:

30 (b) (4) bottles were used for the study. A challenge suspension of *P. aeruginosa* ((b) (4) CFU/mL) was prepared in saline. Each sample was primed 5 times prior to dip the nozzle of each bottle into the challenge suspension. While in an upright position, each bottle was actuated once more. The caps were replaced and the bottles were incubated at 25-30 °C for 9 weeks; however, the priming, microbial solution dipping and actuation were repeated for 4 consecutive days on weeks 1, 4, and 9 (12 times total). Three negative controls were incubated for the entire duration of the challenge. After incubation, an expelled dose analysis was performed on each sample and negative control. The product from each sample was sprayed directly onto a TSA plate. The plates were incubated for a minimum of 3 days and then inspected for colonies.

Following the expelled dose analysis, an analysis on the remaining drug product content in the bottle was performed by removing the head of the pump. The samples were filtered through a membrane which was rinsed, plated onto TSA, and incubated.

Method suitability for the expelled dose and for the content in the bottle was performed.

Results:

The applicant indicated that the expelled dose samples did not contain more than (b) (4) CFU, and there was no recovery of the challenge organism from the bottle content. The suitability samples showed NLT (b) (4)% of recovery.

Note to reviewer: Since the applicant did not include a purposely breach positive control during the nine weeks in-use study, and the samples were not actuated while immersed in the challenge solution, the following deficiencies (in italics) were sent to the applicant on 10/07/2016 (IR # 7):

- 1. We recommend that actuation during microbial immersion should also be included in the test parameters. Thus, provide the results from a microbial challenge study during actuation to demonstrate container integrity and that no microbial ingress is observed after the (b) (4) bottles with the (b) (4) pumps are actuated while submerged in the challenge suspension, and once more immediately after removal from the suspension. Failure of the subject container under these conditions will not necessarily result in non-approval of the (b) (4) system but the inclusion of this test will present a worst-case challenge to the container and provide additional information about container capability.*

Response: On 10/11/2016, a teleconference between the FDA CMC review team for the subject application and representatives from the NDA holder took place to discuss (among other issues) the standing microbiology deficiencies. The NDA holder team indicated that an alternate study had been carried out where the bottles had been actuated while the tip of the pump was immersed in the challenge solution. It was also referenced that several unsuccessful attempts had been

made to create a breached positive control. The applicant committed to submit the corresponding information for review.

On 10/14/2016, an IR amendment was submitted with the following information:

Report: In use feasibility for unidirectional valve efficacy of (b) (4) pump system. Ref. PD-TPROT-00223, dated 06/24/2015. The test was performed by (b) (4).
A summarized report, as well as raw data was provided.

Test description:

30 (b) (4) bottles were used for the study. A challenge suspension of *P. aeruginosa* ((b) (4) CFU/mL) was prepared in saline. Each challenge consisted of inverting the bottle, dipping into the challenge solution, removing, actuating once in the air and performing another actuation in the challenge solution. In between challenges, half of the bottles were incubated upright and the other half are incubated in an inverted position at 30-35°C. The challenge was performed for 4 consecutive days per week during three consecutive weeks. Three negative controls were incubated for the entire duration of the challenge phase. Three days after the last challenge, the following assessment was performed:

Expelled drops:

An expelled dose analysis was performed on each sample and negative control. The product from each sample was sprayed once directly onto a TSA plate. The plates were incubated for a minimum of 3 days and then inspected for colonies.

Contents analysis:

(b) (4)

Method suitability for the expelled dose and for the content in the bottle was performed.

Results:

The recovery for the method suitability for the expelled dose and the contents of the bottles was (b) (4) %, respectively.

For the expelled drops and content analysis, no growth was observed in any of the 30 samples tested or the negative controls.

The applicant concluded that the results demonstrate that the nasal spray device prevented microbial ingress, and that the container closure system maintained integrity although the immersion actuations with inversion of the nasal spray product, which includes a dip-tube to siphon the formulation into the pump, are not consistent with the intended use of the device as designed.

Note to reviewer: On the 10/11/2016 teleconference, the applicant stated that the total content in each bottle presented practical limitations and therefore, said content influenced some of the analytical considerations at or after the last label claimed actuation # 30. For example, the applicant indicated that there was not enough volume to perform the expelled dose analysis and then the determination of desmopressin assay. Therefore, this reviewer deems satisfactory the applicant's approach of 12 actuations total during the microbial ingress test since it is unlikely that the system would break down upon further actuation considering the extreme worst case nature of the CCIT provided (i.e., submerged actuation in the 2nd test and the 9 week duration of the 1st test).

- In addition to the method suitability controls already provided, please indicate if a container positive control (capable of detecting microbial ingress, due to a critical component of the unidirectional valve being removed, for example) was included as part of the microbial challenge study and if not, justify your response.*

Response: The applicant provides a document by (b) (4) indicating that in an effort to stay as close as possible to the commercially available product, (b) (4)



- Alternatively, provide conforming data from the USP <51> Antimicrobial Effectiveness Test (or similar test method) with the complete battery of microbial organisms that demonstrate the inherent antimicrobial properties of the subject drug product for the proposed discard period, at a minimum. Please consider the lowest concentration of ingredient, whichever ingredient or ingredient combination may be responsible for the antimicrobial effectiveness, that would be allowed for release or stability and be sure that the antimicrobial effectiveness test was performed at that minimum concentration.*

Response: The applicant stated that the formulation does not have antimicrobial properties, (b) (4)



Reviewer's Assessment: Although the subject drug product is marketed as non-sterile; and thus container closure integrity test would not be required, since the drug product does not have antimicrobial properties and it did not fully meet the USP<51> test acceptance criteria, the applicant was requested to provide validation of the integrity of the (b) (4) system. The aforementioned validation information was analyzed and it is deemed adequate to support this non sterile product.

Acceptable

Antimicrobial Effectiveness Testing – See Reviewer’s Assessment above and Section 2.A.

P.3 Manufacture**P.3.1 Manufacturers**

(b) (4)

P. 3.3 Description of the Manufacturing Process and Process Controls

(b) (4)

Acceptable

P.5 Control of Drug Product

P. 5.1 Specification

The product release specification includes the following microbiological tests:

Test	Test Method	Specification
Sterility	USP <71>	Meets requirement (no growth)

Notes to reviewer:

1)  (b) (4)

The Agency responded that Serenity could use the sterility test as a measure of microbiological product quality at release and on stability with the understanding that if a batch fails sterility testing, it must be rejected and not retested using microbial limits.

2) The proposed release specifications did not include the absence of *Burkholderia cepacia*. As this is an aqueous non-sterile product, this test is recommended for release. An information request was sent on 04/18/2016 requesting this additional testing. See deficiency (in italics) below, as well as the response submitted on 06/02/2016.

Non-sterile aqueous drug products may potentially be contaminated with organisms in the Burkholderia cepacia complex (BCC). BCC strains have a well-documented ability to ferment a wide variety of substrates and are known to proliferate in the presence of many traditional preservative systems. Thus, despite the presence of otherwise adequate preservative systems, BCC strains can survive and even proliferate in product during storage. For a recent review of FDA’s perspective on BCC please see PDA J Pharm Sci Tech 2011; 65(5): 535-43.

In order to control for the presence of BCC in your product you should consider the following:

a) Identify potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product. We recommend that potential sources are examined and sampled as process controls. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.

b) Provide test methods and acceptance criteria to demonstrate the drug product is free of BCC. Your test method should be validated and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells should be acclimated to the conditions in the manufacturing environment (e.g., temperature) before testing.

As there are currently no compendial methods for detection of BCC, we have provided suggestions for a potential validation approach and some points to consider when designing your validation studies. However, any validated method capable of detecting BCC organisms would be adequate. It is currently sufficient to precondition representative strain(s) of BCC in water and/or your drug product without preservatives to demonstrate that your proposed method is capable of detecting small numbers of BCC. Your submission should describe the preconditioning step (time, temperature, and solution(s) used), the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning of the organisms occurs during these method validation studies to insure that the proposed recovery methods are adequate to recover organisms potentially present in the environment.

*For more information, we refer you to *Envir Microbiol* 2011; 13(1):1-12 and *J. Appl Microbiol* 1997; 83(3):322-6.*

Response: The applicant stated that the product is manufactured as a sterile dosage form with a container closure system designed to maintain the product free of microbial contamination over its shelf-life.

The applicant stated that the findings listed below show that the product is sterile, and that based on that, it is supported that the BCC issue does not need further evaluation.

(b) (4)

Reviewer's Assessment: This reviewer deems that the applicant's justification regarding the BCC monitoring is adequate; thus, no additional information will be requested.

Acceptable

P.5.2 Analytical Procedures - See P.5.1 and P.5.3

P.5.3 Validation of Analytical Procedures

Sterility

Test Method: according to USP

Bacteriostasis/fungistasis testing was performed. The subject drug product was tested using a battery of organisms: compendial

The subject drug product did not inhibit recovery of the test organisms.

Finished lot # 502060 (7.5 µg/mL) met the release specification of “Meets requirement (no growth)”

Reviewer’s Assessment: The applicant provided sufficient information regarding the validation of the sterility test as per USP<71>.

Acceptable

P.7 Container Closure- See P.1.

P.8 Stability

P. 8.1 Stability Summary and Conclusion

Proposed Expiry: 24 months

P. 8.2 Post-Approval Stability Protocol and Stability Commitment

The product stability specification includes the following microbiological tests:

Test	Test Method	Specification
Endotoxins	USP <85>	NMT ^(b) ₍₄₎ EU/mL
Sterility	USP <71>	Meets Requirement (No Growth)

The testing schedule in the stability protocol is as follows:

Stability long term storage conditions: 5 °C/Ambient RH

Test	Time (Months)								
	0	3	6	9	12	15	18	24	36
Bacterial Endotoxins	X	X	X		X		X	X	X
Sterility	X	X	X		X		X	X	X
Microbial limits*	X	X	X		X		X	X	X

*The applicant stated that the drug product was planned to be labelled as a low bioburden product, and therefore, microbial enumeration tests and endotoxins evaluations were conducted at product release and also as part of the drug product stability program. See below.

On 04/18/2016, the following deficiency (in italics) was sent to the applicant in an IR letter. The response shown below was submitted on 06/02/2016.

Reference is made to the FDA Response to Question 7 for the 03/10/2014 Meeting Minutes for the associated IND 076667, where it was stated that the microbial enumeration test would be acceptable for the drug product at release and shelf-life “in the event you choose not to assess microbiological quality using the USP<71>sterility test”. Furthermore, the specification provided in Section P.5.1 of the subject NDA indicates that the sterility test will be performed for release and stability; however, the stability data provided in Section P.8.3, includes microbial

enumeration testing performed as per USP<61> and <62>. Thus, confirm that, as stated in Section P.5.1, the sterility test is the method that will be used to test the microbial quality of the drug product during its shelf-life. Alternatively, provide a revised stability protocol indicating the preferred method to assess the microbiological attributes of the drug product at shelf-life.

Response: The applicant confirm that as stated in Section P.5.1, the sterility test is the method that will be used to test the microbiological quality of the drug product at product release and during its shelf-life. The USP<61> and <62> testing was used earlier in the development of this product.



(b) (4)

Post Approval Stability Commitment

The applicant commits to placing the first three commercial lots of the subject drug product into their stability program. Thereafter, on an annual basis, one production lot will be added to the post-approval stability protocol shown below:

Test	Time (Months)								
	0	3	6	9	12	15	18	24	36
Sterility	X		X		X			X	X

Reviewer’s Assessment: The applicant has provided satisfactory information regarding the stability protocol, as well as the post-approval stability protocol.

Acceptable

P.8.3 Stability Data

The applicant stated that long-term and accelerated stability studies are ongoing for several drug product lots representative of SER-120 manufacturing process. The applicant also indicated that stability studies are complete for lots 008007 and 100305, while others are at various stages of completion. In addition, there are four lots for which switch arm stability studies were undertaken out of which two are complete (300285 and 300438). Switch arm stability studies for 400273 and 400495 are ongoing.

The applicant stated that no microbial growth was seen in any batches at release and during stability testing (long-term, accelerated, and switch-arm) and endotoxin evaluations were below the level of detection in all batches at release and during stability testing, and that the results confirmed that no preservatives are needed for this drug product fitted with the (b) (4) system to keep it sterile.

Reviewer’s Assessment: It seems to this reviewer that the “switch arm” approach used during the stability studies included changing the samples from the long term storage conditions, namely 5 °C/Ambient RH, to 25°C/60% RH. One explanation would be that the applicant was trying to address the in-use stability storage (See Section 2 below), but no clear explanation is provided regarding the relevance of the referenced switch arm stability storage approach. However, this reviewer sees no need to ask for clarification here since a deficiency was issued regarding the recommended in-use storage conditions. See Section 2.A. Package Insert below.

Acceptable

R Regional Information

Executed Batch Records

The executed batches manufactured were as follows:

Batch Number	Date of Manufacture	Dosage Form, Strength and Batch Size	Usage
400495	April 2014	Desmopressin Nasal Spray 15 µg/mL, (b) (4)	Developmental and Primary Stability
502060	Nov. 2015	Desmopressin Nasal Spray 7.5µg/mL, (b) (4)	Engineering run (Demonstration) and Stability



(b) (4)

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1
2.A. Package Insert

The following statements are provided in the package insert:



(b) (4)

On 04/18/2016, the following deficiency (in italics) was sent to the applicant in an IR letter. The response shown below was submitted on 06/02/2016.

On page 11 of the proposed labeling, the following storage instructions (b) (4)

We note that the DP formulation does not contain an antimicrobial preservative; however, the drug product is intended to deliver multiple doses over a two month period. Provide data demonstrating that the drug product meets USP<51>acceptance criteria for a category 2 product over the duration of the in-use period.

Response: The applicant stated that the drug product is actually a sterile product despite the fact that Serenity has chosen not to include this in the label, and that (b) (4) nasal spray pump is specifically designed for preservative free solutions based on tip-seal/filter technology. In addition, during stability studies under long-term and accelerated conditions, no microbial growth was observed well-beyond two-month period as evidenced by microbial enumeration testing during early development and by sterility testing for registration batches. The applicant indicated that an exploratory study according to USP <51> was conducted on this preservative-free formulation (the document provided in Section 3.2.P.2.5 of the NDA, 06/02/2016 submission).

Test Organism	Control (CFU/g)	14 Day (CFU/g)	28 Day (CFU/g)	PASS/ FAIL
E. coli	(b) (4)	(b) (4)	(b) (4)	PASS
P. aeruginosa*	(b) (4)	(b) (4)	(b) (4)	FAIL
S. aureus	(b) (4)	(b) (4)	(b) (4)	PASS
C. albicans	(b) (4)	(b) (4)	(b) (4)	PASS
A. niger	(b) (4)	(b) (4)	(b) (4)	PASS

Of the five compendial organisms tested, *P. aeruginosa* demonstrated growth.

The applicant stated that additional challenge studies simulating product use and *P. aeruginosa* as the challenge organism are in progress to support 60-day discard date., and that those studies will be made available for review at completion in approximately 12 weeks.

On 07/06/2016, the following deficiency (in italics) was sent to the applicant. The response shown below was submitted on 07/15/2016.

We acknowledge that an exploratory study according to USP <51> was conducted on this preservative-free formulation, and that additional challenge studies simulating product use and P. aeruginosa as the challenge organism are in progress to support 60-day discard date. However, please provide the complete and conforming data from the USP <51> Antimicrobial Effectiveness Test (or similar test method) that demonstrate the inherent antimicrobial properties of the subject drug product. Please consider the lowest concentration of ingredient, whichever ingredient or ingredient combination may be responsible for the antimicrobial effectiveness, that would be allowed for release or stability and be sure that the antimicrobial effectiveness test was

performed at that minimum concentration. Alternatively, the antimicrobial effectiveness test can be performed at the end of the proposed discard period (60 days).

Response: The applicant stated that although the AET failed for *P. aeruginosa*, while desmopressin does not have any antimicrobial properties, the desmopressin concentration for SER-120 lot used in the AET study was 5 µg/mL (the lowest desmopressin concentration prepared in the SER-120 program). Nevertheless, based on the available data, the container closure system was designed and tested to assure it prevents microbial contamination during actuation to demonstrate that the preservative-free formulation remains untainted.

On 07/06/2016, the following B Comment (in italics) was sent to the applicant. The response shown below was submitted on 07/15/2016.

Please note that if the results of the antimicrobial effectiveness test are not adequate, then additional studies will be requested to show that the container closure system will not allow microbial ingress during the use period. The aerosol test provided is generally not accepted as a sole test to support container closure integrity and as such additional validation testing would be requested such as a microbial ingress test, or a dye ingress test. Due to the nature of the product it would be preferred that the nasal spray pump be challenged in multiple configurations (i.e., in various positions of the spray pump such as pressed, non-pressed, etc.) in a submerged challenge environment.

Response: The applicant indicated that a 60-day in use test for SER-120 was currently ongoing. However, as noted in section P. 2 of this review, on 10/11/2016, in a teleconference between the FDA CMC review team for the subject application and representatives from the NDA holder he applicant committed to submit for review the validation information an alternate of a CCIT to show that the container-closure system prevents contamination of the bottle contents.

Reviewer's Assessment: The applicant indicated that the AET information for the in-use period will no longer be submitted since additional information has been provided regarding the CCIT. See section P.2 of this review.

Acceptable

Post-Approval Commitments: None

Lifecycle Management Considerations -None

List of Deficiencies: N/A

Primary Microbiology Reviewer Name and Date: Yarery Smith, Ph.D., 10/20/2016

Secondary Reviewer Name and Date (and Secondary Summary, as needed): John Arigo, Ph.D., 10/22/2014



QUALITY ASSESSMENT



END



John
Arigo

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Yarery
Smith

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ATTACHMENT I: Product Quality Risk Assessments

Initial Risk Assessment

Initial Risk Assessment for NDA 201656 Desmopressin Acetate Nasal Spray as indicated for the treatment of nocturia in adults.

Product Attribute / CQA	Factors that can impact the CQA	Probability (O)	Severity of Effect (S)	Detectability (D)	FMECA RPN Number	Comment
Appearance	<ul style="list-style-type: none"> Process Stability 	2	3	3	18	
Identification	<ul style="list-style-type: none"> CGMPs 	1	5	1	5	
Assay (active) / Stability	<ul style="list-style-type: none"> Formulation Raw materials Process Container/Closure Storage conditions 	4	3	3	36	Low dose formulation. Long-term storage at 2-8 C Limited in-use (room temperature) period.
Cyclopentadecan-olide Content	<ul style="list-style-type: none"> Formulation Raw materials Process 	3	3	3	27	Penetration enhancer for enhanced absorption through nasal mucosa needs to be maintained at optimal range
pH	<ul style="list-style-type: none"> Formulation Raw materials Process 	2	3	2	12	Impact on stability
Emulsion particle size	<ul style="list-style-type: none"> Formulation Process 	3	3	3	27	Indicative of consistent emulsification / homogenization of oil phase
Related Substances Impurities / Degradants	<ul style="list-style-type: none"> Formulation Raw materials Process Container/Closure 	4	1	5	20	Based on low daily dose (max. 1.5 mcg), impurities expected to be negligible
Leachables / Extractables	<ul style="list-style-type: none"> Formulation Container/Closure (b) (4) pump component materials 	2	3	5	30	
Uniformity of Dosage Fill Volume	<ul style="list-style-type: none"> Process parameters 	1	1	1	1	
Metered dose spray pump function	<ul style="list-style-type: none"> Formulation (b) (4) pump design and build 	3	3	4	36	Spray content uniformity Pump delivery (shot weight) Spray droplet size
Osmolality	<ul style="list-style-type: none"> Formulation Raw materials Process 	1	1	1	1	Nasal sprays typically <500 mOsm/kg
Foreign Particulate Matter	<ul style="list-style-type: none"> Raw materials Process Container/Closure 	2	1	3	6	Product manufactured (b) (4)
Sterility	<ul style="list-style-type: none"> Process parameters Container/Closure system including (b) (4) pump 	3	4	3	36	Sterility not required for nasal spray (b) (4)
Endotoxins	<ul style="list-style-type: none"> Raw materials 	3	3	3	27	

RPN Values: **Low Risk (1-25)**; **Moderate Risk (26-60)**; **High Risk (61-125)**

Final Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Appearance	<ul style="list-style-type: none"> Process Stability 	18		Adequate	
Identification	<ul style="list-style-type: none"> CGMPs 	5		Adequate	
Assay (active) / Stability	<ul style="list-style-type: none"> Formulation Raw materials Process Container/Closure Storage conditions 	36	Validated manufacturing process with sterility assurance, storage conditions, product specification.	Adequate	Storage at 2-8 C for 24 months. In-use (25 C) for 60 days
Cyclopentadecanolid Content	<ul style="list-style-type: none"> Formulation Raw materials Process 	27	Process controls. Product specification.	Adequate	
pH	<ul style="list-style-type: none"> Formulation Raw materials Process 	12	Formulation and process controls.	Adequate	
Emulsion particle size	<ul style="list-style-type: none"> Formulation Process 	27	Process controls.	Adequate	
Related Substances Impurities / Degradants	<ul style="list-style-type: none"> Formulation Raw materials Process Container/Closure 	20	Quality of raw materials, storage conditions, low bioburden.	Adequate	
Leachables / Extractables	<ul style="list-style-type: none"> Formulation Container/Closure (b) (4) pump component materials 	30	Extensive characterization performed.	Adequate	
Uniformity of Dosage Fill Volume	<ul style="list-style-type: none"> Process parameters 	3	Process controls.	Adequate	
Metered dose spray pump function	<ul style="list-style-type: none"> Formulation (b) (4) pump design and build 	36	Product specification.	Adequate	Any changes to device should be carefully evaluated. Impact of any formulation changes should also be evaluated for impact on performance/functionality
Osmolality	<ul style="list-style-type: none"> Formulation Raw materials Process 	3	Formulation and testing.	Adequate	
Foreign Particulate Matter	<ul style="list-style-type: none"> Raw materials Process Container/Closure 	6	Process conditions.	Adequate	
Sterility	<ul style="list-style-type: none"> Process parameters Container/Closure system including (b) (4) pump 	36	Sterilization process and aseptic processing. Demonstrated CCIT.	Adequate	Sterility assurance demonstrates low bioburden appropriate for this peptide formulation and for nasal spray administration
Endotoxins	<ul style="list-style-type: none"> Raw materials 	27		Adequate	Consistent with low bioburden

Lifecycle Management Considerations:

OPF/DIA recommends that the next scheduled surveillance inspection for (b) (4) include a device investigator that can evaluate the firm's purchasing controls and quality agreements with (b) (4), the manufacturer of the device constituent.

See also recommendations in CDRH-OC consult review.

ATTACHMENT II: Pending labeling issues as of this review

A. Highlight Section

- a. Proprietary name and established name should be revised to,

“Noctiva (desmopressin acetate) nasal spray”.

- b. Dosage forms and Strengths section should be revised to,

“Preservative-free nasal spray emulsion delivering 0.83 mcg of desmopressin acetate (equivalent to 0.75 mcg desmopressin) or 1.66 mcg of desmopressin acetate (equivalent to 1.5 mcg desmopressin) in each spray (0.1 mL) (3)”

B. Full Prescribing Information

- #3 Dosage Forms and Strengths section should be revised to,

“Each spray delivers contains 0.1 mL of NOCTIVA.”

“Each spray contains 0.83 mcg or 1.66mcg of desmopressin acetate (equivalent to 0.75 mcg or 1.5 mcg of desmopressin) for the 0.83 mcg/0.1mL or 1.66 mcg/0.1 mL strength of desmopressin acetate.”

#11 Description section,

- The established name should be revised to,

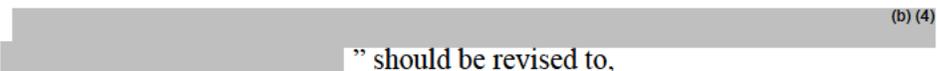
“NOCTIVA (desmopressin acetate) nasal spray”

-  (b) (4)
Should be revised to,

“Desmopressin acetate is a synthetic analogue of the endogenous pituitary hormone 8-arginine vasopressin, an antidiuretic hormone (ADH).”

-  (b) (4)
” should be revised to,

“NOCTIVA (desmopressin acetate) nasal spray is formulated for intranasal use as a milky white emulsion without preservatives at pH 5.5.”

-  (b) (4)
” should be revised to,

“NOCTIVA is available as an oil-in-water emulsion at two dose strengths, 0.83 mcg and 1.66 mcg of desmopressin acetate per spray, for nasal administration. Each spray is 0.1 mL. The dose strengths are expressed as desmopressin acetate

and are equivalent to 0.75 mcg and 1.5 mcg of desmopressin free base per spray, respectively.”

- [REDACTED] (b) (4) ”
should be revised to

“After initial priming, each actuation of NOCTIVA 0.83 mcg/0.1mL or 1.66 mcg/0.1mL delivers a dose of 0.83 mcg and 1.66 mcg of desmopressin acetate, respectively.”

- Inactive ingredient information: “[REDACTED] (b) (4)” should be revised to “citric acid anhydrous”; “[REDACTED] (b) (4)” should be revised to

“sodium citrate dihydrate”.

#16 How Supplied/Storage and Handling

- [REDACTED] (b) (4)
[REDACTED]
should be revised to,

“NOCTIVA (desmopressin acetate) nasal spray is available in a 3.5 mL amber glass bottle (nominal volume) fitted with a nasal actuator, a cartridge pump, and a dip tube, delivering a dose of either 0.83 mcg or 1.66 mcg of desmopressin acetate (equivalent to 0.75 mcg or 1.5 mcg of desmopressin) per spray (0.1mL). Each bottle contains a target amount of 3.8 g formulation with 30 effective doses in addition to the initial priming (5 actuations), the equivalent of 30 days’ medication when used as one spray once a day.”

- The dosage strength with NDC numbers should be revised as follows: (NDC number is provided by the applicant):

“0.83 mcg/0.1mL of desmopressin acetate NDC 0023-5227-35
1.66 mcg/0.1mL of desmopressin acetate NDC 0023-5670-35”



Mark
Seggel

Digitally signed by Mark Seggel
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OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 201656	Submission Type: 505(b)(2) NDA	Established/Proper Name: Desmopressin Nasal Spray
Applicant: Serenity Pharmaceuticals	Letter Date: 2/4/16	Dosage Form: Nasal Spray
Chemical Type: Type 5	Stamp Date: 2/4/16	Strength: 0.75mcg/0.1ml and 1.5mcg/0.1ml

A. FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?	X		
2.	If the application is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	-	-	Not Applicable
3.	Are there any potential review issues to be forwarded to the Applicant, not including any filing comments stated above?	X		See attached Information Request

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
Product Type				
1.	New Molecular Entity ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
2.	Botanical ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
3.	Naturally-derived Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
4.	Narrow Therapeutic Index Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.	PET Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
6.	PEPFAR Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7.	Sterile Drug Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
8.	Transdermal ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.	Pediatric form/dose ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
10.	Locally acting drug ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
11.	Lyophilized product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
12.	First generic ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
13.	Solid dispersion product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
14.	Oral disintegrating tablet ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
15.	Modified release product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
16.	Liposome product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
17.	Biosimilar product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
18.	Combination Product _____	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Drug-device combination product; CDRH-ODE and CDRH-OC consulted
19.	Other _____	<input type="checkbox"/>	<input type="checkbox"/>	

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Regulatory Considerations					
20.	USAN Name Assigned		<input checked="" type="checkbox"/>	<input type="checkbox"/>	
21.	End of Phase II/Pre-NDA Agreements		<input checked="" type="checkbox"/>	<input type="checkbox"/>	See IND 76667 meeting minutes dated 09/17/15
22.	SPOTS (Special Products On-line Tracking System)		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
24.	Comparability Protocol(s) ²		<input checked="" type="checkbox"/>	<input type="checkbox"/>	Transfer to the new automated filling line after NDA approval.
25.	Other _____		<input type="checkbox"/>	<input type="checkbox"/>	
Quality Considerations					
26.	Drug Substance Overage		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
27.	Design Space	Formulation	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
28.		Process	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
29.		Analytical Methods	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
30.		Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
31.	Real Time Release Testing (RTRT)		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
32.	Parametric Release in lieu of Sterility Testing		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
33.	Alternative Microbiological Test Methods		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
34.	Process Analytical Technology ¹		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	<input type="checkbox"/>	<input type="checkbox"/>	TBD
36.		Excipients	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
37.		Microbial	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
38.	Unique analytical methodology ¹		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
39.	Excipients of Human or Animal Origin		<input type="checkbox"/>	<input type="checkbox"/>	
40.	Novel Excipients		<input checked="" type="checkbox"/>	<input type="checkbox"/>	Cyclopentadecanolide (CPD) permeation enhancer
41.	Nanomaterials ¹		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
42.	Hold Times Exceeding 30 Days		<input type="checkbox"/>	<input type="checkbox"/>	TBD
43.	Genotoxic Impurities or Structural Alerts		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
44.	Continuous Manufacturing		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
45.	Other unique manufacturing process ¹		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
47.	New delivery system or dosage form ¹		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
48.	Novel BE study designs		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
49.	New product design ¹		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
50.	Other _____		<input type="checkbox"/>	<input type="checkbox"/>	

¹Contact Office of Testing and Research for review team considerations

²Contact Post Marketing Assessment staff for review team considerations

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C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Needs statement regarding extraordinary circumstances
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? <input type="checkbox"/> Drug Substance <input type="checkbox"/> Drug Product <input type="checkbox"/> Appendices <ul style="list-style-type: none"> <input type="checkbox"/> Facilities and Equipment <input type="checkbox"/> Adventitious Agents Safety Evaluation <input type="checkbox"/> Novel Excipients <input type="checkbox"/> Regional Information <ul style="list-style-type: none"> <input type="checkbox"/> Executed Batch Records <input type="checkbox"/> Method Validation Package <input type="checkbox"/> Comparability Protocols 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
FACILITY INFORMATION					
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: <input type="checkbox"/> Name of facility, <input type="checkbox"/> Full address of facility including street, city, state, country <input type="checkbox"/> FEI number for facility (if previously registered with FDA) <input type="checkbox"/> Full name and title, telephone, fax number and email for on-site contact person. <input type="checkbox"/> Is the manufacturing responsibility and function identified for each facility, and <input type="checkbox"/> DMF number (if applicable)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: <input type="checkbox"/> Is a manufacturing schedule provided? <input type="checkbox"/> Is the schedule feasible to conduct an inspection within the review cycle?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
DRUG SUBSTANCE INFORMATION					

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C. FILING CONSIDERATIONS					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
6.	<p>Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?</p> <ul style="list-style-type: none"> <input type="checkbox"/> general information <input type="checkbox"/> manufacture <ul style="list-style-type: none"> <input type="checkbox"/> Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) <input type="checkbox"/> Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only <input type="checkbox"/> Includes complete description of product lots and their uses during development – BLA only <input type="checkbox"/> characterization of drug substance <input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> <input type="checkbox"/> Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) <input type="checkbox"/> Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only <input type="checkbox"/> reference standards or materials <input type="checkbox"/> container closure system <input type="checkbox"/> stability <ul style="list-style-type: none"> <input type="checkbox"/> Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
DRUG PRODUCT INFORMATION					
7.	<p>Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?</p> <ul style="list-style-type: none"> <input type="checkbox"/> Description and Composition of the Drug Product <input type="checkbox"/> Pharmaceutical Development <ul style="list-style-type: none"> <input type="checkbox"/> Includes descriptions of changes in the 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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	<p style="margin-left: 20px;">manufacturing process from material used in clinical to commercial production lots</p> <ul style="list-style-type: none"> ○ Includes complete description of product lots and their uses during development <p><input type="checkbox"/> Manufacture</p> <ul style="list-style-type: none"> ○ If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? <p><input type="checkbox"/> Control of Excipients</p> <p><input type="checkbox"/> Control of Drug Product</p> <ul style="list-style-type: none"> ○ Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Analytical validation package for release test procedures, including dissolution <p><input type="checkbox"/> Reference Standards or Materials</p> <p><input type="checkbox"/> Container Closure System</p> <ul style="list-style-type: none"> ○ Include data outlined in container closure guidance document <p><input type="checkbox"/> Stability</p> <ul style="list-style-type: none"> ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment <p><input type="checkbox"/> APPENDICES</p> <p><input type="checkbox"/> REGIONAL INFORMATION</p>				
BIOPHARMACEUTICS					
8.	<p>If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies:</p> <ul style="list-style-type: none"> • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided? 	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.	<p>Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

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	the drug product's development and/or manufacturing changes to the clinical product? <i>(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)</i>				
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? <input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> <input type="checkbox"/> manufacturing flow; adjacent areas <input type="checkbox"/> other products in facility <input type="checkbox"/> equipment dedication, preparation, sterilization and storage <input type="checkbox"/> procedures and design features to prevent contamination and cross-contamination <input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> <input type="checkbox"/> avoidance and control procedures <input type="checkbox"/> cell line qualification <input type="checkbox"/> other materials of biological origin <input type="checkbox"/> viral testing of unprocessed bulk <input type="checkbox"/> viral clearance studies <input type="checkbox"/> testing at appropriate stages of production <input type="checkbox"/> novel excipients	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
17.	Are the following information available for Biotech Products: <input type="checkbox"/> Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: <ul style="list-style-type: none"> <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> Mycoplasma 	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

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	Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples			

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OPQ REVIEW TEAM

Quality Review Team	
Branch Chief	Moo Jhong Rhee
ATL	Mark Seggel
Drug Substance reviewer	Ben Stevens/Donna Christner
Drug Product reviewer	Hong Cai
Drug Process reviewer	Li Shan Hsieh / Nallaperumal Chidambaram
Microbiology	Yarery Smith
Biopharm reviewer	Not Applicable
Facility reviewer	Juandria Williams
EA	James Laurenson
CDRH-GHDB	Kathleen Fitzgerald/Alan Stevens
CDRH-OC	Chris Brown

DRUG SUBSTANCE

Desmopressin is a synthetic peptide analogue of human anti-diuretic hormone (vasopressin) and a selective V2 agonist. Chemically, desmopressin is 1-(3-mercaptopropionic acid)-8-D-arginine-vasopressin monoacetate trihydrate. Desmopressin acetate is the subject of a USP monograph.

Type II DMF (b) (4) for Desmopressin Acetate USP, held by (b) (4), was last reviewed in May 2016. It was found adequate to support use in an oral formulation of desmopressin. The DMF appears to be current.

DRUG PRODUCT

Desmopressin is the active ingredient in several approved products (injections, oral stablets and nasal sprays (e.g., DDAVP, Stimite, Minirin)).

DDAVP 0.01 mg/spray
Stimate 0.15 mg/spray
Minirin 0.01 mg/spray

Several of the approved nasal spray formulations are suitable for storage at room temperature (i.e., refrigeration is not necessary).

Noctiva™ (SER120; desmopressin nasal spray) is a low-dose, oil-in-water emulsion formulation containing a permeation enhancer. The product was developed under IND 76667 for the treatment of adult nocturia. Each spray of the preservative-free, nasal spray emulsion delivers

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0.75 mcg or 1.5 mcg desmopressin (express in terms of desmopressin free-base). In accordance with the USP Salt Nomenclature policy, the strength of Noctiva should be expressed based on the free base of desmopressin. However, based on historical usage in other product, it may be appropriate to label the strength based on the acetate salt. This will need to be discussed with the clinical review team, DMEPA, and CMC labeling and nomenclature experts. Note that the available desmopressin nasal sprays are solution formulations.

The recommended dosage is one (1) spray only in either the left or right nostril each night approximately 30 minutes before going to bed.

Noctiva is supplied in an amber glass bottles with a mechanical multi-dose spray device designed to prevent ingress of microbial contamination, thereby eliminating the need for the inclusion of a preservative in the formulation.

After priming, each actuation of the device delivers (b) (4). The composition of the two dose strengths (b) (4).

Components and Composition

Ingredient	7.5 µg/mL		15 µg/mL		Function
	Composition (mg)		Composition (mg)		
	Per (b) (4) Dose	Per Vial ^a	Per (b) (4) Dose	Per Vial ^a	
Desmopressin ^b	7.5	(b) (4)	15	(b) (4)	Active ingredient
Cyclopentadecanolide (CPD)				(b) (4)	Permeation Enhancer
Cottonseed oil					(b) (4)
Polysorbate 20					(b) (4)
Sorbitan monolaurate					(b) (4)
Citric acid, anhydrous					(b) (4)
Sodium citrate dihydrate					(b) (4)
Water for Injection (WFI)	q.s.	q.s.	q.s.	q.s.	(b) (4)

a Typical DP volume per vial is 3.8 mL

b Composition refers to desmopressin free base

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(b) (4)

FILING RECOMMENDATION

Overall, the application for desmopressin nasal spray is fileable from the perspective of the CMC / pharmaceutical quality review team. There are, however, numerous comments to be conveyed to the applicant in the 74-day letter.

Mark R. Seggel
Application Technical Lead (ATL)

Mark R.
Seggel -
S

Digitally signed by Mark R.
Seggel -S
DN: c=US, o=U.S.
Government, ou=HHS,
ou=FDA, ou=People,
cn=Mark R. Seggel -S,
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