

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201656Orig1s000

OTHER REVIEW(S)

The goal of the trial is to compare the systemic exposure of desmopressin following administration of two sprays of the 0.83 mcg NOCTIVA nasal spray and one spray of the 1.66 mcg NOCTIVA nasal spray. These data will help address a potential safety concern with the real-world use of 2 sprays of the 0.83 mcg strength for the 1.66 mcg dose of NOCTIVA nasal spray.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A comparative pharmacokinetic study of two sprays of the 0.83 mcg strength and one spray of the 1.66 mcg strength in healthy subjects

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial

- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

CHRISTINE P NGUYEN
03/02/2017

**REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Application: NDA 201656

Application Type: New NDA

Drug Name(s)/Dosage Form(s): NOCTIVA (desmopressin) nasal spray

Applicant: Serenity Pharmaceuticals, LLC

Receipt Date: February 4, 2016

Goal Date: December 4, 2016 (Action: December 2, 2016)

1. Regulatory History and Applicant's Main Proposals

This NDA 201656 was submitted on February 4, 2016, by Serenity Pharmaceuticals for desmopressin nasal spray. The related IND 76667 was initially reviewed by the Division of Bone, Reproductive, and Urologic Products (DBRUP) when submitted in 2008. The IND was transferred to the Division of Metabolism and Endocrinology Products (DMEP) in 2009, and was transferred back to DBRUP.

Desmopressin is a synthetic analog of the human pituitary hormone, vasopressin. Desmopressin has been in medical use for several decades as replacement therapy for patients with central diabetes insipidus and to treat bedwetting in children. Desmopressin is marketed worldwide in several dosage forms, including a nasal spray, oral tablet of multiple strengths, and injection solution.

SER120 (desmopressin acetate nasal spray) is intended to be administered at bedtime and is proposed for the treatment of adult nocturia. The product is a new emulsion formulation containing the excipient cyclopentadecanolide (CPD) and lower concentrations of desmopressin. This is the first product where CPD is included in a nasal spray formulation.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by May 9, 2016. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- NO** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment: *The Highlights section is about one inch longer than 1/2 a page, and there is no agreement on file for a granted waiver.*

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment:

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
---------	-------------------

Selected Requirements of Prescribing Information

• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading, “**HIGHLIGHTS OF PRESCRIBING INFORMATION**” must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

N/A

Selected Requirements of Prescribing Information

13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- YES** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES

Selected Requirements of Prescribing Information

20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:

Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment:

Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- See 17 for **PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- See 17 for **PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- See 17 for **PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- NO** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
1. Section 5.5 should be: *Concomitant Use of Systemic or Inhaled Pulmonary Corticosteroids May Increase the Risk of Hyponatremia*
 2. Section 8.2 Lactation is not listed in the Table of Contents (TOC).
 3. Section 8.3 Nursing Mothers in the TOC does not appear in the Full Prescribing Information section.
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see *Warnings and Precautions (5.2)*].”

Comment:

Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
 - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

- YES** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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/s/

NENITA I CRISOSTOMO
03/01/2017

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 201656	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: NOCTIVA Established/Proper Name: desmopressin Dosage Form: nasal spray Strengths: 0.75 mcg each spray		
Applicant: Serenity Pharmaceuticals, LLC Agent for Applicant (if applicable): <u>N/A</u>		
Date of Application: February 4, 2016 Date of Receipt: February 4, 2016 Date clock started after UN: <u>N/A</u>		
PDUFA Goal Date: December 4, 2016		Action Goal Date (if different): December 2, 2016
Filing Date: April 4, 2016		Date of Filing Meeting: March 11, 2016
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input checked="" type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): <u>treatment of nocturia in adults who wake up 2 or more times per night to void</u>		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <hr/> <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
The application will be a priority review if:	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none">• A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)• The product is a Qualified Infectious Disease Product (QIDP)• A Tropical Disease Priority Review Voucher was submitted• A Pediatric Rare Disease Priority Review Voucher was submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input checked="" type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): IND 076667

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system? If no, ask the document room staff to make the corrections. Also,	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment

Is the application a 505(b)(2) NDA? (Check the 356h form, cover letter, and annotated labeling). If yes , answer the bulleted questions below:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>				
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes , please list below:				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>				
Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>				
NDA/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	3 years
If yes , # years requested: 3 yrs				

<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	3/16/16: Email sent to sponsor to re-submit with the correct wording.
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff :</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BPCA: Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Submitted on March 14, 2016
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has a review of the available pregnancy and lactation data been included?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

5

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	• COA
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 2/19/09 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 7/28/10 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): 5/22/09; 5/5/11; 6/27/11; 6/14/13 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input checked="" type="checkbox"/>			

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 11, 2016

BACKGROUND: The related IND 76667 was transferred to the Division of Bone, Reproductive and Urologic Products on April 21, 2014. This NDA 201656 was submitted on February 4, 2016, by Serenity Pharmaceuticals for desmopressin nasal spray for the treatment of adult nocturia. Desmopressin is a synthetic analog of the human pituitary hormone, vasopressin. Desmopressin has been in medical use for several decades as replacement therapy for patients with central diabetes insipidus and to treat bedwetting in children. Desmopressin is marketed worldwide in several dosage forms, including a nasal spray, oral tablet of multiple strengths, and injection solution. SER120 (desmopressin acetate nasal spray) is intended to be administered at bedtime and is proposed for the treatment of adult nocturia. The product is a new emulsion formulation containing the excipient cyclopentadecanolide (CPD) and lower concentrations of desmopressin. This is the first product where CPD is included in a nasal spray formulation.

Related meetings were End of Phase 2 on February 9, 2009, Pre-NDA on July 28, 2010 (Preliminary Comments only, no meeting), and Guidance Meeting on August 18, 2015.

This application will be presented at the Advisory Committee Meeting.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Nenita Crisostomo	Y
	CPMS/TL:	Jennifer Mercier	Y
Cross-Discipline Team Leader (CDTL)	Suresh Kaul		Y
Division Director/Deputy	Hylton V. Joffe / Audrey Gassman		Y
Assoc Director of Reg Affairs	Maria Walsh / Richard Ishihara		N
Safety Team	Christine Nguyen / Meredith Alpert		Y
Clinical	Reviewer: Efficacy	Olivia Easley	Y
	Reviewer: Safety	Martin Kaufman	Y
Clinical Pharmacology	Reviewer:	Jihong Shon	Y
	TL:	Myong-Jin Kim	Y
• Genomics	Reviewer:	N/A	
• Pharmacometrics	Reviewer:	N/A	
Biostatistics	Reviewer:	Jia Guo	Y

	TL:	Mahboob Sobhan	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Deepa Rao	Y
	TL:	Mukesh Summan	Y
Statistics (carcinogenicity)	Reviewer:	Jia Guo	Y
	TL:	Mahboob Sobhan	Y
Product Quality (CMC) Review Team:	ATL:	Mark Seggel	Y
	RBPM:	Thao Vu	N
• Drug Substance	Reviewer:	Benjamin Stevens	Y
	TL	Donna christner	Y
• Drug Product	Reviewer:	Hong Cai	Y
• Process	Reviewer:	Li Shan Hsieh	Y
	TL	Nallaperumal Chidambaram	N
• Facility	Reviewer:	Juandria Williams	Y
• Microbiology	Reviewer:	Yarery Smith	Y
• Biopharmaceutics	Reviewer:	N/A	
• Immunogenicity	Reviewer:	N/A	
• Environmental Assessment	Reviewer	James Laurenson	Y
• ORA	Reviewer	Paul Perdue, Jr	N
• CDRH	Reviewer	Kathleen Fitzgerald	Y
	TL	Alan Stevens	Y
• CDRH-OC GHOD	Reviewer	Christopher Brown	Y
• Office of Combined Products	Reviewer	Bindi Nikhar	Y
	TL	Patricia Love	N
Clinical Outcome Assessments (COA)	Reviewer	Sarrit Kovacs	Y
	TL-acting	Selena Daniels	Y
	TL	Electra Papadopoulos	N

Advisory Committee Staff	ACS	Kalyani Bhatt	Y
	TL	Yvette Waples	N
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Karen Dowdy	Y
	TL:	Maria Britt Williams	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Jina Kwak	N
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Denise Baugh	Y
	TL:	Danielle Harris	N
OSE/DEpi	Reviewer	Monique Falconer	Y
	TL	Jie (Jenni) Li	N
OSE/DRISK (REMS)	Reviewer:	Somya Dunn	Y
	TL:	Kimberly Lehrfeld	Y
OSE/DPV1	Reviewer	Ali Niak	N
OSE/DPV2	Reviewer	Rachna Kapoor	N
OSE/DPV TL	TL	Neha Gada	N
PMHS/Regulatory	Supervisor	Rosemary Addy	N
Bioresearch Monitoring (OSI) Good Clinical Practice Assessment Branch	Reviewer	Roy Blay	Y
	SPVR	Janice Pohlman	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Danielle Pearson	N
	TL:	Peter Diak	N

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505 b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
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<ul style="list-style-type: none"> ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <p>Listed drug - Nonclinical: Study 8279849 – “A 28-Day Intranasal Toxicity and Toxicokinetic Study in Rats Evaluating SER120 Nasal Spray Compared to Commercial Desmopressin Nasal Spray Formulation with a 4-Week Recovery Phase”</p> <p>Listed drug - Clinical Pharmacology: Scientific justification that the information in Section 12.3 regarding excretion is regarded as an intrinsic property of the drug molecule, desmopressin, without regard to dosage, formulation and administration route and therefore, a comparative BA study is not necessary.</p> <p>Published Literature: Scientific justification that the literature is scientifically sound and relevant to the proposed drug and the data involved doses that are significantly higher than the proposed doses.</p>
<ul style="list-style-type: none"> ● Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> ● Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> No comments
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input checked="" type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO

BIostatistics Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> <ul style="list-style-type: none"> • Is the product an NME? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<u>Environmental Assessment</u> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility Inspection</u> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Hylton V. Joffe, Director, DBRUP	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): July 20, 2016	
21st Century Review Milestones (see attached) (listing review milestones in this document is	

optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTION ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRA completed: September 2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NENITA I CRISOSTOMO
03/01/2017

505(b)(2) ASSESSMENT

Application Information		
NDA # 201656	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Noctiva Established/Proper Name: desmopressin Dosage Form: nasal spray Strengths: 0.75 mcg or 1.5 mcg desmopressin in each spray		
Applicant: Serenity Pharmaceuticals, LLC		
Date of Receipt: February 4, 2016		
PDUFA Goal Date: December 4, 2016		Action Goal Date (if different): March 3, 2017, 3-month extension
RPM: Neita Crisostomo		
Proposed Indication(s): Treatment of nocturia in adults who wake up 2 or more times per night to void		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 17922 DDAVP	5.0 Warnings and Precautions 7.0 Drug Interactions 10.0 Overdosage 12.0 Clinical Pharmacology 13.0 Nonclinical Toxicology
Published literature	8.0 Use in Specific Populations 12.0 Clinical Pharmacology

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature¹. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

- **Listed drug - Nonclinical:** Study 8279849 – “A 28-Day Intranasal Toxicity and Toxicokinetic Study in Rats Evaluating SER120 Nasal Spray Compared to Commercial Desmopressin Nasal Spray Formulation with a 4-Week Recovery Phase”
- **Listed drug - Clinical Pharmacology:** Scientific justification that the information in Section 12.3 regarding excretion is regarded as an intrinsic property of the drug molecule, desmopressin, without regard to dosage, formulation and administration route and therefore, a comparative BA study is not necessary.
- **Published Literature:** Scientific justification that the literature is scientifically sound and relevant to the proposed drug and the data involved doses that are significantly higher than the proposed doses.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA’s finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES NO

If "NO," proceed to question #5.

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO," proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

¹For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s). Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies). A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s). For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product.

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
DDAVP metered nasal spray, 0.01 mg / 0.1 mL	17922	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES NO

If “YES”, please list which drug(s) and answer question d) i. below.

If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing:

DDAVP (desmopressin acetate), 0.01 mg/spray (needs refrigeration)

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

This application provides for a new indication (adult nocturia) and lower strength (0.75 and 1.5 µg per 100 µL of Noctiva, as compared to 10 µg per 100 µL of DDAVP).

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"
If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.
If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
N/A YES NO

If this application relies only on non product-specific published literature, answer "N/A"
If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “**NO**” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

- **NDA 018938 DDAVP (desmopressin acetate), injection, 0.004 mg/ml**
- **NDA 017922 DDAVP (desmopressin acetate) nasal solution, 0.01 %**
- **NDA 017922 DDAVP (desmopressin acetate), 0.01 mg/spray, nasal, needs no refrigeration**
- **NDA 21333 Minirin (desmopressin acetate) metered nasal spray, 0.01 mg/spray**
- **NDA 20355 Stimate (desmopressin acetate) metered nasal spray, 0.15 mg/spray**
- **NDA 019955 DDAVP (desmopressin acetate) tablets, 0.1 mg**
- **NDA 019955 DDAVP (desmopressin acetate) tablets, 0.2 mg**
- **17 approved generics are listed in the Orange Book**

PATENT CERTIFICATION/STATEMENTS
--

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If “NO”, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

- 15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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/s/

NENITA I CRISOSTOMO
03/01/2017

REVIEW OF HUMAN FACTORS VALIDATION STUDY

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

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

Date of This Review: February 28, 2017

Requesting Office or Division: Office of Bone, Reproductive, and Urologic Products

Application Type and Number: NDA 201656

Product Name and Strength: Noctiva (desmopressin acetate) Nasal Spray
0.83 mcg/spray, 1.66 mcg/spray

Product Type: Combination Product

Rx or OTC: Rx

Applicant/Sponsor Name: Serenity Pharmaceuticals, LLC

Submission Date: September 26, 2016, January 13, 2017

OSE RCM #: 2016-2660

DMEPA Primary Reviewer: Denise Baugh, PharmD, BCPS

DMEPA Team Leader: Lolita White, PharmD

Associate Director for Human Factors: QuynhNhu Nguyen, M.S.

REASON FOR REVIEW

Serenity Pharmaceuticals submitted a Human Factors validation study (Study 1) on September 26, 2016 and Human Factors validation (Study 2) on January 13, 2017 for Noctiva (desmopressin) nasal spray, NDA 201656.

The Division of Bone, Reproductive, and Urologic Products (DBRUP) requested DMEPA review the results of the human factors -validation studies, Instructions for Use (IFU), and the container label and carton labeling^a as part of the evaluation of the 505(b)(2) submission for Noctiva.

1.1 PRODUCT INFORMATION

The proposed Noctiva nasal spray combination product is a multi-dose, preservative-free nasal spray which delivers 0.8^{(b)(4)} mcg^b/spray^c or 1.66 mcg^d/spray of demopressin acetate for the treatment of adult nocturia.

The recommended starting dose is 0.83 mcg or 1.66 mcg delivered as a single spray in either the left or right nostril 30 minutes before going to bed. In patients > 65 years of age, the starting dose is 0.83 mcg and, if needed, may be increased to 1.66 mcg after 2 to 4 weeks based on patient efficacy and serum sodium level. The setting of use is in the home and the patient self-administers the medication.

The reference listed drug DDAVP nasal spray, 0.1 mg/mL (NDA 017922) was approved February 21, 1978 for the treatment of central diabetes insipidus and for the management of polyuria and polydipsia following head trauma or surgery in the pituitary region.

1.2 REGULATORY HISTORY

- On February 4, 2016, this NDA was submitted without a use risk analysis as requested at the August 15, 2015 Guidance Meeting.
- On March 16, 2016, an information request (IR) was sent to the sponsor requesting this information.
- On April 5, 2016, during a teleconference held with the Sponsor, Serenity was asked to complete a use risk analysis and, if no new risks were identified, submit their justification to forego a human factors validation study.
- On April 29, 2016, a risk analysis was submitted by Serenity but we found the analysis lacking critical information to review.
- On September 22, 2016, an IR was sent to notify the Sponsor that their risk analysis did not provide adequate data to justify why a HF validation study was not needed.

^a The revised container label and carton labeling submitted January 13, 2017 is reviewed separately.

^b 0.83 mcg desmopressin acetate = 0.75 mcg desmopressin

^c One spray = 0.1 mL

^d 1.66 mcg demopressin acetate = 1.5 mcg desmopressin

- On September 26, 2016, the Sponsor submitted the results of their HF validation study 1. The human factors validation protocol used to perform this study was not submitted to the Agency for review prior to the initiation of the HF validation study.
- On October 28, 2016, we communicated our review conclusions and recommendations to the Applicant via e-mail and, per the Applicant’s request, we conducted a teleconference November 1, 2016 to clarify the rationale for the Agency’s decision (see Appendix F).
- On January 13, 2017, the second validation study was submitted to the NDA.

MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other – Response to Information Request	F
Labels and Labeling – Instructions for Use (IFU)	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

1.3 HUMAN FACTORS VALIDATION STUDY 1

A human factors (HF) validation study of Noctiva nasal spray was conducted with 16 participants of varying levels of experience with nasal sprays (ranging from naïve to experienced). To mimic real life , the HF validation study was conducted with untrained participants representative of the disease state population. In the first trial, participants were presented with a packaged product along with the product insert and Instructions for Use. In the second and third trials, the same participants were presented with the same device to simulate repeated use of the product. In the fourth trial, the same participants were issued a new product and told to assume it had been 30 days and they have just picked up their refill of a new nasal spray device. There were one hundred and thirty-three (n=133) use errors including three close calls and one operational difficulty described in the narrative of the

summary of results from the HF validation study 1 . Thirty-five of the one hundred and thirty-three use errors were related to improper priming and failure to hold the device or position the head correctly during administration of the nasal spray (Tasks 1C/1D, 2C, 2D) and we provide recommendations to address those critical failures in Appendix F.

Our review of the results of the human factors validation study 1 identified areas of the IFU that require revisions to improve clarity and promote the safe and efficient use of the Noctiva nasal spray to decrease the risk of an underdose or an incomplete dose. We find that the IFU lacks clarity surrounding the critical use tasks of priming upon initial use, not priming upon repeated use and the correct positioning of the head and the device during dose administration. As a result modifications were made to mitigate these failures. Given that these modifications affect the critical use tasks for this product, we recommend that a focused HF validation study surrounding these failures should be completed to confirm that the changes have adequately addressed the use errors and that new errors have not been introduced. Based upon our discussion during the teleconference on November 1, 2016, Serenity agreed to revise the IFU and perform a human factors validation study in support of those revisions prior to the approval of this product. We provided recommendations to the IFU and the HF validation protocol to improve outcomes. The Sponsor agreed to the recommendations, we reviewed the revised IFU and the revised protocol prior to initiation of validation study 2.

3.2 HUMAN FACTORS VALIDATION STUDY 2

A human factors (HF) revalidation study of Noctiva nasal spray was conducted with 32 participants of varying levels of experience with nasal sprays (ranging from naïve to experienced users) and no training was provided to any of the participants. The HF validation study 2 was performed over three trials. We find the methodology acceptable. We provide a summary of use steps, failures, close calls and operational difficulties for these three trials in Appendix C.

Based on previous recommendations and comment, the focus of HF validation study 2 is to test the following critical task failures from HF validation study 1 which were:

1. Prime prior to initial use – safety and efficacy may be compromised if the user does not press the nasal spray pump 5 times prior to its first use;
2. Do not prime with daily, repeated use – priming repeatedly is not needed and will likely result in emptying the contents of the container prematurely; and
3. Tilt head back slightly and keep bottle upright during administration – failure to position the head and the bottle correctly may lead to reduced delivery of the product and reduced effectiveness.

Additionally, based on recommendations from Chemistry, Manufacturing, and Controls (CMC), the Agency determined that the following task was required to use this device safely and effectively. As such, we added this step as a critical task:

4. Re-prime if product has not been used in 3 or more days – safety and efficacy may be compromised if the user does not press the nasal spray pump 2 times after non-use for 3 days or more

We note as presented in Section 8.2.9.1 (Use Errors), there were 173 use errors, 7 close calls, and 4 operational difficulties (see Appendix C). Of the 173 use errors, 50 failures involve critical tasks which are the focus of our review. We describe those failures, associated subjective feedback and our evaluation of the mitigation below in Table 2.

Table 2. Summary of failures, subjective feedback, and mitigation	
A. Failure to Prime	
Participants’ subjective feedback	What mitigation strategies have been done or will be recommended?
Saw only one side of the IFU(n = 1) – participants did not always access all sections of the IFU due to the layout of the “package insert” (PI). Specifically, the layout of the PI was such that the IFU was on 2 different sides of the paper. Therefore, depending upon the way in which the user unfolded the IFU, s/he may have only accessed one side therefore limiting their reading of all the instructions. Post-study participants suggested including the instructions on one side to improve access to all of the instructions.	The applicant proposes to improve users’ accessibility to all of the instructions by ensuring the instructions are on the same side of the page. If this is not an option, provide a ‘cue’ for the user to indicate that there is additional information on subsequent pages. We find either strategy acceptable.
Didn’t see the priming instructions – see explanation above (n = 1)	The applicant proposes to improve users’ accessibility to all of the instructions by ensuring the instructions are on the same side of the page. If this is not an option, provide a ‘cue’ for the user to indicate that there is additional information on subsequent pages. We find either strategy acceptable.
Didn’t notice instructions on the carton/label (N=3)	The Applicant proposes including a boxed statement on the carton labeling AND on the top flap which reads: “IMPORTANT: Read enclosed instructions before using for dosing, priming, and re-priming information”. DMEPA agrees with this proposal as it is sufficiently prominent and it directs the user to more detailed instructions to use the product safely and effectively. The applicant does not propose changes to the container label because there is insufficient space to include additional statements. We find this proposal acceptable.
Thought priming meant to ‘shake’ the bottle (n = 1)	The following statement is in the IFU and appears with the first step for priming: “Do not shake the bottle”.

	<p>DMEPA agrees with the location of this statement and its prominence.</p> <p>Additionally, we recommend revising the heading (which appears prior to Figure B) from “Before your First Use” to read “PRIMING INSTRUCTIONS”. The statement “Donot shake the bottle” should then be followed by the statement “Follow the next 5 steps to prepare your Noctiva for priming”. Precede each statement with a step number. For example, the statement “Pull the cap off and set aside” should be preceded by the statement ‘Step 1’.</p>
Didn’t completely actuate the device (n = 2)	The Applicant did not propose any changes to the IFU. We propose to revise the IFU language from “Pump the nasal applicator 5 times by squeezing your fingers and thumb together (see Figure E)” to read “Completely press the nasal applicator 5 times by squeezing your . . .”
Miscounted the number of sprays (n = 1)	No changes to the IFU; number of sprays sufficiently prominent
Primed with cap on to avoid making a mess (n = 1)	No changes to the IFU; wrong technique intentional
B. Tilts head back slightly and keeps bottle upright	
Bottle was almost parallel to the floor on all 3 trials for this 1 experienced participant; did not read the IFU (n = 1)	No changes to the IFU were proposed by the Applicant. It appears that the majority of the participants positioned their head/bottle correctly and therefore we do not have any additional recommendations at this time.
C. User does not prime prior to each use	
Assumed priming was required prior to each use (n = 3)	The Applicant did not propose changes to the IFU. Our assessment concluded that there is nothing in the IFU that suggests priming is required with repeated use. Additionally, Section 17 (Patient Counseling) of the PI reinforces when to prime (initially and if not used more than 3 days) and does not suggest otherwise. Therefore, we do not have any additional recommendations at this time.
Participant did not prime in Trial 1 so decided to do so with the next administration time (n = 1)	The participant’s feedback suggests that this error was related to a performance deficit and therefore cannot be addressed in labeling. No changes to the IFU were recommended.
A. Re-Prime after non-use for over 3 days	
Did not read re-priming section; didn’t notice it, didn’t turn the page (n = 3)	<p>The applicant proposes to improve users’ accessibility to all of the instructions by ensuring the instructions are on the same side of the page. If this is not an option, provide a ‘cue’ for the user to indicate that there is additional information on subsequent pages.</p> <p>We find either strategy acceptable.</p>
Sprayed enough to see mist to avoid ‘overdoing it’ (n = 1)	The Applicant did not propose changes to the IFU. We propose to revise the statement “(b) (4)

	(b) (4) to read “Completely pump the nasal applicator 2 times” to minimize the risk of under-dosing when re-priming.
Believed that the steps to prime and re-prime were the same (n = 2)	<p>The Applicant proposes that all of the instructions (in the IFU) are on the same side. If restricting the instructions to one page is not an option, they will provide a ‘cue’ for the user to indicate that there is additional information on subsequent pages.</p> <p>We find this strategy acceptable. Additionally, we propose increasing the prominence of the information in the box with the heading “Important Information”. Although this information is currently boxed, the statements within the box are presented in similar font style and size other statements in the IFU. This presentation does not emphasize the importance of the boxed information and sufficiently elevate its prominence.</p>
Didn’t see instructions on carton labeling (n = 1)	<p>The Applicant proposes including a boxed statement on the carton labeling AND on the top flap which reads: “IMPORTANT: Read enclosed instructions before using for dosing, priming, and re-priming information”.</p> <p>We find this proposal acceptable as it is sufficiently prominent and it directs the user to more detailed instructions to use the product safely and effectively.</p> <p>The applicant does not propose changes to the container label because there is insufficient space to include additional statements. We find this acceptable.</p>
Re-priming not needed with other nasal sprays (n = 2)	The participants’ feedback suggests that this wrong technique error was intentional and based on confirmation bias. The Applicant did not propose any changes to the IFU or labeling and we do not recommend any changes.
Forgot to re-prime (n = 2)	The participants’ feedback suggests that this wrong technique error is related to a performance deficit. The Applicant did not propose any changes to the IFU or labeling and we do not recommend any changes.
A. Administration Error	
Doubled the dose to catch up (n = 1)	The Applicant does not propose changes to the IFU. We recommend adding instructions to the PI for what to do if a dose is missed and also propose the following statement to the re-priming section of the IFU: “If a dose is missed, do not double the dose at the next use”. This statement should follow the statement: “If you do not use Noctiva for more than 3 days, you will need to re-prime . . .”
Gave multiple doses into nostril with cap on (n = 1)	The Applicant does not propose any changes. There is a statement along with a graphic which clearly states to remove the cap. We do not recommend changes to the IFU since this step is clearly stated.

Instructions for Use (IFU)

DMEPA noted that several different versions of the IFU were included in the HF study submitted January 13, 2017 (referred to as 'Study 2'). In response to DMEPA's information request sent January 27, 2017, Serenity Pharmaceuticals stated that the IFU on 'page 126' is the version used in the HF revalidation study and they plan to revise this version to a single page to market post-approval.

During the HF validation study 2, participants specifically stated they did not know or did not see that priming is a requirement for the use of this product. As a result, the Sponsor changed from a multiple page IFU to a single page IFU. The single page IFU was folded during the study and therefore the priming and re-priming instructions were not accessed at the same time and some participants were not aware of an additional page of instructions. We note that based on this subjective feedback, the IFU was changed and submitted to the Agency to be marketed as a single page IFU, not folded. We reviewed the proposed IFU and identified an area that requires modification to reduce the risk of confusion and to decrease the risk of medication errors which may result in incomplete or a reduced dose. The failures, subjective feedback from participants, assessment by Sponsor and recommendations to improve the IFU are provided in Section 5.2 Table 1..

CONCLUSION & RECOMMENDATIONS

The human factors validation study 2 showed that the Instructions for Use require additional improvements. Our review identified areas of the IFU that require further revision to minimize the risk for medication error and to provide further clarity. However, we acknowledge that there is no other desmopressin nasal spray available on the market for the treatment of nocturia and the introduction of this new dosage form may provide a public health benefit for this patient population. As such, we will not require additional human factors to support the changes recommended for the IFU. Additionally, we will monitor for medication errors post-approval.

1.4 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information (PI)

1. The PI lacks instructions to inform the user of actions that they should take in the event of a missed dose. We are concerned that an overdose error may occur based on a use error from one participant in the HF validation study 2, where the patient administered two doses in one day to make up for doses missed. We recommend adding instructions to the PI regarding what to do if a dose is missed.

1.5 RECOMMENDATIONS FOR SERENITY PHARMACEUTICALS

We recommend implementation of the changes below prior to approval of this supplement. These modifications will not require additional human factors testing.:

A. Instructions for Use (IFU)

1. You propose that the IFU be limited to one page to minimize the risk that users may overlook or do not read important steps to use your product safely and effectively. We agree with your proposal. Alternatively, if it is necessary to use more than one page, we agree to include a 'cue' to the reader to indicate that there is additional information on subsequent pages.
2. We recognize that the information about priming and repriming are critical, and three of the study participants in the HF validation study 2 did not notice these instructions. We notice that as currently presented, the font weight and size of the statements for priming and re-priming are identical to that for non-critical information. We recommend you improve the prominence of these statements further by bolding them or by other means.
3. Please address the following regarding the "Before your first use section" of the IFU:
 - a. As proposed, the headings used do not accurately reflect the contents of the sections. In particular, the heading "Before your first use" does not sufficiently convey that this section of the IFU also includes instructions for preparing the device for priming as well as for the priming step. Your study results indicated that three study participants in the HF validation study 2 did not notice the priming instructions and two study participants in the HF validation study 2 did not perform the priming steps correctly. We suggest you consider revising the headings to better reflect the section contents. For example, revise the heading (which appears in the box with Figure B) "Before your First Use" to read "Before your First Use, following these instructions to prime the product".
 - b. In addition, we ask that you modify this section to include a step number prior to each statement. For example, the statement "Pull the cap off and set aside" should be preceded by the statement 'Step 1'.
4. The specific statement on how to prime the nasal spray prior to use is unclear. The inability to properly prime the device may lead to the risk of under-dosing. We recommend you consider revising the language in the IFU from "Pump the nasal applicator 5 times by squeezing your fingers and thumb together (see

Figure E)” to read “Completely press the nasal applicator 5 times by squeezing your . . .”

5. Please address the following regarding the instructions contained in the re-priming section of the IFU:
 - a. Based on the study results, we find that these instructions are not clear and may lead to wrong technique errors resulting in under doses and reduced efficacy. We recommend that you consider changing the language from “(b) (4)” to read “Completely pump the nasal applicator 2 times” to minimize the risk of under-dosing when re-priming.
 - ii. The re-priming section lacks instructions to inform the user of actions to take in the event of a missed dose. One participant in the HF validation study 2 administered two doses in one day to make up for a missed dose. Given the criteria for re-priming (non-use for over 3 days), we are concerned that users may decide to give multiple doses. To mitigate such errors, we recommend the inclusion of a statement in the re-priming section of the IFU which instructs the user on what actions to take if a dose is missed. Consider adding the following statement or something similar: “If a dose is missed, do not double the dose at the next use”. This statement should follow the statement: “If you do not use Noctiva for more than 3 days, you will need to re-prime . . .”

B. Carton labeling

1. Based on participant feedback, the instructions on the carton labeling are not prominently placed and may lead to medication dosing error. We agree with your proposed language for inclusion on the carton labeling and on the top flap to instruct the user to access the IFU. For more clarity, consider revising the statement “IMPORTANT: Read enclosed instructions before using for dosing, priming, and re-priming information” to read “IMPORTANT: Read enclosed instructions for dosing, priming, and re-priming information” or “IMPORTANT: Before using read enclosed instructions for dosing, priming, and re-priming information”.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Noctiva that Serenity Pharmaceuticals submitted on May 6, 2016.

Table 2. Relevant Product Information for Noctiva	
Initial Approval Date	N/A
Active Ingredient	Desmopressin acetate
Indication	Treatment of nocturia
Route of Administration	intranasal
Dosage Form	Nasal spray
Strength	0.83 mcg (0.1 mL) per spray and 1.66 mcg (0.1 mL) per spray
Dose and Frequency	The recommended starting dose is 0.83 mcg or 1.66 mcg in either the left or right nostril 30 minutes before going to bed. In patients \geq 65 years of age, the starting dose is 0.83 mcg in either the left or right nostril each night 30 minutes before going to bed. The dose may be increased to 1.66 mcg after 2 to 4 weeks if needed based on patient efficacy and serum sodium level ^e .
How Supplied	Available in a 3.5 mL amber glass bottle fitted with a nasal actuator, a cartridge pump, and a dip tube
Storage	<u>Pharmacist</u> : prior to dispensing, store in a refrigerator, 2°C to 8°C (36°F to 46°F) <u>Patient</u> : store at room temperature 20°C to 25°C (68°F to 77°F). Discard 60 days after opening.

^e At the time of this review, the Agency and Applicant were in labeling negotiations, thus the dosage and administration section is subject to change.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On January 30, 2017, we searched the L: drive (also known as the 'shared drive') and AIMS using the term, "Noctiva" to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified no previous reviews relevant to this review.

APPENDIX C. HUMAN FACTORS VALIDATION STUDY 2

C.1 Study Design- Study 2

Use Scenario	Critical Tasks
<p>Scenario 1 (Task 1): Initial Use</p> <p>“Your doctor has prescribed you a nasal spray. Today is Day 1 of your treatment. Your doctor has prescribed one spray in either the left or right nostril each night approximately 30 minutes before going to bed. Please administer the nasal spray.”</p>	<p>Read the Information for Use</p> <p>Remove the cap</p> <p>Remove the clip</p> <p>Prime the device</p> <p>Blow nose</p> <p>Keep applicator upright during administration</p> <p>Tilt head back slightly, but does not tilt back too far</p> <p>Insert the nasal applicator into the nostril</p> <p>Pinch the other nostril closed</p> <p>Pull down on the base of nasal applicator (to administer the dose)</p> <p>Wipe the tip of the nasal applicator</p> <p>Re-cap the device</p>
<p>Scenario 2 (Task 2): Repeated Use</p> <p>“Today is Day 2 of your treatment. Please administer the nasal spray (one spray in either the left or right nostril each night approximately 30 minutes before going to bed).”</p>	<p>Read the Information for Use</p> <p>Remove the cap</p> <p>Blow nose</p> <p>Keep applicator upright during administration</p> <p>Tilt head back slightly, but does not tilt back too far</p> <p>Insert the nasal applicator into the nostril</p> <p>Pinch the other nostril closed</p>
Use Scenario	Critical Tasks
	<p>Pull down on the base of nasal applicator (to administer the dose)</p> <p>Wipe the tip of the nasal applicator</p> <p>Re-cap the device</p>
<p>Scenario 3: Treatment after 3 days of non-use</p> <p>You went on vacation, and accidentally left your nasal spray at home. You have returned, and it is now four nights since you last used your nasal spray. Please administer the nasal spray as per your doctor’s prescription (i.e., one spray in either the left or right nostril each night approximately 30 minutes before going to bed).</p>	<p>Read the Information for Use</p> <p>Remove the cap</p> <p>Re-prime the device</p> <p>Blow nose</p> <p>Keep applicator upright during administration</p> <p>Tilt head back slightly, but does not tilt back too far</p> <p>Insert the nasal applicator into the nostril</p> <p>Pinch the other nostril closed</p> <p>Pull down on the base of nasal applicator (to administer the dose)</p> <p>Wipe the tip of the nasal applicator</p> <p>Re-cap the device</p>

Table 11: Critical Tasks and Success Criteria

Task	Successful performance
Read the Information for Use	User reads the Information for Use
Remove the cap	User removes the cap
Remove the clip	User removes the clip
Prime the device	User primes the device
Blow nose	User Blows nose
Keep applicator upright during administration	User keeps applicator upright during administration
Tilt head back slightly, but does not tilt back too far	User tilts back slightly, but does not tilt back too far.
Insert the nasal applicator into the nostril	User inserts the nasal applicator into one of their nostrils
Pinch the other nostril closed	User pinches the other nostril closed
Pull down on the base of nasal applicator (to administer the dose)	User pulls down on the base of the nasal applicator and the dose is administered.
Wipe the tip of the nasal applicator	User wipes the tip of the nasal applicator
Re-cap the device	User re-caps the device

C.2 Results

Task	Successful performance	# of Use Errors		# of Close Calls		# of Operational Difficulties	
		E	I	E	I	E	I
Read the Information for Use	User reads the Information for Use	7	4	0	0	---	---
Remove the cap	User removes the cap	1	0	0	2	0	2
Remove the clip	User removes the clip	0	0	2	3	1	1
Prime the device for initial use	User primes the device	9	8	0	0	0	0
No priming of device on repeat use	User does not prime the device	2	2	0	0	0	0
Re-prime the device after more than 3 days of non-use	User re-primed the device	14	12	0	0	0	0
Blow nose	User Blows nose	34	29	0	0	0	0
Keep applicator upright during administration	User keeps applicator upright during administration	3	0	0	0	0	0
Tilt head back slightly, but does not tilt back too far	User tilts back slightly, but does not tilt back too far.	3	0	0	0	0	0
Insert the nasal applicator into the nostril	User inserts the nasal applicator into one of their nostrils	0	0	0	0	0	0
Pinch the other nostril closed	User pinched the other nostril closed	27	26	0	0	0	0

Task	Successful performance	# of Use Errors		# of Close Calls		# of Operational Difficulties	
		E	I	E	I	E	I
Pull down on the base of nasal applicator (to administer the dose)	User pulls down on the base of the nasal applicator and the dose is administered.	8	7	0	0	0	0
Wipe the tip of the nasal applicator	User wipes the tip of the nasal applicator	32	30	0	0	0	0
Re-cap the device	User re-caps the device	13	19	0	0	0	0

USE ERRORS

Remove the cap

One (1) of sixteen (16) Experienced Participants (P^{(b)(6)}_EXP) *failed to remove cap*; left cap on during administration of nasal spray on Trial 3 only

Prime the device (prior to initial use)

- Two (2) of sixteen (16) Experienced Participants (P^{(b)(6)}_EXP) and two (2) of sixteen (16) Inexperienced Participants (P^{(b)(6)}_INX) failed to prime prior to initial use at all (under-delivery).
- One (1) of sixteen (16) Experienced Participants (P^{(b)(6)}_EXP) and one (1) of sixteen (16) Inexperienced Participants (P^{(b)(6)}_INX) primed into the air, but fewer than 5 times (possible under-delivery).
- Two (2) of sixteen (16) Experienced Participants (P^{(b)(6)}_EXP) and two (2) Inexperienced Participants (P^{(b)(6)}_INX) “primed into the nose”. If participants did not know to prime, some continued to actuate the device until they “felt” the spray which may lead to under or over delivery.
- P^{(b)(6)}_INX sprayed five times into the air, but *with the cap on*.
- P^{(b)(6)}_EXP *didn't complete full strokes of the applicator* when priming.
- P^{(b)(6)}_INX pumped the applicator six times (rather than five times) into the air.

Re-prime the device (after more than three days of non-use)

- Four (4) of sixteen (16) Experienced Participants (P (b) (6) _EXP) and three (3) of sixteen (16) Inexperienced Participants (P (b) (6) _INX) *did not re-prime correctly as per the Instructions for Use (i.e., two pumps)*. Namely, all primed by pumping the applicator five (5) times, as they have on the initial use.
- Ten (10) of sixteen (16) Experienced Participants (P (b) (6) _EXP) and nine (9) of sixteen (16) Inexperienced Participants (P (b) (6) _INX) *failed to re-prime at all (under-delivery)*.

Blow nose

- Ten (10) of sixteen (16) Experienced Participants (P (b) (6) _EXP) and eight (8) of sixteen (16) Inexperienced Participants (P (b) (6) _INX) failed to blow nose on all trials.

Keep applicator upright during administration

- One (1) of sixteen (16) Experienced Participants (P (b) (6) _EXP) tilted head back too far (i.e., the applicator was almost parallel to the floor) on all Trials.

Tilt head back slightly, but does not tilt back too far

- One (1) of sixteen (16) Experienced Participants (P (b) (6) _EXP) tilted head back too far (i.e., the applicator was almost parallel to the floor) on all Trials.

Pinch the other nostril closed

- Nine (9) Experienced Participants (P (b) (6) _EXP) and eight (8) Inexperienced Participants (P (b) (6) _INX) failed to pinch nostril not being dosed on all trials.
- P4_INX *failed to pinch nose not being dosed on Trials 1 and 2*, but did so correctly on Trial 3.

Pull down on the base of nasal applicator (to administer the dose)

The proper dose is one spray into one nostril before bedtime. The following use errors were observed.

Wipe the tip of the nasal applicator

- Ten (10) of the Experienced participants (P (b) (6) _EXP) and nine (9) of the Inexperienced participants (P (b) (6) _INX) did not wipe the tip of the nasal applicator on any of the trials.
- One (1) additional Experienced participant (P (b) (6) _EXP) and 2 Inexperienced participants (P (b) (6) _INX) failed to wipe the tip on at least one of the trials.

Recap the device

- Three (3) of sixteen (16) Experienced Participants (P (b) (6) _EXP) and six (6) of sixteen (16) Inexperienced Participants (P (b) (6) _INX) failed to re-cap the bottle on all trials.

8.2.9.2 Close Calls

Remove the cap

- Two (2) of sixteen (16) Inexperienced Participants (P (b) (6) _INX) initially failed to remove the cap.
- On Trial 2, P (b) (6) _INX attempted to use the device (i.e., actuated the device) with the cap on. This participant realized the error and recovered independently.
- On Trial 3, P (b) (6) _INX almost actuated the device with the cap on, and realized the need to remove the cap independently.

Remove the clip

- Two (2) of sixteen (16) Experienced Participants (P (b) (6) _EXP) and three of (16) Inexperienced Participants (P (b) (6) _INX) initially failed to remove the clip. Specifically,
- P (b) (6) _EXP realized the error and recovered independently. This participant did not read the Instructions for Use at any point during the session.

- F (b)(6)_INX realized the error as it was clear that the device was not working properly, consulted the Instructions for Use, and removed the clip independently.

8.2.9.3 Operational Difficulties

Read the Information for Use

- Despite the fact that the Package Insert was folded to display the Instructions for Use first, some participants had a difficult time locating the Instructions for Use within the Package Insert. See the discussion of root cause in [Section 8.2.3](#) for more detail and [Appendix B, Section 3.1.1](#). This difficulty stemmed from (1) the layout of the Package Insert (i.e., the Instructions for Use was on two sides of the page), and (2) the fact that the font style, size, and weight were similar to that of the Patient/Prescribing Information (i.e., the Information for Use got “buried” in the Package Insert).

Remove the cap

- Two (2) of sixteen (16) Inexperienced Participants (F (b)(6)_INX) had difficulty removing the cap. These participants kept trying to unscrew the cap rather than pulling to remove.

Remove the clip

- One (1) of sixteen (16) Experienced Participants (P (b)(6)_EXP) and one (1) Inexperienced Participant (P (b)(6)_INX) had difficulty removing the clip.

HUMAN FACTORS VALIDATION STUDY 2: FEEDBACK FROM STUDY PARTICIPANTS

Read the Information for Use (IFU)

For the purposes of this report, “locating” the IFU is defined as the participant finding the Instructions for Use within the Package Insert; “accessing” a particular panel or section of the IFU is defined as the participant opening the Package Insert such that a particular panel or section was revealed; and “reading” the IFU is defined the participant reading portions of the Instructions for Use (either aloud, or as inferred by their behavior).

As a result of the structured interview and observation the following were found to be at the root cause of use errors encountered with the IFU:

- Some Experienced Participants indicated that they would not likely read the instructions since they had used a nasal spray in the past.
- The Package Insert was folded such that the Instructions for Use was on the top side of the Package Insert (i.e., the first thing the user should encounter). However, if a participant unfolded the Package Insert in a particular way, s/he may first encounter the patient/prescribing information.
- Some participants had a difficult time locating the Instructions for Use since it was printed on the same sheet as the Package Insert despite the fact that the Package Insert was folded to display the Instructions for Use first.

Prime the Nasal Applicator by Pumping into the Air 5 times prior to initial use

As a result of the structured interview and observation the following were found to be at the root cause of use errors encountered with correct priming:

- Participants did not refer to IFU where initial priming was described (6 Experienced and 2 Inexperienced)
- Other participants either primed too many times, fewer than the required number, or primed into their nose. The root cause of these use errors can all be traced back to the IFU: it was not read, miscounting, and or did not access the correct panel in the IFU that described correct priming.

Re-priming after a period of non-use:

As a result of the structured interview and observation the following were found to be at the root cause of use errors encountered with re-priming:

- Participants had not read the IFU
- Participants assumed that re-priming was the same as initial priming
- Participants assumed it was not necessary, as they also had not re-primed other nasal sprays.

Blow nose

As a result of the structured interview and observation the following were found to be at the root cause of use errors encountered about blowing the nose:

- Participants had not read the IFU.
- Participants felt that their nose was already clear.
- Participant had never done this with other nasal sprays.

Keep applicator upright during administration. Tilt head back slightly, but does not tilt back too far

As a result of the structured interview and observation the following was found to be at the root cause of use errors encountered with keeping the applicator upright during administration and tilting the head back slightly:

The participant indicated they had held their head and the device at the proper angle to prevent the spray from dripping. It should be noted that the participant had NOT read the IFU.

Pinch the other nostril closed

As a result of the structured interview and observation the following were found to be at the root cause of use errors encountered:

- Participants did not read the IFU
- Participant said they would only do this if they were stuffed up
- Experienced participants indicated that they had not done this with other nasal sprays .

Pull down on the base of nasal applicator (to administer the dose)

As a result of the structured interview and observation the following were found to be at the root cause of use errors encountered:

- The participants sprayed a varying dose, either more or less than the one spray. The root cause of the variation was due to:
 - not reading the IFU
 - not priming correctly and so did not feel any spray in their nose
 - that they administer a double dose to make up for missed dose.
 - that the actuator was not pushed all the way

Wipe the tip of the nasal applicator

As a result of the structured interview and observation the following were found to be at the root cause of use errors encountered:

- Participants did not read the IFU
- Participants felt it was for their use only, so need to wipe the nasal applicator.

Recap the device

As a result of the structured interview and observation the following were found to be at the root cause of use errors encountered:

- Participants had not read the IFU
- Participants felt they were going to use the device again, immediately. Hence, this could be considered an artifact of the testing situation.

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

APPENDIX F. INFORMATION REQUEST HF VALIDATION STUDY 2
F1. RESPONSE TO INFORMATION REQUEST SENT JANUARY 27, 2017

3. *We also refer to your Human Factors re-validation study report for NDA 201656 Noctiva (desmopressin acetate) nasal spray submitted January 13, 2017. Your submission includes several versions of your Instructions for Use (IFU) presented in two different formats. For example, the submission includes a single page IFU on page 126, a multiple page prior IFU on page 183, a revised IFU on page 186, and a multiple page recommended changes IFU on page 192. We are unclear regarding the version of IFU used during your validation study and what you intend to market with your combination product. We ask that you clarify the following for your Noctiva nasal spray product:*

- *State which version of the IFU was used in your validation study.*
- *State which version of the IFU you intend to market.*
- *To better inform our review of your human factors validation study results, inform us on what specific page of your submission we may locate these IFU's.*

The IFU on page 126 is the typed set version of the revised IFU starting on page 186 in [Serial 0051](#) submitted on January 13, 2017. The texts, pictures and sequence of information presentation are the same. This revised IFU was developed based on recommendations from the first human factor summative study ([SPC-SER120-HF-201601](#)) and in collaboration with DMEPA. The IFU on page 126 was used in the supplemental human factor summative study ([SPC-SER120-HF2-201602](#)) conducted in December 2016.

Serenity's intent is to take the version of the IFU on page 126 to market with the configuration that all 4 panels appear on the same side of the package insert.

The IFU starting on page 183 was the original version used in the initial human factor study and the IFU starting on page 192 contains a few minor revisions suggested by the vendor which conducted the supplemental human factor summative study.

The results of the supplemental summative study demonstrated that this revised IFU on page 126 when read was felt by participants to be clear and comprehensible, providing them with the necessary directions to properly use the device. Most subjects also indicated that the device was easy to use as intended. These results support the conclusion that the revised IFU is effective in enabling subjects to properly use the device. Therefore, based on the cumulative results of both Human Factors summative studies which have been conducted and the resulting optimization of the configuration and contents of the IFU, it can be concluded that the NOCTIVA™ (SER120) Nasal Spray combination product is safe and effective for the intended users, uses and use environments.

APPENDIX F. RECOMMENDATIONS COMMUNICATED TO SERENITY NOVEMBER 1, 2016

F2. RECOMMENDATIONS FOR SERENITY PHARMACEUTICALS, LLC (HF VALIDATION STUDY 1)

Our review of the results from your human factors validation study 1 showed multiple use related risk error. We are concerned with your study results which reports: failure to prime upon initial use, re-priming inappropriately upon repeated use, failure for the user to position their head correctly to receive a complete dose and the failure to hold the device in the correct position to administer a dose. These critical use tasks require further mitigation to increase clarity and promote the safe use of your product. We find these failures to indicate a need for mitigation and repeat validation. We recommend this to ensure that the proposed changes have effectively addressed the use errors identified in the HF study and that these changes have not introduced new errors. The validation study should be conducted prior to approval of your application and the results submitted to the Agency for review and comment. We have the following recommendations:

1. Your task within the Noctiva IFU instructing the user to prime only at first use is not prominently presented. We are concerned that the failure to prime the device before administering the first dose will increase the risk of an underdose. We recommend increasing the prominence of the priming step to decrease the risk of this error. We suggest you increase its prominence by adding numbers, bullet points or something similar to draw attention to this critical use task.
2. Your task within the Noctive IFU regarding do not reprime upon repeated use is not prominent. The user who inappropriately primes upon repeated use is at risk of running out of product and ultimately causing an underdose. We recommend increasing the prominence of the task by either bolding, color blocking or something similar to draw attention to this critical use task.
3. Your graphic depiction of the position of the user's head and the nasal spray device is not clear as presented in your IFU (see step 3 Figure H). The failure to correctly position the bottle or the user's head may lead to an incomplete dose and therefore this graphic should be revised for clarity.

APPENDIX G. LABELS AND LABELING - INSTRUCTIONS FOR USE (PAGE 126 OF SUBMISSION January 13, 2017)

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^f along with post-market medication error data, we reviewed the following Noctiva labels and labeling submitted by Serenity Pharmaceuticals on January 13, 2017.

- Instructions for Use

G.2 Label and Labeling Images (Instructions for Use)



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

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/s/

DENISE V BAUGH
02/28/2017

LOLITA G WHITE
02/28/2017

QUYNHNHU T NGUYEN
02/28/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum: February 13, 2017
Requesting Office or Division: Division of Bone, Reproductive, and Urologic Products
Application Type and Number: NDA 201656
Product Name and Strength: Noctiva (desmopressin acetate) Nasal Spray,
0.83 mcg/0.1 mL, 1.66 mcg/01 mL
Submission Date: February 9, 2017
Applicant/Sponsor Name: Serenity Pharmaceuticals, LLC
OSE RCM #: 2016-393-2
DMEPA Primary Reviewer: Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader: Lolita White, PharmD

1 PURPOSE OF MEMO

The Division of Bone, Reproductive, and Urologic Products (DBRUP) requested that we review the revised container label and carton labeling for Noctiva (see Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised container label and carton labeling for Noctiva is acceptable from a medication error perspective. We have no further recommendations at this time.

^a Baugh, D. Label and Labeling Review for NOCTIVA (NDA 201656). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 Feb 1, 5 p. OSE RCM No: 2016-393-1.

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/s/

DENISE V BAUGH
02/13/2017

LOLITA G WHITE
02/14/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum: February 1, 2017
Requesting Office or Division: Division of Bone, Reproductive, and Urologic Products
Application Type and Number: NDA 201656
Product Name and Strength: Noctiva (desmopressin acetate) Nasal Spray,
0.83 mcg/0.1 mL, 1.66 mcg/01 mL
Submission Date: January 13, 2017
Applicant/Sponsor Name: Serenity Pharmaceuticals, LLC
OSE RCM #: 2016-393-1
DMEPA Primary Reviewer: Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader: Lolita White, PharmD

1 PURPOSE OF MEMO

The Division of Bone, Reproductive, and Urologic Products (DBRUP) requested that we review the revised container label and carton labeling for Noctiva (see Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

We acknowledge the revisions made to the container label and carton labeling as recommended in our previous review. However, the differentiation between the strengths on the carton labeling and container label remains insufficient and is unacceptable from a medication error perspective. Specifically, the color ('aqua') used for the strength "1.66 mcg/0.1 mL" is similar to that used for the proprietary name, 'Noctiva'. As such, the color used for the strength overlaps with that which is used in the trade dress and dilutes the impact of the

^a Baugh, D. Label and Labeling Review for NOCTIVA (NDA 201656). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Nov 16. 13 p. OSE RCM No: 2016-393.

strength differentiation and may lead to error in strength selection. In addition, we note the established name (desmopressin acetate) as presented on the carton label and container labeling lacks prominence commensurate with the proprietary name (Noctiva). See Section 3 for our recommendations.

3 RECOMMENDATIONS FOR SERENITY PHARMACEUTICALS

We recommend the following be implemented prior to approval of this NDA:

A. Carton labeling and Container label

- a. There is a lack of differentiation between the two strengths on the container label and carton labeling. The strength statements for both strengths have (b) (4) presentations (b) (4) which may result in wrong strength errors. Revise the (b) (4) so that the strength appears (b) (4) does not overlap with (b) (4) the trade dress. Alternatively, you may consider (b) (4) other means to better differentiate between the strengths. We recommend this revision to improve upon the strength differentiation and to increase the prominence of the strength statement.
- b. The established name (desmopressin acetate) lacks prominence commensurate with the proprietary name (Noctiva). Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2). We recommend you revise the established name to be at least half the size of the proprietary name in accordance with 21 CFR 201.10(g)(2).

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/s/

DENISE V BAUGH
02/02/2017

LOLITA G WHITE
02/02/2017

MEMORANDUM

REVIEW OF REVISED HUMAN FACTORS VALIDATION STUDY PROTOCOL

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

Date of This Memorandum: December 14, 2016

Requesting Office or Division: Division of Bone, Reproductive, and Urologic Products

Application Type and Number: NDA 201656

Product Name and Strength: Noctiva (desmopressin acetate) nasal spray
0.83 mcg/spray, 1.66 mcg/spray

Product Type: Combination Product

Rx or OTC: Rx

Applicant/Sponsor Name: Serenity Pharmaceuticals, LLC

Submission Date: December 2, 2016

OSE RCM #: 2016-2660-1

DMEPA Primary Reviewer: Denise Baugh, PharmD, BCPS

DMEPA Team Leader: Lolita White, PharmD

DMEPA Associate Director for Human Factors QuynhNhu Nguyen, M.S.

1 PURPOSE OF MEMO

The Division of Bone, Reproductive, and Urologic Products requested that we review the revised Human Factors Validation Protocol for Noctiva (desmopressin acetate) nasal spray to determine if the methodology is acceptable. The revisions are in response to recommendations that we made during a previous human factors validation study protocol review.^a

^a Baugh D. Review of Human Factors Validation Study Protocol for Noctiva (NDA 201656). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Nov 22. . 24 p. OSE RCM No.: 2016-2660.

2 CONCLUSION

The revised Human Factors Validation Study Protocol for Noctiva (desmopressin acetate) nasal spray is acceptable. We have no further recommendations at this time.

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/s/

DENISE V BAUGH
12/14/2016

LOLITA G WHITE
12/14/2016

QUYNHNHU T NGUYEN
12/14/2016

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

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

Date of This Review: November 22, 2016
Requesting Office or Division: Office of Bone, Reproductive, and Urologic Products
Application Type and Number: NDA 201656
Product Name and Strength: Noctiva (desmopressin acetate) nasal spray
0.83 mcg/spray, 1.66 mcg/spray
Product Type: Combination Product
Rx or OTC: Rx
Applicant/Sponsor Name: Serenity Pharmaceuticals, LLC
Submission Date: November 7, 2016
OSE RCM #: 2016-2660
DMEPA Primary Reviewer: Denise Baugh, PharmD, BCPS
DMEPA Team Leader: Lolita White, PharmD
Associate Director for Human Factors: QuynhNhu Nguyen, MS

1 REASON FOR REVIEW

The Division of Bone, Reproductive, and Urologic Products (DBRUP) requested a review of the human factors (HF) validation study protocol, use related risk analysis (URRA) and Instructions for Use (IFU) as part of their evaluation of the 505(b)(2) submission for Noctiva (desmopressin acetate) nasal spray NDA 201656 submitted on November 7, 2016.

1.1 PRODUCT INFORMATION

Serenity Pharmaceuticals is developing a preservative-free desmopressin acetate nasal spray in a multi-dose container. The proposed indication is for the treatment of adult nocturia. The combination product interface consists of a nasal spray that delivers 0.83 mcg^a/spray^b or 1.66 mcg^c/spray of desmopressin acetate. The recommended starting dose is 1.66 mcg in either the left or right nostril 30 minutes before going to bed each night. In patients > 65 years of age, the starting dose is 0.8^(b)₍₄₎ mcg and this may be increased to 1.66 mcg after 2 to 4 weeks if needed. The nasal spray is intended to be self-administered in the home setting.

The reference listed drug is DDAVP nasal spray, 0.1 mg/mL, (NDA 017922 approved February 21, 1978) which is approved for the treatment of central diabetes insipidus and for the management of polyuria and polydipsia following head trauma or surgery in the pituitary region.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Protocol	C
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other –Regulatory History	F
Label and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

^a 0.83 mcg desmopressin acetate = 0.75 mcg desmopressin

^b One spray = 0.1 mL

^c 1.66 mcg desmopressin acetate = 1.5 mcg desmopressin

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

3.1 HUMAN FACTORS STUDY PROTOCOL

A summary of the HF validation study protocol is provided in Appendix C. Our review of the proposed HF protocol identified the following areas of concern:

1. The user group is separated by age, however no unique tasks are assessed by age group. We do not find the further categorization by age is representative of the user population.
2. The Applicant states that the users should have ‘varying degrees’ of experience with nasal sprays. It is unclear if this includes naïve users.
3. The facilitator script contains leading instructions and is not representative of real world scenarios.
4. The protocol does not provide a clear definition of task success, task failure, close calls or use difficulty defined at each individual use task step. This information should be provided in the protocol.
5. The Applicant uses the statement ‘ease of use’ in several places within the protocol (e.g., page 11, Section 9.3, page 28, Appendix E question, and on page 29, Appendix F “Ease of Use” feedback). We do not consider ease of use a valuable data point within the evaluation of simulated use human factors validation and data on ease of use does not constitute the necessary data that we need to evaluate safe and effective use of the product.
6. The Structured Cognitive Interview uses questions that are too broadly stated. The questions should focus on obtaining the subjective data from study participants that experience use errors, close calls and use difficulty.
7. The PI for the combination product recommends the nasal spray device be re-primed if the product is not used for more than three days. However, the human factors validation protocol does not assess the use task of re-priming.

In addition to reviewing the protocol, we compared the device design, user interface, and user tasks for the proposed combination product to that of currently marketed desmopressin acetate nasal sprays (e.g., DDAVP, NDA 017922 approved February 21, 1978 and Stimat, NDA 020355 approved March 7, 1994) for any known risk of medication error. We determined that the proposed product is similar to already approved products and are not aware of any safety concerns with the existing products.

3.2 CARTON LABELING, CONTAINER LABEL, PRESCRIBING INFORMATION AND INSTRUCTIONS FOR USE

We reviewed the carton labeling, container label, PI and IFU for risk of medication error. We provide recommendations to improve upon the carton labeling and container labels under separate cover ^d. However, our review of the proposed carton labeling for use in the HF protocol identified the following additional area of needed improvement:

1. The carton labeling includes abbreviated instructions for how to use the product. This presentation is misleading and may increase the risk of improper use of your product since users may use this as a source of information exclusively.

4 CONCLUSION & RECOMMENDATIONS

Our review of the human factors validation protocol and carton labeling identified areas that require revisions. We recommend that Serenity Pharmaceuticals to address the identified concerns before commencing their validation study. We provide letter-ready recommendations in Section 4.1 below that can be conveyed to Serenity.

4.1 RECOMMENDATIONS FOR SERENITY PHARMACEUTICALS

Our review of the human factors validation protocol, container labeling identified several areas of concern. Please address the following prior to conducting your human factors validation study for NDA 201656:

Protocol for Validation Human Factors Study

1. User Groups
 - a. Your protocol identifies one user group, which is further divided into age categories, but the use tasks are identical. It is unclear on your rationale for specifying the different categories and whether the categorization is representative of the user population. In addition, your protocol does not clearly identify if any naïve users (users that do not have any experience in using nasal sprays) are included in your user group. Given the proposed indications and the associated intended users, we expect that there should be two distinct user groups enrolled in your study. Modify your protocol to include 15 naïve user and 15 experienced users.

^dBaugh, D. Review of Label, Labeling, and Packaging for Noctiva (desmopressin acetate) nasal spray, NDA 201656. Silver Spring (MD): Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), Office of Surveillance and Epidemiology (OSE), Division of Medication Error Prevention and Analysis (DMEPA), US; 2016 Nov 17. RCM No. # 2016-393.

2. Training

- a. Your facilitator script includes language which is ‘leading’ and does not reflect real world scenarios that simulate what happens when a patient picks up a prescription. Specifically, on page 25 (“Introduction”) of the facilitator script, the facilitator tells the participant that “the product you will be using is packaged with a label, and includes a product insert with Instructions for Use. You may refer to the Instructions as often as you wish when using the product”. We expect participants should be given the product without any advance discussion of the package contents to realistically represent receipt of the product from the pharmacy. Modify your facilitator script to remove leading language and to allow the study participants to interact with the product naturally.
- b. In addition, in your facilitator script (page 25, “Usability Trials”), you refer to individual ‘task sheets’ which are given to the user during the HF study (see “Appendix C: Test Session Facilitator Script” in the HF protocol submission). We expect that the user would only be given the ‘to-be-marketed’ product (device and its associated labeling including the IFU) in a real world scenario. Therefore, ‘task sheets’ should not be used in the study since they are not part of the ‘to be marketed’ labeling for your product.

3. Data Collection

- a. Note that results focusing on ‘ease of use’ do not constitute as necessary human factors validation data that the Agency will take into consideration when assessing the effective and safe use of your product. A product which is viewed as ‘easy to use’ does not necessarily convey that it has been used safely or effectively and thus, medical care may be compromised despite the ‘ease of use’ of the product. Therefore, any assessments of ease of use (for example, sections 9.2 (System Usability Scale) and 9.3 (Ease of Use) are not included in our analysis. Similarly, as defined in Section 10 (Data Analysis), ‘mean SUS scores’ and ‘structured interview’ will not be included in our analysis.
- b. As currently proposed, the tasks listed in Table 3 (page 10, titled “Primary Operating Functions as per IFU”) do not state what specific user actions would constitute success, failure, close call or use difficulty. These details are needed to determine task success, failures, and whether the participants experience any close call and use difficulties while using this product. Ensure that your final protocol includes the definition of task success and failure at the task level.

- c. In addition, task completion accuracy is stated to be “accurate or inaccurate completion of the task with or without assistance” (Section 9.1 Task Completion Accuracy). These definitions do not clearly define the term ‘accurate’ and providing assistance to participants during the trial may compromise the goal of the study which is to see if users can use your product safely and effectively using only the ‘to be marketed’ labeling. We recommend you revise the categories for task completion accuracy (Section 9.1) to read “success”, “failure”, “close call” and “use difficulties”. This information is needed as the basis for data collection so that the study observer correctly categorizes use task performance.
- d. As proposed in Appendix F (page 29, ‘Structured Cognitive Interview’, the questions are broadly stated (“What was difficult about using the . . . product”?) and not focused on specific task performance. While it may be appropriate to collect data on the general use experience from study participants, we ask that you revise your questions to focus on obtaining the subjective feedback from study participants on any use errors, close calls, or use difficulties that may be observed during the study.
- e. Your protocol does not assess the re-priming of your product. Re-priming is a critical task for the use of your product and is required if the product is not used in three days. We expect the final human factors protocol to include the assessment of the performance and knowledge on the steps of re-priming of the nasal spray at the appropriate interval of time.

4. Carton Labeling

We remind you that we provide carton labeling and container label recommendations under separate cover, however in addition, we have the following recommendation.

- a. We find the abbreviated IFU instructions on the side panel of the carton labeling as presented to be misleading and may lead to improper dosing. Generally, the Agency does not support affixing instructions from the IFU onto carton labeling if the instructions must be abbreviated as a result of the limited space. Abbreviated instructions may result in ineffective or unsafe use of the product because the user is unlikely to refer to the more detailed and complete instructions packaged with the product. As such, they pose a risk of wrong technique errors. We recommend the abbreviated instructions be removed to decrease risk of medication error.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Noctiva that Serenity Pharmaceuticals submitted on May 6, 2016.

Table 2. Relevant Product Information for Noctiva	
Initial Approval Date	N/A
Active Ingredient	desmopressin acetate
Indication	Treatment of nocturia
Route of Administration	intranasal
Dosage Form	nasal spray
Strength	0.83 mcg (0.1 mL) per spray and 1.66 mcg (0.1 mL) per spray
Dose and Frequency	The recommended starting dose is 0.8 ^(b) ₍₄₎ mcg or 1.66 mcg in either the left or right nostril 30 minutes before going to bed. In patients \geq 65 years of age, the starting dose is 0.8 ^(b) ₍₄₎ mcg in either the left or right nostril each night 30 minutes before going to bed. The dose may be increased to 1.66 mcg after 2 to 4 weeks if needed based on patient efficacy and serum sodium level ^e .
How Supplied	Available in a 3.5 mL amber glass bottle fitted with a nasal actuator, a cartridge pump, and a dip tube
Storage	<u>Pharmacist</u> : prior to dispensing, store in a refrigerator, 2°C to 8°C (36°F to 46°F) <u>Patient</u> : store at room temperature 20°C to 25°C (68°F to 77°F). Discard 60 days after opening.

^e At the time of this review, the Agency and Applicant were in labeling negotiations, thus the dosage and administration section is subject to change.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On November 15, 2016, we searched the L: drive and AIMS using the term, “desmopressin” to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified no previous reviews relevant to this review.

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APPENDIX D. ISMP NEWSLETTERS

Not applicable.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

Not applicable.

APPENDIX F. REGULATORY BACKGROUND

NDA 201656 for the proposed Noctiva (desmopressin acetate) Nasal Spray was submitted on February 4, 2016 without a use risk analysis as requested at the August 18, 2015 Guidance Meeting. An information request (IR) was sent to the sponsor on March 19, 2016 requesting this information to determine the need for a human factors validation study. On April 5, 2016, a teleconference was held with the Sponsor to clarify the details of the Agency request. Serenity was asked to conduct a use risk analysis and submit the results, and, if no new risks were identified, then they needed to submit their determination with justification. On April 29, 2016, the risk analysis was submitted to the Agency by Serenity. On September 22, 2016, an IR was sent to notify the Sponsor that their risk analysis was not found to justify that a HF study was not needed, and more data was requested to support that claim. On September 26, 2016, the Sponsor submitted the results of a HF validation study. After review of these results, an IR from DMEPA was sent to inform Serenity of the Agency concerns with the failures and close calls the study reported. We requested mitigations to the proposed Instructions for Use and the carton labeling in response to the reported user errors. Serenity Pharmaceuticals agreed to revise the labels and labeling according to recommendations and to perform a repeat human factors validation study. Serenity sent their updated IFU and proposed protocol on November 7, 2016 for Agency review.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^f along with postmarket medication error data, we reviewed the following Noctiva labels and labeling submitted by Serenity Pharmaceuticals on November 7, 2016.

- Combination Product diagram
- Carton labeling
- Instructions for Use

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

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/s/

LOLITA G WHITE on behalf of DENISE V BAUGH
11/22/2016

LOLITA G WHITE
11/22/2016

QUYNHNHU T NGUYEN
11/23/2016

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

PATIENT LABELING REVIEW

Date: November 22, 2016

To: Hylton Joffe, MD
Director
Division of Bone, Reproductive and Urologic Products (DBRUP)

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

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Karen Dowdy, RN, BSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Jina Kwak, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (established name): NOCTIVA (desmopressin)

Dosage Form and Route: nasal spray, for intranasal use

Application Type/Number: NDA 201656

Applicant: Serenity Pharmaceuticals, LLC

1 INTRODUCTION

On February 4, 2016, Serenity Pharmaceuticals, LLC submitted for the Agency's review an original 505(b)(2) New Drug Application (NDA) 201656 for NOCTIVA (desmopressin) nasal spray. The Reference Listed Drug (RLD) is DDAVP nasal spray (0.1mg/mL), NDA 017922. The proposed indication for NOCTIVA (desmopressin) nasal spray is for the treatment of nocturia in adults who wake up 2 or more times per night to void.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Bone, Reproductive, and Urologic Products (DBRUP) on February 19, 2016, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for NOCTIVA (desmopressin) nasal spray.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on November 16, 2016.

2 MATERIAL REVIEWED

- Draft NOCTIVA (desmopressin) nasal spray MG received on February 4, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 2, 2016.
- Draft NOCTIVA (desmopressin) nasal spray IFU received on November 8, 2016 and received by DMPP and OPDP on November 8, 2016.
- Draft NOCTIVA (desmopressin) nasal spray Prescribing Information (PI) received on February 4, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 18, 2016.
- Division of Medication Error, Prevention, and Analysis (DMEPA) Label, Labeling, and Packaging Review for Noctiva (desmopressin acetate) Nasal Spray dated November 16, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

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

accessible for patients with vision loss. We reformatted the MG and IFU documents using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- The enclosed IFU review comments are collaborative DMPP and DMEPA.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
11/22/2016

JINA KWAK
11/22/2016

LASHAWN M GRIFFITHS
11/22/2016

REVIEW OF LABEL, LABELING, AND PACKAGING

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

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

Date of This Review: November 16, 2016
Requesting Office or Division: Division of Bone, Reproductive, and Urologic Products
Application Type and Number: NDA 201656
Product Name and Strength: Noctiva (desmopressin acetate) Nasal Spray,
0.83 mcg/0.1 mL, 1.66 mcg/0.1 mL
Product Type: Combination Product
Rx or OTC: Rx
Applicant/Sponsor Name: Serenity Pharmaceuticals, LLC
Submission Date: May 6, 2016
OSE RCM #: 2016-393
DMEPA Primary Reviewer: Denise Baugh, PharmD, BCPS
(Acting) DMEPA Team Leader: Lolita White, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed container label, carton labeling, and prescribing information (PI) for Noctiva (NDA 201656) for areas of vulnerability that could lead to medication errors. The Division of Bone, Reproductive, and Urologic Products (DBRUP) requested this review as part of their evaluation of the 505(b)(2) submission for Noctiva which is proposed to treat adult nocturia. The reference listed drug DDAVP nasal spray, 0.1 mg/mL, (NDA 017922 approved February 21, 1978) is approved for the treatment of central diabetes insipidus and for the management of polyuria and polydipsia following head trauma or surgery in the pituitary region.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The proposed combination product consists of desmopressin acetate delivered intranasally as 0.83 mcg and 1.66 mcg desmopressin acetate per actuation for the treatment of adult nocturia. This dose is delivered as a single spray in either the right or left nostril each night approximately 30 minutes before going to bed. The recommended starting dose¹ is 0.86 mcg or 1.66 mcg in either the left or right nostril 30 minutes before going to bed. In patients \geq 65 years of age, the starting dose is 0.86 mcg in either the left or right nostril each night 30 minutes before going to bed. The dose may be increased to 1.66 mcg after 2 to 4 weeks if needed based on patient efficacy and serum sodium level.

¹ This regimen is different from the May 6, 2016 labeling submission because at the time of this review, the Agency and the Applicant were in the midst of labeling negotiations.

We reviewed the proposed container label, carton labeling, and prescribing information for risks of medication errors and identified the following areas of needed improvement that may contribute to medication errors:

1. The presentation of the drug product (e.g., the proprietary name, established name, active moiety, and equivalency statement) and the strength presentation on the container and carton are not in accordance with the salt policy.
2. The important product identifying information on the carton labeling and container label (e.g. established name, dosage form, and strength) are presented in such a way that they appear cluttered .
3. There is a lack of differentiation between the available strengths as presented on the container label and carton labeling.
4. Important information is absent from the label and labeling such as an NDC, a net quantity, and a complete statement of strength (e.g., '0.XX mcg/0.1 mL' and 'X.XX mcg/0.1 mL').
5. We note use of the statement “(b) (4)” on the container label and carton labeling. The statement may be revised to better convey when priming should occur.
6. The product should not be used 60 days from the date of opening. However, there is no space on the container label or carton labeling for the user to write the date that the product is opened and to therefore know when the product should be discarded.

We provide our recommendations in Sections 4.1 and 4.2 in order to help minimize the potential for medication errors to occur with the use of the product.

4 CONCLUSION & RECOMMENDATIONS

Based upon our review of the PI labeling, container label and carton labeling, we find areas that can be revised to improve the presentation of drug identifying information, increase readability, and differentiate between the strengths. See section 4.1 and 4.2 for specific recommendations.

4.1 RECOMMENDATIONS FOR THE DIVISION

Prescribing Information

1. As currently proposed, there is a placeholder (“XXXX-XXXX-XX”) where the NDC number should be in Section 16.1 How Supplied of the PI. NDC numbers are often used as an additional verification prior to drug dispensing in the pharmacy and it is an important safety feature that should be prominently displayed on the labeling. Revise the PI to reflect the

actual NDC number to be used for each of the strengths in accordance with 21 CFR 207.35(b)(3)(i).

APPEARS THIS WAY ON ORIGINAL

4.2 RECOMMENDATIONS FOR SERENITY PHARMACEUTICALS, LLC

We recommend the following be implemented prior to approval of this NDA:

A. Carton Labeling and Container Label

1. The presentation of the drug product and the strength presentation are not in accordance with the salt policy. The proposed presentation of the drug product should be as follows:

Noctiva
(desmopressin acetate) Nasal Spray, 0.83 mcg/0.1mL*
(equivalent to 0.75 mcg/0.1mL of desmopressin)
*each spray contains 0.1 mL

and

Noctiva
(desmopressin acetate) Nasal Spray, 1.66 mcg/0.1mL*
(equivalent to 1.5 mcg/0.1ml of desmopressin)
*each spray contains 0.1 mL

2. The drug-identifying information for your product (established name, dosage form, and strength) is difficult to read. This important drug-identifying information is presented on one line, in thin font and closely spaced. We recommend you re-locate the statement of strength to the next line and increase the spacing between the letters of the established name and dosage form to improve readability.
3. There is a lack of differentiation between the two strengths on the container label and carton labeling. The strength statements for both strengths have (b) (4) presentations (b) (4) which may result in wrong strength errors. Revise the (b) (4) so that each strength appears (b) (4) (b) (4) does not overlap with (b) (4) the trade dress. We recommend this revision to improve upon the strength differentiation and to increase prominence of the strength statement.
4. As proposed, the net quantity does not appear on the principal display panel. We recommend you add the net quantity to the principle display panel in accordance with 21 CFR 201.51 and our guidance for industry "Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors"
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>

5. As currently proposed, there is a placeholder (“XXXX-XXXX-XX”) where the NDC number should be. NDC numbers are often used as an additional verification prior to drug dispensing in the pharmacy and it is an important safety feature that should be prominently displayed on the labeling. Revise the container label and carton labeling to reflect the actual NDC number to be used for each of the strengths in accordance with 21 CFR 207.35(b)(3)(i).
6. We note the statement “(b) (4)” on the container and carton lacks clarity, thus there is a risk that the user will use your product beyond 60 days. Consider revising the statement to read: “Date of first opening _/_/_. Discard unused portion 60 days after first opening”. To allow space for this information, consider revising the ‘Usual dosage’ statement on the container and the carton to read “See Package Insert”.

B. Carton Labeling

1. The statement “(b) (4)” may lead to confusion when preparing to administer the product. Revise the statement to better convey when priming should occur with this product and to minimize user confusion.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Noctiva that Serenity Pharmaceuticals, LLC submitted on May 6, 2016, and the listed drug (LD).

Table 2. Relevant Product Information for Noctiva and the Listed Drug		
Product Name	Noctiva	DDAVP, NDA 017922
Initial Approval Date	N/A	February 21, 1978
Active Ingredient	Desmopressin acetate	Desmopressin acetate
Indication	Treatment of nocturia in adults who wake up 2 or more times per night to void	Anti-diuretic replacement therapy in the management of central cranial diabetes insipidus and for the management of the temporary polyuria and polydipsia following head trauma or surgery in the pituitary region.
Route of Administration	nasal	nasal
Dosage Form	spray	spray
Strength	0.75 mcg per spray and 1.5 mcg per spray	0.1 mL (10 mcg) per spray
Dose and Frequency	The recommended starting dose is 0.86 mcg or 1.66 mcg in either the left or right nostril 30 minutes before going to bed. In patients \geq 65 years of age, the starting dose is 0.86 mcg in either the left or right nostril each night 30 minutes before going to bed. The dose may be increased to 1.66 mcg after 2 to 4 weeks if needed based on patient efficacy and serum sodium level.	0.1 mL to 0.4 mL daily as a single dose or divided into 2 to 3 doses; most adults require 0.2 mL daily in two divided doses
How Supplied	3.5 mL glass bottle fitted with a nasal actuator, a cartridge pump, and a dip tube	5 mL bottle with spray pump delivering 50 sprays of 10 mcg; also available as

	delivering either 0.83 mcg or 1.66 mcg of desmopressin acetate per actuation	DDAVP Rhinal Tube, a refrigerated product with 2.5 mL per bottle, packaged with two rhinal tube applicators per carton.
Storage	<p><u>Pharmacist (before dispensing)</u>: refrigerate from 2°C to 8°C (36°F to 46°F)</p> <p><u>Patient (after dispensing)</u>: room temperature (20°C to 25°C (68°F to 77°F); discard 60 days after opening</p>	<p><u>DDAVP Nasal Spray</u> (Room Temperature);</p> <p><u>DDAVP Rhinal Tube</u> (Refrigerate; stable for 3 weeks at controlled room temperature)</p>

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On July 19, 2016, we searched the L: drive and AIMS using the terms, “Noctiva” and “desmopressin nasal spray” to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified no previous reviews relevant to this review.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,² along with post-market medication error data, we reviewed the following Noctiva labels and labeling submitted by Serenity Pharmaceuticals, LLC on the dates as stated below.

- Container label – submitted September 9, 2016
- Carton labeling – submitted September 9, 2016
- Instructions for Use (no image) – submitted May 6, 2016
- Prescribing Information (no image) – submitted May 6, 2016

² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

DENISE V BAUGH
11/16/2016

LOLITA G WHITE
11/16/2016

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

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

Memorandum

Date: November 10, 2016

To: Nenita Crisostomo, R.N.
Regulatory Health Project Manager
Division of Bone, Reproductive and Urologic Products (DBRUP)

From: Jina Kwak, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 201656**
OPDP labeling comments for NOCTIVA™ (desmopressin acetate)
nasal spray, for intranasal use

OPDP has reviewed the draft package insert (PI) and proposed carton and container labeling for NOCTIVA (desmopressin) nasal spray, as requested in the consult from DBRUP dated February 19, 2016.

OPDP's comments on the labeling, which are based on the draft version of the PI emailed by Nenita Crisostomo on November 2, 2016, are provided below.

OPDP has no comments on the proposed carton and container labeling emailed by Nenita Crisostomo on November 9, 2016.

The Division of Medical Policy Programs (DMPP) and OPDP will provide comments on the Medication Guide and Instruction for Use under separate cover.

If you have any questions, please feel free to contact me:

Jina Kwak: 301-796-4809; Jina.Kwak@fda.hhs.gov

Thank you! OPDP appreciates the opportunity to provide comments on these materials.

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/s/

JINA KWAK
11/10/2016

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA CONSULT TRACKING NUMBER	AT 2016-035
IND/NDA/BLA NUMBER	NDA 201656
REFERENCED IND FOR NDA/BLA	IND 76667
LETTER DATE/SUBMISSION NUMBER	0
PDUFA GOAL DATE	December 2, 2016
DATE OF CONSULT REQUEST	February 19, 2016
REVIEW DIVISION	Division of Bone, Reproductive and Urologic Products (DBRUP)
MEDICAL REVIEWER/TEAM LEADER	Olivia Easley, M.D./Suresh Kaul, M.D.
REVIEW DIVISION PM	Nenita Crisostomo
PRIMARY COA REVIEWER	Sarrit M. Kovacs, Ph.D.
COA TEAM LEADER/SECONDARY COA REVIEWER	Selena Daniels, Pharm.D., M.S.
ASSOCIATE DIRECTOR, COA STAFF (ACTING)	Elektra Papadopoulos, M.D., M.P.H.
REVIEW COMPLETION DATE	November 4, 2016
ESTABLISHED NAME	Desmopressin acetate nasal spray (SER120)
TRADE NAME	NOCTIVA [®]
APPLICANT	Serenity Pharmaceuticals, LLC
CLINICAL OUTCOME ASSESSMENT TYPE	Patient-reported outcome (PRO)
ENDPOINT(S) CONCEPT(S)	Impacts of nocturia
MEASURE(S)	Impact of Nighttime Urination (INTU) instrument
INDICATION	Treatment of nocturnal polyuria in adults who wake up 2 or more times per night to void
INTENDED POPULATION(S)	Adults (≥50 years of age) with documented nocturia (≥2 nocturic episodes/night) at least 6 months by history
PLEASE CHECK ALL THAT APPLY:	<input type="checkbox"/> Rare Disease/Orphan Designation <input type="checkbox"/> Pediatric

Clinical Outcome Assessment Review

Sarrit M. Kovacs, Ph.D.

NDA 201656

Desmopressin acetate nasal spray (SER120); NOCTIVA

Impact of Nighttime Urination (INTU) instrument

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Bone, Reproductive and Urologic Products (DBRUP) regarding NDA 201656. The applicant is currently post-phase 3 in their drug development program and awaiting an approval decision from the FDA. The proposed indication is treatment of nocturnal polyuria in adults who wake up 2 or more times per night to void.

The Applicant proposed the Impact of Nighttime Urination (INTU) instrument for the measurement of impacts of nocturia as the first-ranked secondary endpoint in a single pivotal phase 3 clinical trial (SPC-SER120-DB4-201301; hereinafter referred to as Trial DB4) in adults (≥ 50 years of age) with documented nocturia (≥ 2 nocturic episodes/night) for at least 6 months by history.

The targeted labeling claim is:

(b) (4)

(b) (4)

The review concludes that the evidence submitted by the Applicant demonstrates that the INTU instrument's content validity and measurement properties and performance are acceptable. While the INTU was deemed acceptable for inclusion as a pre-specified secondary endpoint in the Trial DB4, the Agency cautions against its future use, without modification, as it may have floor effects for some of the items leading to insensitivity in detecting treatment effects.

Interpreting the efficacy findings from the Trial DB4 is challenging because there was no *a priori* specified threshold for a meaningful change in INTU Overall Impact scores for use with the phase 3 data. In order to help determine what constitutes a clinically meaningful change in INTU Overall Impact scores, the Agency reviewed exploratory post-hoc analysis of the INTU data from the DB4 clinical trial and concludes that the INTU can reasonably detect changes in nocturia impacts over time. In addition, the Agency concludes that the mean, within-group INTU Overall Impact score improvement (reduction) of 14 points (on a 0-100 point scale) for the SER120 1.5 mcg arm in Trial DB4 appears clinically meaningful. However, the 12-point mean, within-group improvement (reduction) in INTU scores for the placebo arm in Trial DB4 appears clinically meaningful as well. While the 2.6 mean treatment difference in INTU scores between the SER120 1.5 mcg and placebo arms in Trial DB4 is statistically significant ($p=0.02$), the

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exploratory analyses were unable to inform whether this small difference is adequate and meaningful.

B. BACKGROUND

During clinical development of desmopressin acetate nasal spray (SER120 nasal spray formulation; hereinafter referred to as SER120), the Applicant proposed an existing patient-reported outcome (PRO) instrument (Nocturia Quality of Life Questionnaire; N-QoL) for inclusion in their phase 3 trial; however, the FDA concluded that this instrument was not fit-for-purpose to assess the impacts of nocturia on daily living. Therefore, the Applicant, with advice from the FDA, developed the INTU instrument for use as the first key secondary endpoint in one of their phase 3 clinical trials (Trial DB4) to support the efficacy assessment of SER120.

Materials reviewed:

- *FDA Briefing Document for the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) meeting on October 19, 2016*
- *Applicant Briefing Document for the BRUDAC meeting on October 19, 2016*
- *INTU PRO evidence dossier (including qualitative study report and interview transcripts, and psychometric evaluation report), Trial DB4 protocol, study report, statistical analysis plan, and other documents (received in DARRTS on February 4, 2016)*
- *Applicant's replies to Agency's information requests for post-hoc exploratory analysis (i.e., anchor-based analyses, CDF plots, INTU results for nocturnal polyuria [NP] and no NP subpopulations)*
- *Agency-conducted post-hoc exploratory analysis (i.e., CDF plots)*
- *Previous COA Reviews during IND 76667 phase:*
 - *AT 2015-217; Kovacs, finalized in DARRTS on May 8, 2016*
 - *AT 2015-125; Kovacs; finalized in DARRTS on September 13, 2015*
 - *AT 2013-069; Stansbury; finalized in DARRTS on May 28, 2013*

C. CLINICAL OUTCOME ASSESSMENT (COA) REVIEW

The review concludes that the evidence submitted by the Applicant demonstrates that the INTU instrument's content validity, domain structure, and measurement properties and performance (i.e., internal consistency reliability, test-retest reliability, convergent validity, known-groups validity, and ability to detect change over time) are acceptable.

While the INTU instrument was deemed acceptable for inclusion as a pre-specified secondary endpoint in Trial DB4, the Agency cautions against its future use, without modification, in future drug development programs as it may have floor effects for some of the items, leading to its insensitivity in detecting treatment effects. Also, there is concern with using paper data for a

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daily diary with no time and date stamp; back-filling of data by patients may introduce recall error and potentially lead to inaccurate data, unlike with the use of electronic modes of administration. Given the large floor effects of several of the items in the INTU, the current instrument would benefit from modification (e.g., through removal of items of lesser relevance and re-evaluation of the domain structure), if it is to be used in future drug development programs.

Interpreting the efficacy findings from Trial DB4 is challenging because there was no *a priori* specified threshold for a meaningful change in INTU Overall Impact scores for use with the phase 3 data. Small changes in PRO endpoint scores can be statistically significant, but not necessarily clinically meaningful. Both clinical and statistical significance should be demonstrated. Also, given that the INTU instrument was included only in a single pivotal trial, determination of the INTU Overall Impact score being fit-for-purpose and yielding meaningful results needs to be evaluated in the overall context of evidence.

In order to help determine what constitutes a clinically meaningful change in INTU Overall Impact scores, the Agency reviewed exploratory post-hoc analysis of the INTU data from Trial DB4 and concludes that the INTU can reasonably detect changes in nocturia impacts over time. In addition, the Agency concludes that the mean, within-group INTU Overall Impact score improvement (reduction) of 14 points (on a 0-100 point scale) for the SER120 1.5 mcg arm in Trial DB4 appears clinically meaningful. However, the 12-point mean, within-group improvement (reduction) in INTU scores for the placebo arm in Trial DB4 appears clinically meaningful as well. While the 2.6 mean treatment difference in INTU scores between the SER120 1.5 mcg and placebo arms in Trial DB4 is statistically significant ($p=0.02$), the exploratory analyses were unable to inform whether this small difference is adequate and meaningful.

1 CONTEXT OF USE

1.1 Clinical Trial Population

Main inclusion criteria:

1. Male or female subject ≥ 50 years of age.
2. Documented nocturia by history (≥ 2 nocturic episodes/night for at least 6 months)
3. Documented nocturia by diary administered for 3 days during each week of the 2-week screening period:
 - a. Mean of ≥ 2.16 nocturic episodes/night or
 - b. ≥ 13 total nocturic episodes
4. 24-hour urine output ≤ 57 mL/kg or up to 4500 mL/24 hours.
5. Normal serum sodium concentration

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There were numerous exclusion criteria, including severe daytime lower urinary tract symptoms (LUTS) secondary to BPH, OAB or severe stress urinary incontinence. Daytime urinary frequency >8 episodes per day by medical history or by 24-hour urine frequency/volume chart during screening.

1.2 Clinical Trial Design

Trial DB4 evaluated two doses (0.75 or 1.5 mcg) of SER120. There were no restrictions on fluid intake during the trial. Study medication (SER120 or placebo, depending on randomization group) was taken nightly for 12 weeks. Patients completed consecutive 3-day voiding diaries every week for the first two weeks of treatment (i.e., at weeks 3 and 4 of the trial) and then every two weeks thereafter until the end of the 12-week double-blind treatment phase (i.e., at weeks 6, 8, 10, 12 and 14). In Trial DB4, patients also completed the INTU each evening on the same days that they completed the 3-day voiding diaries during screening (screening weeks 1 and 2) and at treatment weeks 8 and 14.

1.3 Endpoint Hierarchy and Definition

The co-primary efficacy endpoints for Trial DB4 were:

1. Change from screening to the treatment period in the mean number of nocturic episodes per night
2. Percentage of patients with $\geq 50\%$ reduction in the mean number of nocturic episodes per night between screening and the treatment period (responders)

The secondary efficacy endpoints in order of pre-specified testing hierarchy were:

1. Change in the Impact of Night-time Urination (INTU) Overall Impact score between screening (average of screening weeks 1 and 2) and average of weeks 8 and 14 of the treatment period.
2. Change in the time interval from when the patient went to sleep to the first nocturic episode or the first morning void in the absence of a nocturic episode from screening to the treatment period.
3. Change in the percentage of nights with 0 nocturic episodes per night on a per patient basis.
4. Change in the percentage of nights with ≤ 1 nocturic episode per night on a per patient basis.
5. Change in the nocturnal urine volume between the screening period and the last week of the treatment period.

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1.4 Labeling or promotional claim(s) based on the COA

(b) (4)



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(b) (4)

2 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

The Applicant did not provide an *a priori* conceptual framework for the INTU instrument's domain structure (daytime versus nighttime domains) based on qualitative research with patients or clinicians. Rather, the Applicant conducted an exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) to determine the number of domains or factors that were present within the INTU instrument. EFA was performed on week 1 (day 4) data to identify the underlying factor structure for the INTU instrument with no pre-specified numbers of factors. The total sample size for the EFA was 182 patients. The INTU instrument had two factors with eigenvalues greater than one; the first was 4.22 and the second was 1.21. The Applicant interpreted this to mean that the INTU may have two underlying factors – nighttime impact and daytime impact.

The final INTU conceptual framework consisted of two nocturia impact domain scores and an overall impact score:

- Daytime Impact score (Items 1-4, 6, 10)
- Nighttime Impact score (Items 5, 7, 8, 9)
- Overall Impact score (avg. of Daytime & Nighttime Impact scores)

Reviewer's comments: Before conducting the INTU psychometric evaluation study, the Applicant did not provide a conceptual framework proposing separate Nighttime Impact and Daytime Impact domains. Items should not be placed into domain scores based only on statistical considerations, such as factor analysis. It is important to also include conceptual considerations based on clinical knowledge of the disease or condition and patient input. Additionally, the item content should have been modified to only include the most relevant items in the target population prior to conducting further psychometric analyses (i.e., items with high floor effects

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should have been removed prior to proceeding further). Therefore, many of the Applicant's statistical analyses, such as factor analysis and Rasch modeling, may be difficult to interpret and are not further discussed in this review.

If this instrument is used in future trials, it seems appropriate to also consider a single overall score (without the use of domain scores) that includes only the most relevant and important items based on qualitative and quantitative research.

If the INTU instrument is unidimensional, it may be inappropriate to average the domains before calculating the Overall Impact score. Therefore, the FDA requested that the Applicant recalculate the Overall Impact score by taking the mean of all 10 transformed items (without taking into account separate domains) to compare with the original transformed scores. These scoring algorithms did not differ much; the alternative calculation supports the pre-specified efficacy analysis results.

3 CLINICAL OUTCOME ASSESSMENT (COA)

The Impact of Nighttime Urination (INTU) instrument includes 10 items and is administered as a pen-and-paper self-reported instrument (Appendix A). The aim of the INTU instrument is to assess the impact of nocturia on daily living, including impact on restfulness, concentration, and level of emotional concern about needing to get out of bed to urinate. The first four items ask patients to think back over the day since awakening and evaluate the frequency with which they experienced difficulty concentrating, feeling tired, difficulty getting things done, and irritability. These items are assessed using a five-point response scale ranging from "Not at all" to "All day." Item 5 asks patients to think about the evening and report their level of concern with having to get up "tonight" to urinate. The final five items, items 6-10, ask patients to think about how they felt when they awoke and assess their level of concern regarding feeling rested, having to get up at night to urinate, starting the day earlier because of having to get up to go to the bathroom, difficulty getting enough sleep, feeling bothered by getting out of bed to go to the bathroom, and feeling drowsy. These items are assessed using a four-point response scale that ranges from "Not at all" to "Very Much."

In Trial DB4, patients completed the INTU each evening on the same day that they completed the 3-day voiding diaries.

The Applicant provided the Agency with a user manual for the INTU instrument, including some training materials for the site and patient.

Reviewer's comments: The Applicant used a paper-and-pen mode of administration for the INTU instrument. When appropriate and feasible, the FDA recommends electronic data capture for daily diaries, using a device with a reminder or alarm function to minimize the extent of missing data and potential back-filling of data by patients. The concern with paper data is that there is

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no time and date stamp, as with an electronic mode of administration; back-filling of data by patients would introduce recall error and potentially lead to inaccurate and/or “noisy” data.

Each item in the INTU was transformed to a scale ranging from 0 to 100 points. The transformation was done by changing the range of scores to have zero as the lowest response category, dividing by the value of the highest response category, and multiplying by 100.

$$\text{Transformed Scale Score} = \left[\frac{\text{Actual Raw Score} - \text{Lowest Possible Raw Score}}{\text{Possible Raw Score Range}} \right] \times 100$$

These transformed scores were then used to generate domain scores (i.e., subscores that in the case of the INTU instrument are combined to calculate an overall score) and a total score (i.e., Overall Impact score). The domain scores were calculated by averaging the transformed item scores for each domain after any necessary reverse-scoring (i.e., item 6 [“How rested did you feel this morning?”]), so that higher scores for the INTU indicate more severe impacts of nocturia.

The Overall Impact Score was computed by taking the mean of the Daytime and Nighttime Impact scores:

- INTU Daytime Impact score: mean of items 1, 2, 3, 4, 6, and 10
- INTU Nighttime Impact score: mean of items 5, 7, 8, and 9

4 CONTENT VALIDITY

In line with recommendations from the FDA’s PRO Guidance for Industry,¹ the INTU instrument was developed using a qualitative approach. The Applicant’s qualitative research consisted of a systematic review of published literature and input from patients with nocturia (one-on-one qualitative interviews). The qualitative sample of 28 English-speaking patients from four United States (U.S.) sites appears to be representative of the Trial DB4 patient population. Within the qualitative sample, 50% were men with a mean age of 64 years (SD 8, range 52-79 years) and a mean of 3 nocturia episodes per night (SD 1, range 2-5). The majority of patients were Caucasian ($n= 21/28$, 75%), and the remaining ethnic groups were African American/Black ($n= 3/28$, 11%), Hispanic ($n= 2/28$, 7%), and Asian ($n= 2/28$, 7%).

The patient interviews were conducted in-person and combined both concept elicitation and cognitive debriefing elements; patients were asked both open-ended questions, targeted at

¹ US Food and Drug Administration. Guidance for Industry—Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Silver Spring, MD: Food and Drug Administration, 2009. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>.

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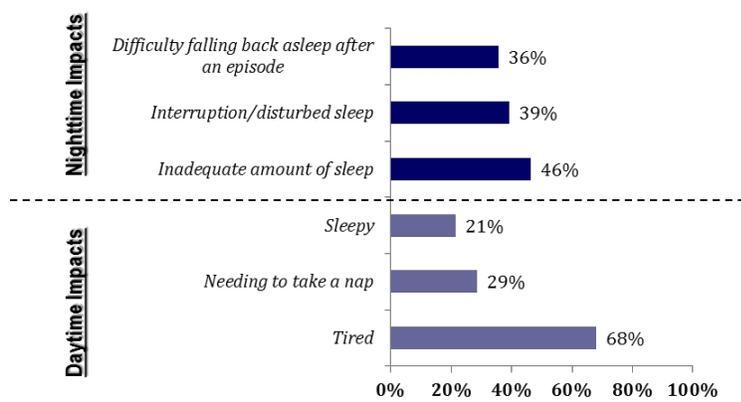
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eliciting the relevant and important impacts of nocturia, as well as targeted questions about the PRO items and response options to ensure that the questions were understandable and that the response options made sense and were meaningful to the patients.

The three most frequently reported nighttime and daytime impacts associated with nocturia, based on spontaneous input from the concept elicitation interviews are summarized in Figure 1.

Figure 1. Most frequently patient-reported impacts of nocturia



n=28

Reviewer's comments: The findings from the Applicant's systematic literature review and concept elicitation/cognitive interviews support the assertion that nocturia affects multiple aspects of patients' lives and identify the key impacts associated with nocturia (e.g., feeling tired, inadequate sleep). In general, patients appear to understand and interpret the final INTU instructions, item stems, response options, and recall period appropriately.

The Applicant created item tracking matrices from each of the four rounds of the interviews (seven patients in each of the four rounds) from four different U.S. sites. The item tracking matrices documented any deletion, addition, or modification made to the items or response options included in the instrument, along with documentation of the rationale for the changes to the instrument based on the patient interview data.

Reviewer's comments: This reviewer has the following general comments about the INTU items:

1. In general, the Nighttime Impact items measure the intensity or severity of sleep-related impacts of nocturia on patients' lives and appear likely to be sensitive to treatment effects. However, item 5 ("have you been concerned about having to get up tonight to urinate?") appears to relate to patients' feelings of concern (or worry) about the future, which might be based on the feelings encompassed by items 7, 8, and 9 relating to how the patient felt when they awoke in the morning (i.e., whether they had to start their day earlier than they would have liked due to getting up to urinate, having a difficult time getting enough sleep the prior

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night, and how bothered they felt by having to get out of bed to urinate the prior night). Items which assess patients' feelings of concern and worry about the future are most likely related to their previous experience and may not be indicative of, or sensitive to, treatment effects. Furthermore, five of the seven (71%) patients in Round 1 and six of the seven (86%) patients in Round 2 of the qualitative interviews stated that an item asking about their worry about having to get up to urinate is not relevant to their experience. Based on the first round, this reviewer might have dropped the item from the questionnaire; however, the Applicant changed the wording from "[REDACTED] (b) (4)" to "concerned" based on patients' suggestions in Round 2 and tested it in Rounds 3 and 4 where four of the seven (57%) patients in each respective round stated that this item was relevant to their experience with nocturia.

2. Some of the Daytime Impact items appear to be less common (see comment #3 below) and less direct impacts on patients' lives (i.e., ability to concentrate, get things done, and level of irritability), which are less likely sensitive to treatment effects and could be impacted by factors other than nocturia (e.g., other comorbidities, psychosocial stressors). While the emotional and physical concepts covered by Daytime Impact items 2, 6, and 10 (i.e., feeling tired, feeling rested, and feeling drowsy) appear to overlap conceptually, a large number of patients in qualitative research (68%) endorsed the concept of tiredness during the day, which supports the inclusion of one, or perhaps more than one item, assessing this concept.
3. Based on the qualitative patient interviews, item 1 (difficulty concentrating) was not highly endorsed by patients; four of the seven (57%) patients in Round 1, three of the seven (43%) patients in Round 2, and six of the seven (86%) patients in Round 3 reported this item was not relevant to their nocturia, but this item was retained by the Applicant for testing in Round 4 and found to be relevant to those patients. In addition, item 3 (difficulty getting things done) was not highly endorsed; four of the seven (57%) patients in Round 1, four of the seven (57%) patients in Round 2, and five of the seven (71%) patients in Round 3 felt that this item was not relevant to their experiences with nocturia. However, the Applicant retained the item for testing in Round 4 and found that six of the seven (86%) patients stated that this item was relevant to their experiences. Only Round 4 patients endorsed "irritability" as a daytime impact of nocturia. In summary, there was greater endorsement of the more distal or indirect impacts of nocturia by the Round 4 patients compared to the previous three rounds of patients. The reason(s) for this are unclear.
4. Inclusion of some of these Daytime Impact items may increase variability ("noise") in the INTU Overall Impact score and impair the interpretability of any treatment effect. See below for information about the floor effects observed for some of the INTU items.
5. After review of the patients' transcripts from the interviews, we found the following patient input worthy of mention:

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- *Patients' interpretation of meaningful change in number of nocturnal voids: Interviewers asked 21* patients whether decreasing the number of nocturic episodes by one episode per night would have a meaningful impact on how they feel and function.*
 - *10/21* patients (48%) stated that decreasing the number of nocturic episodes by one episode per night would be a "good night" or make a significant difference to them.*
- *Patients' interpretation of the INTU response options:*
 - *7/21* (33%) patients could not differentiate between the response options "quite a bit" and "very much," and 5/21* (24%) patients could not differentiate between the response options "most of the day" and "all day." Most of these patients suggested eliminating the "very much" and "all day" response options given that they were synonymous with "quite a bit" and "most of the day," or irrelevant as they would never select them. Therefore, a 1-category change moving from "very much" to "quite a bit" or moving from "all day" to "most of the day" may be less meaningful than a 1-category change from "quite a bit" to "somewhat" or from "most of the day" to "about half of the day."*

**Note: The final response options were only tested in 21 patients (rounds 2-4).*

In a two-week observational study to psychometrically evaluate the INTU instrument in 193 patients with clinically-confirmed nocturia, the Applicant item level analysis of the INTU. See Section 5 below for details on this patient sample.

Item-level scores for the INTU instrument were evaluated on day 5 of the observational study. On day 5, patients generally used the entire range of the scale when responding to each item with the exception of item 1 (difficulty concentrating) where the response option "all day" was not endorsed at all. Most of the INTU items were skewed towards lower impact response options (i.e., "Not at all"/"A little of the day"/"Somewhat"), except for item 9 (bothered by getting out of bed to go to the bathroom last night) where 10% (n=20) of patients reported being bothered "Very much". The Applicant reported no notable ceiling effects for the INTU items (a ceiling effect is when a high percentage of patients select the most severe response option).

However, the Applicant found that some INTU items had floor effects (a floor effect is when a high percentage of patients select the least severe response option, i.e., "Not at all") indicating that some of the items were not relevant to, or experienced by, many of the patients. With the exception of the item assessing whether patients "felt tired," the items showing floor effects did not appear to be among the most frequently-reported impacts of nocturia from the qualitative research with patients. The floor effects indicate that a significant proportion of the patients are not experiencing those particular nocturia impacts and, therefore, would not be able to show improvement on those impacts. The Applicant specified thresholds greater than 25% for items 1–4 and 20% for items 5–10 to determine the presence of floor or ceiling effects.

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The following items had floor effects based on these criteria:

- Item 1 “Have you had difficulty concentrating?” (49% responded “Not at all”);
- Item 2 “Have you felt tired?” (22%);
- Item 3 “Have you had difficulty getting things done?” (43% responded “Not at all”);
- Item 4 “Have you been irritable?” (57% responded “Not at all”);
- Item 5 “Have you been concerned about having to get up tonight to urinate?” (35% responded “Not at all”);
- Item 7 “Did getting up out of the bed to go to the bathroom this morning cause you to start your day earlier than you would have liked?” (50% responded “Not at all”); and
- Item 10 “How drowsy did you feel this morning?” (29% responded “Not at all”).

The Applicant believes that the floor effects were due to inclusion of patients with mostly mild or moderately severe nocturia in the observational study, without inclusion of many severely-affected patients.

Reviewer’s comments: The observed floor effects indicate that some of the items were not relevant to, or experienced by, the patients.

With the exception of item 2 (felt tired), the items showing floor effects did not appear to be among the most frequently-reported impacts of nocturia from the qualitative research (Figure 1). It is unclear why items 1, 3, 4, and 7 with the highest floor effects appear in the final INTU instrument. The floor effects indicate that a significant proportion of the patients are not experiencing those particular nocturia impacts and, therefore, would not be able to show improvement on those impacts. These items should have been dropped from the INTU instrument; however, the Applicant did not make any modification to the INTU items based on these floor effects.

The FDA could not find descriptive statistics, including floor effect analysis, for the Trial DB4 population within the Applicant’s submission. However, an FDA analysis using the histograms of the response option distribution for each INTU item in the Trial DB4 data appears to show that high floor effects for some INTU items are present in the Trial DB4 data for the same items that had the highest floor effects in the two-week observational study – items 1 (difficulty concentrating), 3 (difficulty getting things done), 4 (been irritable), and 7 (getting out of bed to go to the bathroom this morning caused you to start your day earlier than you would have liked).

5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

The Applicant conducted a two-week multicenter, U.S.-based, prospective, interventional (behavioral modification), observational study to psychometrically evaluate the INTU instrument

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in 193 patients with clinically-confirmed nocturia. During week 1, patients were given a three-day voiding diary (to be completed during the mornings of days 4, 5, and 6) and three INTU instrument forms (to be completed during the evenings of days 4, 5, and 6). On Day 8 (first day of week 2), patients completed a patient global impression of change (PGI-C; see Appendix B) scale, which asked the patients to rate the change in their nocturia symptoms over the past 7 days of the study. On Day 8, patients also received three more voiding diaries and INTU instrument forms to complete during week 2 (voiding diaries were to be completed in the mornings of days 11, 12, and 13 and INTU instruments were to be completed during the evenings of days 11, 12, and 13). For the behavioral modification intervention, patients qualifying for the week 2 assessment period were instructed to maintain normal fluid intake until 8:00 PM and stop fluid intake from 8:00 PM until the start of the next day. During the final visit (day 15), patients were asked to complete another PGI-C scale and other questionnaires.

All patients who met the inclusion and exclusion criteria and who completed the INTU instrument at least one of the days (4, 5, or 6) in week 1 and at least one of the days (11, 12, and 13) in week 2 were included in the cross-sectional analysis population.

Most of the patients (>80%) reported either mild (two to three episodes/night, n=90) or moderate (three to four episodes/night, n=83) nocturia, while about one-tenth of the patients reported severe nocturia (>4 episodes/night, n= 20). Similarly, clinicians classified the majority of patients (>80%) as mild (n=89) and moderate (n=81).

The Agency requested that the Applicant conduct exploratory analyses using their Trial DB4 data, to provide support for the INTU's psychometric properties and performance. The results from these INTU psychometric evaluation analyses (i.e., reliability, validity, ability to detect change) using the Trial DB4 data were compared with the INTU psychometric evaluation results obtained in the two-week observational study, and were found to be similar and acceptable.

The psychometric evaluation results from both studies are summarized below.

Reliability

- *Internal consistency reliability*
 - Observational study findings: Internal consistency reliability was evaluated using day 5 INTU data. A Cronbach's alpha coefficient of 0.88 was obtained for the assessment of internal consistency of the INTU Overall Impact score, which exceeded the Applicant's specified threshold of ≥ 0.70 . The magnitude of the Cronbach's alpha coefficient did not show any appreciable change with potentially removing any of the items from the INTU Overall Impact score. Cronbach's alpha coefficients for the two INTU domain scores were 0.83 (Daytime Impact) and 0.78 (Nighttime Impact).
 - Trial DB4 study findings: The Cronbach's alpha coefficients for the INTU Overall Impact, Daytime Impact, and Nighttime Impact scores obtained from about 770 patients in the Trial DB4 data (0.91, 0.89, and 0.83, respectively) informing the internal

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consistency of the INTU appear to be similar to those obtained in the observational study (0.88, 0.83, and 0.78, respectively). The Cronbach's alpha coefficient for the INTU Overall Impact score would increase from 0.91 to 0.92 and for the Daytime Impact score would increase from 0.89 to 0.90 if item 6 ("How rested did you feel this morning?"; the only reverse-scored item) were deleted. The Nighttime Impact score's Cronbach's alpha coefficient would increase from 0.83 to 0.84 if item 7 ("Did getting up out of bed to go to the bathroom this morning cause you to start your day earlier than you would have liked?") were deleted. These changes appear small. The Applicant did not delete any items from the INTU instrument.

- *Test-retest reliability*
 - **Observational study findings:** Test-retest reliability was evaluated using day 4 and day 6 INTU data, with patient stability assumed based on no treatment/intervention during these 48 hours. An intra-class coefficient (ICC) of 0.89 was derived for the assessment of test-retest reliability of the INTU Overall Impact score, which exceeded the Applicant's specified threshold of ≥ 0.70 . Test-retest reliability (using ICC) for the INTU domain scores were 0.81 (Daytime Impact) and 0.88 (Nighttime Impact).
 - **Trial DB4 findings:** ICCs were calculated on INTU scores from 782 patients obtained during both weeks 1 and 2 of the Trial DB4 screening phase, comparing the average of the three consecutive daily INTU instruments from each week. The ICCs for the INTU Overall Impact, Daytime Impact, and Nighttime Impact scores were 0.94, 0.92, and 0.92, respectively.

Reviewer's comments: The INTU instrument's internal consistency and test-retest reliability results are acceptable and comparable across both studies. However, it remains unclear why some items with high floor effects were retained in the INTU instrument.

Construct Validity

- *Convergent validity*

Convergent validity was measured in the observational study only using the day 8 correlations (correlation coefficients) of the INTU scores with two other PRO instruments, the Pittsburgh Sleep Quality Index (PSQI) and the Nocturia Quality of Life (N-QOL) questionnaire. A moderate positive correlation was observed between the INTU Overall Impact and domain scores with the PSQI scores. Higher INTU Overall Impact scores (implying worsening nocturia impact) also had moderate negative correlations with the N-QOL total score and with the N-QOL domains (Sleep/Energy, Bother/Concern) (greater scores on N-QOL indicate an improvement in health-related quality of life).

Reviewer's comments: The INTU instrument's convergent validity results are acceptable. However, it remains unclear why some items with high floor effects were retained in the INTU instrument.

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- *Known-groups validity*

- **Observational study findings:** Known-groups validity was performed for weeks 1 and 2 using the INTU weekly average scores to categorize the severity of nocturia as mild (1 to <2 episodes/night), moderate (2-3 episodes/night) or severe (>3 episodes per night). The INTU Overall Impact score and domain scores differed (nominal $p < 0.05$) across these nocturia severity groups. The INTU Overall Impact score and INTU domain scores moved monotonically, with greater nocturia severity resulting in greater nocturia impacts.
- **Trial DB4 findings:** Patients were classified into severity groups based on whether they experienced ≤ 3 or > 3 daily average nocturic episodes per day. The average of the daily INTU scores and daily total nocturic episodes during the treatment phase was used for the known-groups validity analysis. The results obtained from Trial DB4 showed that the greatest magnitude in score difference between known groups was obtained for the Nighttime Impact score, followed by the Overall Impact score, and then the Daytime Impact score, with 9-point, 7-point, and 4-point score differences, respectively.

Reviewer's comments: The INTU instrument's known-groups validity results are acceptable and comparable across both studies in that the greatest magnitude in score difference between known groups was obtained for the Nighttime Impact score, followed by the Overall Impact score, and then the Daytime Impact score. It appears that the Nighttime Impact domain may be more sensitive to treatment than the other two scores.

Ability to Detect Change Over Time

- **Observational study findings:** The Applicant used three anchor scales to create responder groups, or improvement categories, of patients in order to evaluate the ability of the INTU Overall Impact scores to detect change over time (Table A). This analysis evaluated how the INTU scores relate to actual change in patients' nocturia severity status, and was performed by categorizing patients as responders based on three anchor scales. The following three scales were used to anchor the responder groups for the evaluation:
 - The PGI-C (day 15)
 - A 50% reduction in nocturic events between days 4 (week 1) and 8 (week 2)
 - A mean decrease in one nocturic event between week 1 and week 2.

Table A. Change in INTU scores between days 4 and 8 by responder groups

INTU Score ^[1]	Improved ^[2]							
	2-Grade Change in PGI-C (n=193)		1-Grade Change in PGI-C (n=193)		50% Reduction in Nocturic Events (n=193)		Mean Decrease of One Nocturic Event (n=193)	
	n	Mean Change score (SD)	n	Mean Change score (SD)	n	Mean Change score (SD)	n	Mean Change score (SD)
INTU Overall Impact score	17	-9 (13)	63	-3 (11)	14	-10 (14)	38	-6 (12)

^[1] INTU scores are calculated as the average score over week 1 (days 4-8) and week 2 (days 11-13). INTU scores range from 0 to 100, with higher scores associated with greater negative impact of nighttime urination on health-related quality of life.

^[2] Evaluation of "Improved" categorization used week 1 to week 2 change scores.

Source: Adapted from Table 26 in Applicant's Psychometric Study Report

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Reviewer's comments: The "improved group" appeared to have fairly small mean changes in the INTU Overall Impact score from week 1 (day 4) to week 2 (day 8), ranging from -3 to -10 depending on the anchor used (a negative score reflects a decrease in impact of nocturia). While the INTU Overall Impact score is able to detect change, it remains unclear why some items with high floor effects were retained in the INTU instrument. It is likely that the INTU's ability to detect change could have been improved if the items with floor effects had been omitted; patients cannot show improvements on such items if they are not experiencing those nocturia impacts at baseline.

Trial DB4 findings: The FDA requested that the Applicant conduct exploratory, anchor-based analyses to evaluate the INTU's ability to detect change over time using the Trial DB4 data with the following anchor scales:

- Treatment Benefit Scale (TBS; see Appendix C)
- Mean reduction of ≥ 1 vs. < 1 nocturic episodes per night between screening and treatment (in the qualitative patient transcript review, patients reported that a decrease in one nocturic episode per night would constitute a meaningful change or benefit in how they feel and function in their daily lives.)
- 50% reduction in nocturic episodes per night between screening and treatment

The TBS was completed by patients only at the week 14 (day 99) exit visit. The TBS consisted of the following item: "My condition (waking up at night to urinate) is now:" The response options for the TBS were on a five-point scale (i.e., Much better, Somewhat better, Not changed, Somewhat worse, Much worse). The 3-day voiding diary was used for the other two anchor scales (mean reduction of ≥ 1 versus < 1 nocturic episodes per night and a 50% reduction in nocturic episodes per night from screening to the treatment phase).

The mean change in INTU scores from screening to the treatment phase was calculated for each of the three anchors (Tables B-D). For example, among the patients in Trial DB4 who reported feeling "Much Better" on the TBS, the mean improvement (reduction) in the INTU Overall Impact Score was a reduction of 19 points, whereas those who reported "Not Changed" had a mean improvement (reduction) of 5 points (Table B). Similarly, those who had a mean reduction of at least one nocturic episode per night had a mean improvement (reduction) in the INTU Overall Impact Score of 16 points compared to a 5-point improvement (reduction) among those who had a reduction of less than one nocturic episode per night (Table C).

Table B. Change in INTU Overall Impact score between screening and treatment phases by TBS anchor responder categories

INTU Score	Treatment Benefit Scale (TBS) Categories		
	"Much Better" (n=298)	"Somewhat Better" (n=288)	"Not Changed" (n=185)
Change in INTU Overall Impact Score Mean (SD); min, max	-19 (18); min, max (-92 , 16)	-10 (14); min, max (-61 , 25)	-5 (11); min, max (-58 , 22)

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Table C. Change in INTU Overall Impact score between screening and treatment phases by mean reduction of ≥ 1 versus < 1 nocturic episodes responder categories

INTU Score	Mean reduction of ≥ 1 versus < 1 nocturic episodes	
	Reduction of ≥ 1 (n=504)	Reduction of < 1 (n=278)
Change in the INTU Overall Impact Score Mean (SD)	-16 (16)	-5 (12)

Table D. Change in INTU Overall Impact score between screening and treatment phases by reduction of $\geq 50\%$ versus $< 50\%$ in nocturic episodes

INTU Score	50% reduction of nocturic episodes	
	$\geq 50\%$ Reduction (n=273)	$< 50\%$ Reduction (n=278)
Change in the INTU Overall Impact Score Mean (SD)	-20 (18)	-8 (12)

Reviewer's comments: Improvements in the TBS categories and nocturic episode anchors corresponded with improvements in INTU change scores (Tables B-D). The INTU's ability to detect change over time is acceptable. Based on these anchor-based analyses, a reduction in the INTU Overall Impact score within the range of 10 and 20 points appears to correspond with an improvement between "somewhat better" and "much better" using the TBS anchor categories, and a reduction in nocturic episodes (reduction or ≥ 1 nocturic episode and a $\geq 50\%$ reduction of nocturic episodes).

In general, the Applicant's cross-sectional psychometric evaluation results from the Trial DB4 data appear consistent with the results obtained in the observational study and are acceptable.

6 INTERPRETATION OF SCORES

In order to explore what would be considered a meaningful change in INTU Overall Impact scores from week 1 to week 2 in the observational study, the FDA requested that the Applicant treat both the PGI-C and reduction in number of nocturic episodes as improvement anchor scales in cumulative distribution function (CDF) plots.

In the two CDF plots below (Figures 2 and 3), the change in the INTU Overall Impact scores from week 1 to week 2 are plotted on the x-axis. The y-axis represents the cumulative percentage of the patients having up to a particular change in the INTU Overall Impact score (from the x-axis). When exploring a meaningful change score, we typically look at the intersection between the median line on the y-axis (representing one-half of the patients) and each curve, then trace those intersection points down to the x-axis to see the corresponding change in the INTU Overall Impact score.

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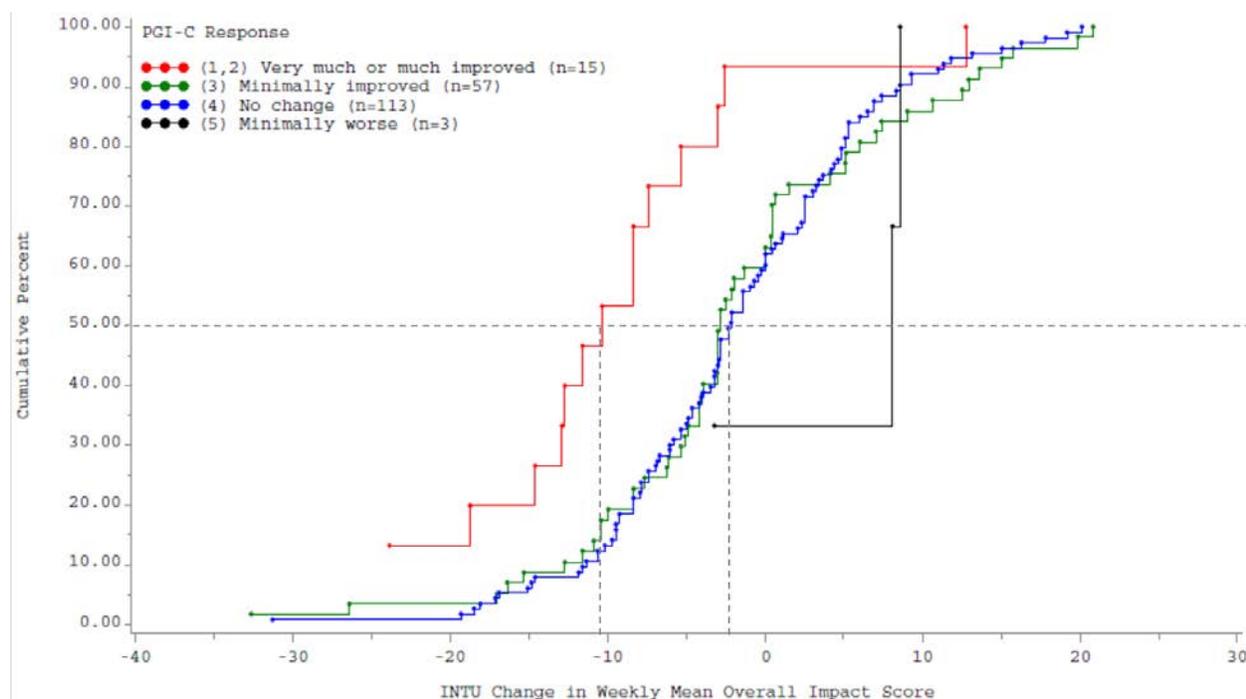
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The curves shown in Figure 2 represent each PGI-C category response option (“Very much or much improved,” “Minimally improved,” “No change,” or “Minimally worse”). (Note: The category responses “Very much improved” and “Much improved” were collapsed together.) Looking at the median line in Figure 2 (the superimposed dashed horizontal line), 50% of patients who reported that their nocturia symptoms were “very much or much improved” on the PGI-C achieved an 11-point or greater improvement (reduction) in the INTU Overall Impact score (x-axis values to the left of the superimposed dashed vertical line corresponding with the red curve). In contrast, 50% of patients who reported that their nocturia symptoms had “no change” on the PGI-C achieved a 2.5-point or greater improvement (reduction) in the INTU Overall Impact score (x-axis values to the left of the superimposed dashed vertical line corresponding with the blue curve).

Figure 2. Change in INTU Overall Impact score from Week 1 to Week 2 by PGI-C



Source: Applicant's NDA submission²

Reviewer's comment: The results of the CDF plot in Figure 2 are consistent with changes seen in the anchor scale categories, as expected.

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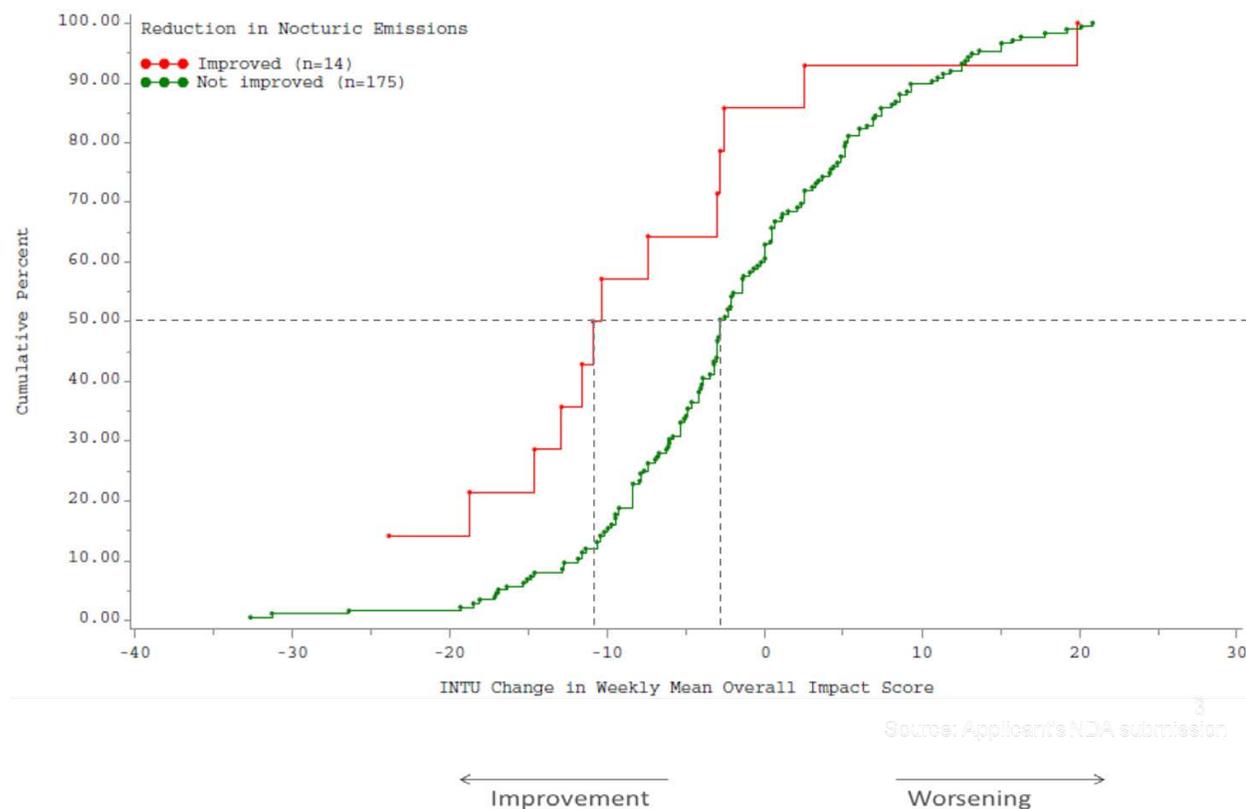
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The curves shown in Figure 3 represent the responders (“Improved”) and non-responders (“Not improved”) based on reduction of nocturic episodes. “Improved” was defined as $\geq 50\%$ decrease in nocturic episodes between week 1 and week 2 and “Not improved” was defined by a $< 50\%$ decrease or an increase in nocturic episodes).

Looking at the median line in Figure 3 (superimposed dashed horizontal line), similar to the results from Figure 2, 50% of patients who had “improved” (a $\geq 50\%$ decrease in nocturic episodes) achieved at least an 11-point improvement (reduction) in the INTU Overall Impact score (leftmost superimposed dashed vertical line corresponding with the red curve), whereas 50% of patients who did not improve” ($< 50\%$ decrease or an increase in nocturic episodes) achieved at least a 3-point improvement (reduction) in the INTU Overall Impact score (rightmost superimposed dashed vertical line corresponding with the green curve).

Figure 3. Change in INTU Overall Impact score from Week 1 to Week 2 by Nocturic Emissions



Reviewer's comment: The results of the plot in Figure 3 are very similar to those obtained in Figure 2 and are consistent with changes seen in the anchor scale categories, as expected.

The FDA requested that the Applicant submit CDF plots from the Trial DB4 data by treatment group (1.5 mcg, 0.75 mcg, and placebo) for the change in INTU Overall Impact scores, as well

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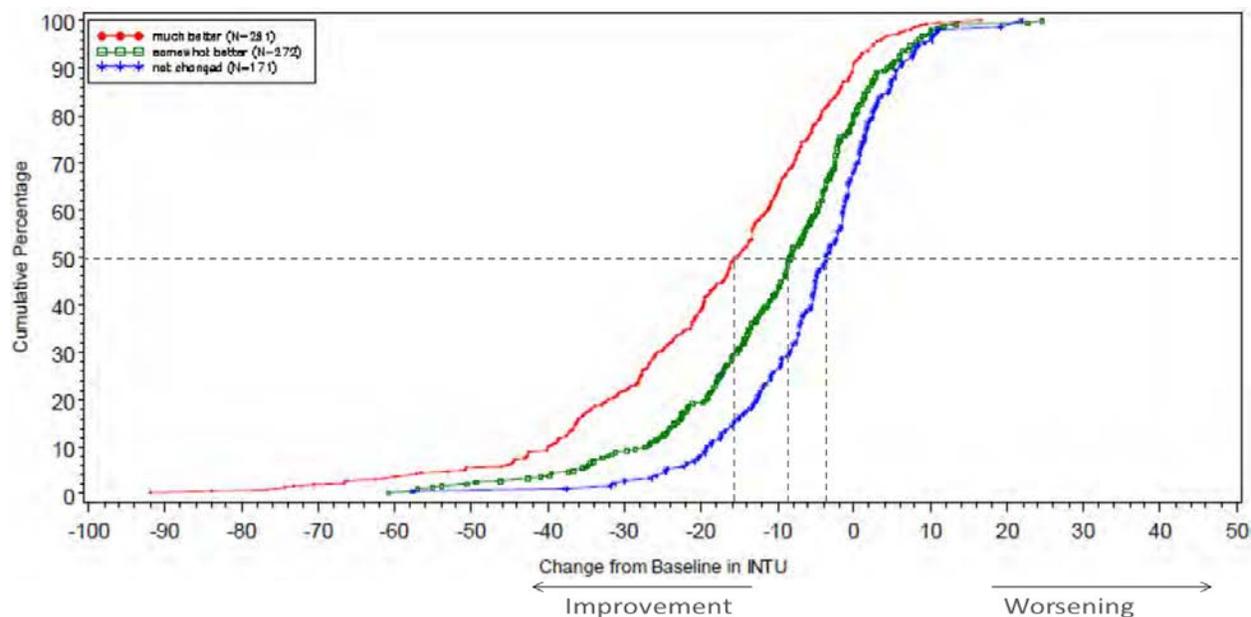
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as CDF plots (pooled treatment and placebo groups) using both the TBS as an improvement anchor scale and any other potential anchor scales.

Figure 4. Change in INTU Overall Impact score from screening to post-treatment by TBS (pooled treatment and placebo groups)



Looking at the median line in Figure 4 (superimposed dashed horizontal line), 50% of patients who reported that their nocturia symptoms were “much better” achieved about a 16-point or greater improvement (reduction) in the INTU Overall Impact score (leftmost superimposed, dashed, vertical line corresponding with the red curve), 50% of patients who reported that their nocturia symptoms were “somewhat better” achieved about an 8-point or greater improvement (reduction) in the INTU Overall Impact score (middle superimposed, dashed, vertical line corresponding with the green curve), and 50% of patients who reported “no change” in their nocturia symptoms achieved about a 4-point or greater improvement (reduction) in the INTU Overall Impact score (rightmost superimposed, dashed, vertical line corresponding with the blue curve).

To examine whether the within-group improvement (reduction) in the INTU Overall Impact score of 14 points observed in Trial DB4 for the SER120 1.5 mcg group is meaningful to patients, one can superimpose a vertical line corresponding with a 14-point improvement (reduction) onto Figure 4. Doing so, it appears that approximately 52% of patients would characterize their nocturia symptoms as “much better,” approximately 33% would characterize their symptoms as “somewhat better,” and about 17% would characterize their symptoms as “not changed.” Note, however, that this exploratory analysis cannot take into account how the

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Desmopressin acetate nasal spray (SER120); NOCTIVA

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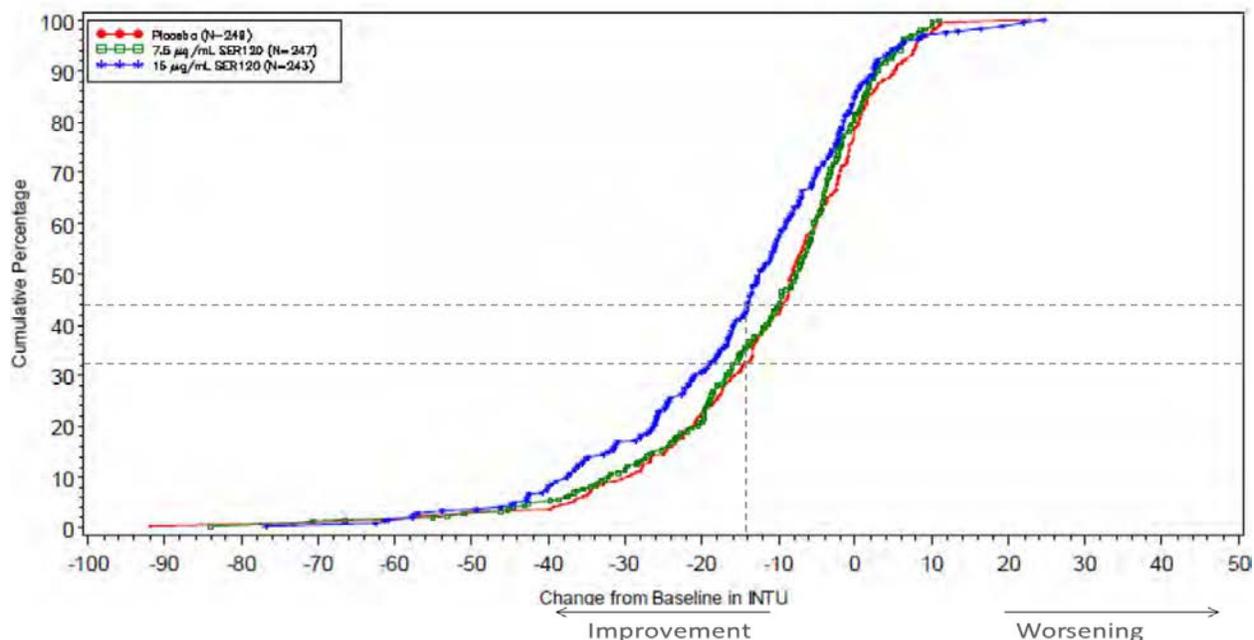
SER120 1.5 mcg group compared with placebo in Trial DB4 with regard to change in INTU score.

Reviewer's comments: The findings observed in Figure 4 are in line with the anchor-based analyses conducted to evaluate the INTU's ability to detect change over time. It appears that a 10- to 16-point improvement (reduction) in the INTU Overall Impact score appears to correspond with an improvement between the "somewhat better" and "much better" TBS anchor categories.

It is also important to mention that the above threshold for meaningful change relies on the assumption that the current INTU instrument is fit-for-purpose. However, given the large floor effects and that the INTU Overall Impact score is comprised of a 2-domain composite score, we suggest that the current INTU instrument should be modified before use in future drug development programs to minimize the risk of failure to detect clinical benefit.

Because the treatment difference in INTU scores between the SER120 1.5 mcg and placebo groups cannot be assessed in Figure 4 (that figure pools data from all treatment groups), the FDA requested CDF curves for the treatment and placebo groups separately (Figure 5).

Figure 5. Change in INTU Overall Impact score from screening to post-treatment by treatment group



When looking at Figure 5 and considering the 14-point within-group, mean improvement (reduction) in the INTU Overall Impact score for the SER120 1.5 mcg group, obtained in Trial DB4 (superimposed dashed, vertical line), approximately 44% of patients in the 1.5 mcg group (top superimposed dashed horizontal line) achieved a 14-point or greater improvement

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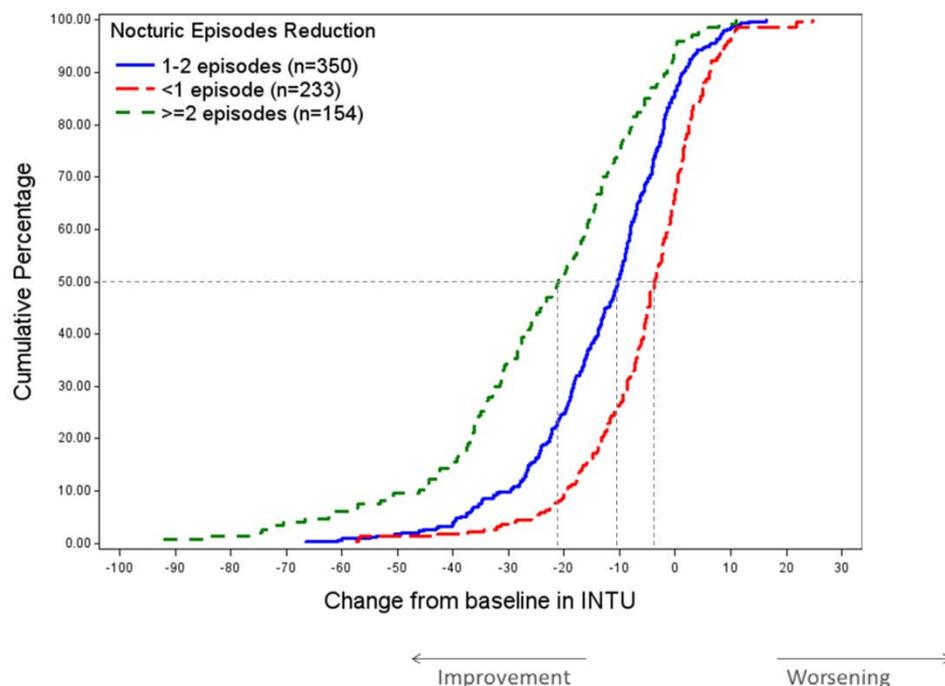
Desmopressin acetate nasal spray (SER120); NOCTIVA

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(reduction) in the INTU Overall Impact score compared to approximately 32% of patients in the placebo group (bottom superimposed dashed horizontal line). This corresponds to about a 12% absolute difference between SER120 1.5 mcg and placebo groups. However, it is important to note that the 12-point within-group, mean improvement (reduction) achieved by the placebo group also falls between the “somewhat better” and “much better” improvement TBS anchor categories.

The FDA conducted one additional exploratory analysis aimed at interpreting the clinical meaningfulness of the INTU results in Trial DB4. Because patients interviewed in the Applicant’s qualitative study had stated that a reduction of at least one nocturic episode would be meaningful to how they functioned in their daily lives, the FDA created a CDF plot of the INTU Overall Impact change scores from screening to post-treatment according to the reduction in nocturic episodes (reduction of <1 episode, 1-2 episodes, and ≥ 2 episodes).

Figure 6. Change in INTU Overall Impact score from screening to post-treatment by nocturic episodes



Looking at the median line in Figure 6 (superimposed dashed, horizontal line), 50% of patients who reported a decrease of ≥ 2 nocturic episodes achieved about a 21-point or greater improvement (reduction) in the INTU Overall Impact score (leftmost superimposed, dashed, vertical line corresponding with the green curve), 50% of patients who reported a decrease of 1-2 nocturic episodes achieved about an 11-point or greater improvement (reduction) in the INTU Overall Impact score (middle superimposed, dashed, vertical line corresponding with the blue curve), and 50% of patients who reported a decrease of <1 nocturic episodes achieved about a 4-

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point or greater improvement (reduction) in the INTU Overall Impact score (rightmost superimposed, dashed, vertical line corresponding with the red curve).

When superimposing the within-group, mean change (reduction) in INTU score of 14 points observed in Trial DB4 for the 1.5 mcg group onto this graph, this 14-point improvement (reduction) appears to be meaningful to patients reporting a reduction of at least one nocturic episode. However, it is important to note that the 12-point improvement (reduction) achieved by the placebo group falls into the 1-2 nocturic episode reduction anchor category, which also appears to be a clinically meaningful change to patients.

Reviewer's comments: In comparison to the 14-point improvement (reduction) in the mean score achieved by the 1.5 mcg group, the placebo group achieved a 12-point mean improvement (reduction), which also appears to be meaningful to patients reporting a reduction of at least one nocturic episode.

7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

The INTU has not been translated into other languages.

3 Page(s) of Copyright Material has been Withheld in Full immediately following this page

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/s/

SARRIT M KOVACS
11/04/2016

SELENA R DANIELS
11/04/2016

ELEKTRA J PAPADOPOULOS
11/04/2016

Clinical Inspection Summary

Date	November 2, 2016
From	Roy Blay, Ph.D., Reviewer, GCPAB\OSI Janice K. Pohlman, M.D., M.P.H., Team Leader, GCPAB\OSI Kassa Ayalew, M.D., M.P.H., Branch Chief, GCPAB\OSI
To	DBRUP\Team Leader\Suresh Kaul DBRUP\Medical Officer\Olivia Easley DBRUP\Project Manager\Nita Crisostomo
NDA/BLA #	NDA 201656
Applicant	Serenity Pharmaceuticals, LLC
Drug	Noctiva (Desmopressin Nasal Spray)
NME (Yes/No)	No
Therapeutic Classification	Standard Review
Proposed Indication(s)	Treatment of adult onset nocturia
Consultation Request Date	March 15, 2016
Summary Goal Date	November 2, 2016
Action Goal Date	December 2, 2016
PDUFA Date	December 4, 2016

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Edelman and Mills were inspected in support of this NDA. Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

The final classification of the inspection of Dr. Edelman was Voluntary Action Indicated (VAI). The final classification of the inspections of Dr. Mills was No Action Indicated (NAI).

2. BACKGROUND

The Applicant submitted this NDA to support the use of Noctiva for the treatment of adult onset nocturia.

Protocols SPC-SER120-DB3-201101 (DB3) and SPC-SER120-DB4-201301 (DB4), both entitled "A Randomized, Double Blind, Placebo Controlled, Parallel Group, Multicenter Study to Investigate the Efficacy and Safety of SER120 Nasal Spray Formulations in Patients with Nocturia" were inspected in support of this application.

Study SPC-SER120-DB3-201101 was conducted at 80 sites across the U.S. and Canada with a projected enrollment of 750 subjects.

Study SPC-SER120-DB4-201301 was conducted at 97 sites across the U.S. and Canada with a projected enrollment of 750 subjects.

According to the sponsor, the results of these studies demonstrated that SER120 at doses of 1.5 µg, 1.0 µg and 0.75 µg was safe, well tolerated and effective for the treatment of nocturia in the adult patient population.

Protocols SPC-SER120-DB3-201101

The primary objectives of this study were to:

1. evaluate the efficacy of three dose levels of SER120 nasal spray formulations in terms of reduction in mean number of nocturic episodes between screening and the treatment period in patients given SER120 versus placebo, and
2. evaluate the efficacy of three dose levels of SER120 nasal spray formulations in terms of percentage of patients with $\geq 50\%$ reduction between screening and the treatment period with respect to the mean number of voids per night in the treatment groups compared to placebo.

This was a randomized, double blind, placebo controlled, parallel group, multi-center study to investigate the dose response relationship, efficacy and safety of three (3) dose levels of SER120 nasal spray formulations in patients with nocturia. Subjects deemed eligible for the study were randomized to one of the three dose levels of SER120 nasal spray formulations (7.5 µg/mL, 10 µg/mL and 15 µg/mL) or placebo.

The primary efficacy endpoints for this study were:

1. Mean number of nocturic episodes per night during the efficacy assessment period (change from screening versus the treatment period), and
2. Percentage of patients with $\geq 50\%$ reduction between screening and the treatment period with respect to the mean number of voids per night.

Protocol SPC-SER120-DB4-201301

The primary objectives of this study were to:

1. evaluate the efficacy of the two dose levels of SER120 nasal spray formulation in terms of reduction in mean number of nocturic episodes between screening and the treatment period in patients given SER120 versus placebo and
2. evaluate the efficacy of the two dose levels of SER120 nasal spray formulation in terms of percentage of patients with $\geq 50\%$ reduction between screening and the treatment period with respect to the mean number of voids per night in patients given SER120 versus placebo.

Please note that this protocol was very similar though not identical to Protocol SPC-SER120-DB3-201101. The primary difference was that this protocol investigated the efficacy and safety of two dose levels (7.5 µg/mL and 15 µg/mL) of SER120 nasal spray formulation in patients with nocturia, rather than three dose levels as described for Protocol SPC-SER120-DB3-201101.

The sites of Drs. Edelman and Mills were selected because of relatively large enrollments into both Phase 3 pivotal studies.

3. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol #/ # of Subjects (enrolled)	Inspection Dates	Classification
Site # 12/18 Edelman, Robert, M.D. 601 Franklin Ave., Suite 300 Garden City, NY 11530	SPC-SER120-DB3-201101/ 27 SPC-SER120-DB4-201301/ 38	3 May-1 Jun, 2016	VAI
Site #29/42 Mills, Richard, M.D. 180 Wingo Way, Suite 203 Mount Pleasant, SC 29464	SPC-SER120-DB3-201101/ 26 SPC-SER120-DB4-201301/ 23	23-26 May, 2016	NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Robert Edelman, M.D.

At this site for Protocol SPC-SER120-DB3-201101, 37 subjects were screened and 27 subjects were enrolled in the study. For Protocol SPC-SER120DB4-201301, 61 subjects were screened and 38 subjects were enrolled in the study. Review of the study records for both protocols included, but was not limited to, IRB and sponsor correspondence, training records, subject diaries, electronic Case Report Forms (eCRFs), financial disclosure forms, adverse event reporting, the primary efficacy endpoint, and test article accountability and storage.

Appropriate informed consent was obtained from all subjects in both protocols prior to any study-related testing.

At the conclusion of the inspection, a Form FDA 483, Inspectional Observations was issued for the following deficiencies:

Several subjects met exclusion criteria but were enrolled in study protocol DB3 and DB4 without the approval of the medical monitor.

Subject Number	Study	Exclusion Criteria
(b) (6)	DB3	melanoma
	DB3	tongue carcinoma
	DB4	lung cancer; > 8 voids/24 hrs
	DB4	melanoma
	DB4	urinary incontinence
	DB4	hepatitis C history

Multiple subjects were dispensed the test article prior to their documentation of study eligibility. For example, Subjects (b) (6) in Study DB3 were dispensed the test article between one and three days prior to having their study participation eligibility documented. Similarly, Subjects (b) (6) in Study DB4 were dispensed the test article between four and 13 days prior to having their study participation eligibility documented.

The amount of test article dispensed was incorrectly calculated for Subject (b) (6) on Day (b) (6) was documented as using 1.85 g of the test article. As the bottle weighed 30.92 g prior to dispensation and 29.7 g afterwards, the correct amount of test article used was 1.22 g.

Subject (b) (6) in Study DB4 had nine daytime voids (exceeding the maximum eight daytime voids).

Dr. Edelman submitted a written response dated June 10, 2016. It was determined to be adequate.

The isolated protocol deviations noted above would not appear to have a significant impact on safety or efficacy considerations. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Richard Mills, M.D.

At this site for Protocol SPC-SER120-DB3-201101, 36 subjects were screened, ten subjects were screen failures, 26 subjects were enrolled, two subjects withdrew prematurely from the study, and 24 subjects completed the study. For Protocol SPC-SER120-DB4-201301, 42 subjects were screened, 19 subjects were screen failures, 23 subjects began the lead-in phase, two subjects withdrew prior to randomization, 21 subjects

were randomized, five subjects withdrew prior to study completion, and 16 subjects completed the study.

Protocol SPC-SER120-DB3-201101

Informed consent was obtained appropriately for all 36 subjects in the study. The records for 14 subjects were reviewed in depth for this protocol. Source data were compared with electronic Case Report Forms (eCRFs) and data listings. Records reviewed included, but were not limited to, IRB communications, financial disclosure, inclusion/exclusion criteria, randomization, subject diaries, concomitant medications, and test article accountability and storage. The primary efficacy endpoint and adverse events were verified for all subjects.

Protocol SPC-SER120-DB4-20130

Informed consent was obtained appropriately for all 42 subjects in the study. The records for 14 subjects were reviewed in depth for this protocol. Source data were compared with electronic Case Report Forms (eCRFs) and data listings. Records reviewed included, but were not limited to, IRB communications, financial disclosure, inclusion/exclusion criteria, randomization, subject diaries, concomitant medications and test article accountability and storage. The primary efficacy endpoint and adverse events were verified for all subjects.

A Form FDA 483 was not issued at the conclusion of the inspection. These studies appear to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

{See appended electronic signature page}

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OSI\ DCCE\Program Analysts\Joseph Peacock\Yolanda Patague
OSI\Database Project Manager\Dana Walters

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/s/

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11/02/2016

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