

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022517Orig1s000

OTHER REVIEW(S)

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: June 19, 2018
Requesting Office or Division: Division of Bone, Reproductive, and Urologic Products
Application Type and Number: NDA 022517
Product Name and Strength: Nocdurna^a (desmopressin acetate) sublingual tablet
27.7 mcg, 55.3 mcg
Applicant/Sponsor Name: Ferring Pharmaceuticals
FDA Received Date: June 18, 2018, and June 19, 2018
OSE RCM #: 2018-13-1
DMEPA Safety Evaluator: Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader: Lolita G. White, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Bone, Reproductive, and Urologic Products (DBRUP) requested that we review the revised blister labels, carton labeling and prescribing information (PI) for Nocdurna (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.^b

2 CONCLUSION

The revised blister label, carton labeling and PI for 'Nocdurna' is acceptable from a medication error perspective. We have no further recommendations at this time.

^a The proprietary name, Nocdurna is being reviewed separately (OSE Review # 2018-20697639 dated April 18, 2018)

^b Baugh, D. Label, Labeling, and Packaging Review for NOCDURNA (NDA 022517). 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); 2018 Jun 07. RCM No.: 2018-13.

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/s/

DENISE V BAUGH
06/19/2018

LOLITA G WHITE
06/19/2018

LABEL, LABELING, AND PACKAGING REVIEW

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)

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Date of This Review:	June 7, 2018
Requesting Office or Division:	Division of Bone, Reproductive, and Urologic Products
Application Type and Number:	NDA 022517
Product Name and Strength:	Nocdurna ^a (desmopressin acetate) sublingual tablet 27.7 mcg, 55.3 mcg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Ferring Pharmaceuticals
FDA Received Date:	March 9, 2018 and May 9, 2018 and June 5, 2018
OSE RCM #:	2018-13
DMEPA Safety Evaluator:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Lolita G. White, PharmD

^a The proprietary name, Nocdurna is being reviewed separately (OSE Review # 2018-20697639 dated April 18, 2018)

1 REASON FOR REVIEW

The Division of Bone, Reproductive, and Urologic Products (DBRUP) has requested the Division of Medication Error Prevention and Analysis review the blister label, carton labeling, and prescribing information (PI) for desmopressin acetate sublingual tablet, NDA 022517 for areas of vulnerability that may lead to medication errors

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.

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 (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other (Information Request)	F
Labels and Labeling	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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We note that the PI labeling, carton labeling and blister label use the established name 'desmopressin', the strengths '25 mcg' and '50 mcg', and the dosage form 'orally disintegrating sublingual tablets' which is inconsistent with the Agency's current thinking. We defer to the Office of Pharmaceutical Quality (OPQ) to address these issues within the labels and labeling.

As part of our review, we assessed the packaging configurations and noted a lack of clarity in the packaging and labeling of the (b)₄-count blister package^b. We requested clarification of the proposed packaging configurations and labels via Information Request (IR) dated April 30, 2018. The applicant provided clarity in their response dated May 4, 2018 and we find their response acceptable. See Appendix F for the contents of our IR and the applicant's response.

Our review of the blister label, carton labeling and prescribing information (PI) identified the following areas of concern which may contribute to medication errors with this product:

^b At the time of this review, the Applicant has not confirmed their intent to offer this package size.

- In Section 16 (How Supplied), the NDC number is denoted by a placeholder. This information should be provided to ensure appropriate product identification.
- In Section 16 (How Supplied), the proposed packaging configuration is not clearly stated.
- As presented on the blister label and carton labeling, the expiration date is not defined which may pose vulnerability to a ‘degraded drug’ medication error.
- There is lack of prominence and inadequate differentiation between the strengths on the carton labeling. Thus, we are concerned for risk of wrong strength medication error.
- (b) (4) lacks a linear barcode which may contribute to the risk of ‘wrong drug’ medication errors.
- As currently presented on the carton labeling, the statement of strength is not expressed in terms of mcg per single unit. Thus, we are concerned with the risk of ‘wrong dose’ medication errors.
- The principle display panel of the carton labeling contains information which takes away from the readability of important product information and contributes to clutter.
- Details of the carton contents (e.g., the number of blister cards which make up the net quantity) are not identified on the carton labeling and may lead to confusion.
- The presentation of the middle digits of the NDC number on the carton labeling are sequential which is not an effective differentiating feature.

We provide recommendations to help minimize the potential for medication errors with the use of this product. See Sections 4.1 and 4.2 below.

4 CONCLUSION & RECOMMENDATIONS

We identified areas of the blister label and carton labeling where additional information should be added, revised, or removed to help ensure the safe use of this product. See our recommendations below in Section 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information (PI) - Section 16 (How Supplied)

1. Ensure that the intended NDC numbers are inserted in the ‘How Supplied’ (Section 16) of the PI and in alignment with the NDC numbers as presented on the product packaging.
2. To decrease the risk of confusion, ensure that the proposed packaging configuration is clearly stated in the ‘How Supplied’ (Section 16) of the PI. For example, the 30-count carton includes three 10 count blister cards and may be stated as “30 XXXX tablets (3 x 10 count blister cards)”.

4.2 RECOMMENDATIONS FOR FERRING PHARMACEUTICALS

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

A. Blister Labels & Carton Labeling – Trade and Professional Sample

1. The expiration date is not provided or it is identified by a placeholder (e.g. 'xxxxx'). To minimize confusion and reduce the risk of 'deteriorated drug' medication errors, identify the format you intend to use. We recommend choosing one of the following formats:

DDMMYYYY (e.g., 31JAN2013)

MMYYYY (e.g., JAN2013)

YYYY-MMM-DD (e.g., 2013-JAN-31)

YYYY-MM-DD (e.g., 2013-01-31)

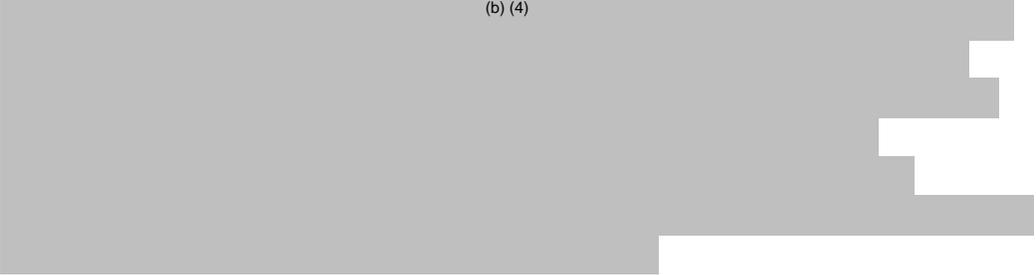
B. Blister Labels (Trade and Professional Sample)

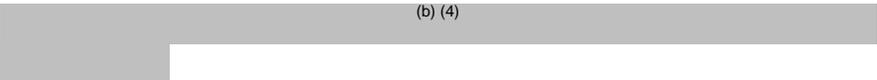
1. (b) (4) does not include a linear barcode. The drug barcode is often used as an additional verification before drug administration; therefore, it is an important safety feature that should be part of the label whenever possible. We request you add the product's linear barcode to each individual blister label as required per 21CFR 201.25(c)(2).

C. Carton Labeling (Trade and Professional Sample)

1. The strength statements (e.g. 25 mcg, 50 mcg) lack prominence and may lead to 'wrong strength' selection errors. We note both strength statements on the carton labeling use the same black font against the same white background which minimizes the difference between the strengths. We recommend further differentiation of the two strengths in accordance with 21 CFR 201.15(a)(6), taking into account all pertinent factors including, background contrast, boxing, bolding, and other printing features. Furthermore, we recommend that the colors used to denote the statement of strength do not overlap with the carton trade dress as an overlap in colors with the trade dress can decrease the prominence of the strength statement.
2. As currently presented on the carton labeling, the statement of strength is not expressed in terms of 'mcg per unit'. As such, this may lead to confusion about how much product is contained in a single unit and contribute to 'wrong dose' medication errors. Revise the product strength on the principal display panel

and other panels of the blister carton labeling to describe the microgram amount of drug per single unit (e.g., tablet). Specifically, we recommend you revise 'XX mcg' to read 'XX mcg per tablet'.

3.  (b) (4)

4. The carton labeling does not clearly define how the product is supplied and may contribute to confusion. We recommend you revise the net quantity for both strengths from "30 XXXX Tablets" to read "30 XXX Tablets (3 x 10 count blister cards)"  (b) (4)

5. The similarity of the product code numbers has led to the selection and dispensing of the wrong strength and wrong drug. The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Additionally, the assignment of sequential numbers for the middle digits is not an effective differentiating feature. If for some reason the middle digits cannot be revised, increase the prominence of the middle digits of the NDC on the carton labeling by increasing their size in comparison to the remaining digits in the NDC number or put them in bold type. For example, xxxx-**XXXX**-xx.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Nocdurna (desmopressin acetate) received on March 9, 2018 from Ferring Pharmaceuticals.

Table 2. Relevant Product Information for Nocdurna (desmopressin acetate)	
Initial Approval Date	N/A
Active Ingredient	Desmopressin acetate
Indication	Treatment of nocturia due to nocturnal polyuria in adults who awaken two or more times each night to void
Route of Administration	sublingual ^c
Dosage Form	tablet
Strength	27.7 mcg, 55.3 mcg ^d
Dose and Frequency	(women) 27.7 mcg sublingually 1 hour before bedtime every evening without water; (men) 55.3 mcg sublingually 1 hour before bedtime every evening without water
How Supplied	Unit dose blister carton of 30 (3 x 10 count blisters); (b) (4))
Storage	(b) (4) excursions permitted to 15°C to 30°C (59°F to 86°F). Keep in original package to protect from moisture and light. Use immediately upon opening individual blister.

^c The Applicant referred to their product as an ‘orally disintegrating sublingual tablet’ in their submission. However, in preliminary discussion with the Office of Pharmaceutical Quality (OPQ), they have determined that the dosage form for this product is a ‘sublingual tablet’.

^d (b) (4) mcg of desmopressin acetate is equivalent to 25 mcg desmopressin and (b) (4) mcg of desmopressin acetate is equivalent to 50 mcg desmopressin per preliminary discussions with the Office of Pharmaceutical Quality (OPQ).

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 30, 2018, we searched DMEPA's previous reviews using the terms, Nocdurna. Our search identified four previous reviews^{efgh}, and we confirmed that our previous recommendations were implemented or considered.

^e Toombs, L. Label and Labeling Review for Nocdurna, NDA 022517. 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): 2010 Apr 15. OSE No.: 2009-1554.

^f Vee SK. Label, Labeling, and Packaging Review for Nocdurna, NDA 022517. 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): 2012 Dec 06. OSE No.: 2012-1748.

^g Vee SK. Label and Labeling Memo for Nocdurna, NDA 022517. 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): 2012 Dec 06. OSE No.: 2012-1748-1

^h Vee SK. Label and Labeling Review for Nocdurna, NDA 022517. 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): 2014 Nov 10. OSE No.: 2014-1544

APPENDIX F. Information Request sent to applicant April 30, 2018

2 DMEPA

Question 2a:

(b) (4)

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Response to Question 2a:

(b) (4)

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Question 2b:

We acknowledge receipt of the 10 count trade blister labels submitted March 9, 2018. However, we note that only 2 of the 10 spaces are completed for our review. Re-submit the 10-count trade blister label graphic with all of the information you intend to include on the label.

Response to Question 2b:

Please see attached the revised mock-up labeling for 30 count (3 x 10 tablets) for both configurations: 25 mcg and 50 mcg in [Appendix 5](#) and [Appendix 6](#), respectively.

Question 2c:

Please forward 3 samples of your to be marketed blister labels for our review and comments.

Response to Question 2c:

At this time, we are not able to provide representative samples for the (b) (4) count blisters as manufacturing of the intended commercial package has not been completed. In the interim, for illustration we are providing the Agency with available placebo blisters, which have been over-labeled with the current blister labels for the drug product, NOCDURNA 25 mcg and NOCDURNA 50 mcg.

Representative blister samples (3 each for both the strengths- 25 mcg and 50 mcg) for the following configurations have been shipped to the FDA (FedEx Tracking No. 7721 8110 4209):

Product Code	NDC	Component
6424-02	55566-5050-0	25 mcg TRADE Blister - 10 Tablets x 3(30-count)0
6425-02	55566-5051-0	50 mcg TRADE Blister – 10 Tablets x 3 (30-count)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

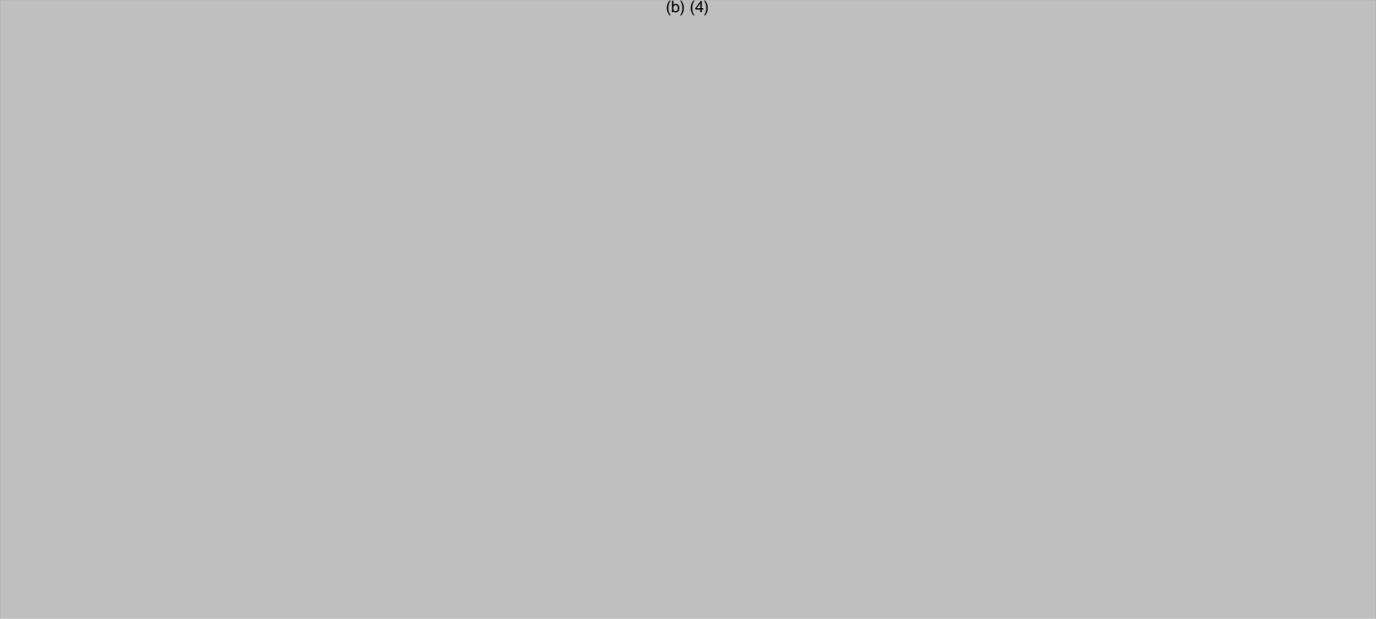
Using the principles of human factors and Failure Mode and Effects Analysis,ⁱ along with post-market medication error data, we reviewed the following Nocurna labels and labeling submitted by Ferring Pharmaceuticals.

- Blister label (b) (4) count and 10 count) received on March 9, 2018 and May 9, 2018
- Carton labeling (b) (4)] and 30 count [two 10 count blisters]) received on March 9, 2018 and May 9, 2018
- Professional Sample Blister label (b) (4) count) received on March 9, 2018
- Professional Sample Carton Labeling (b) (4)]) received on March 9, 2018 and May 9, 2018
- Medication Guide received on December 21, 2017
- Prescribing Information (Image not shown) received on December 21, 2017

G.2 Label and Labeling Images

25 mcg TRADE Blister – 10 count

(b) (4)



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

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/s/

DENISE V BAUGH
06/07/2018

LOLITA G WHITE
06/08/2018

**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: May 21, 2018

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: Aman Sarai, BSN, RN
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)

Drug Name (established name): NOCDURNA (demospressin acetate)

Dosage Form and Route: Sublingual Tablets

Application Type/Number: 22517

Applicant: Ferring Pharmaceuticals

1 INTRODUCTION

On December 21, 2017, Ferring Pharmaceuticals resubmitted for the Agency's review a New Drug Application for NOCDURNA (desmopressin acetate) orally disintegrating sublingual tablets 25mcg and 50mcg. Reference is made to the New Drug Application for NOCDURNA dated June 19, 2009. Additionally, the application was resubmitted on July 30, 2012 which included additional confirmatory phase 3 studies. Additional reference is also made to the Complete Response letter dated January 30, 2015 and the minutes from the October 19, 2017 Type C meeting minutes where additional analysis and resubmission were agreed to with the Agency.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Bone, Reproductive and Urologic Products (DBRUP) on May 15, 2018 and March 13, 2018 respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for NOCDURNA (desmopressin acetate) sublingual tablets.

2 MATERIAL REVIEWED

- Draft NOCDURNA (desmopressin acetate) MG received on December 21, 2017 and received by DMPP and OPDP on May 11, 2018.
- Draft NOCDURNA (desmopressin acetate) Prescribing Information (PI) received on December 21, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 11, 2018.
- Approved NOCTIVA (desmopressin acetate) nasal spray comparator labeling dated March 3, 2017.

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. In our review of the MG the target reading level is at or below an 8th grade 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.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

- rearranged information due to conversion of the PI to Physicians Labeling Rule (PLR) format
- removed unnecessary or redundant information
- ensured that the MG is 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 meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is 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 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.

Please let us know if you have any questions.

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/s/

AMANPREET K SARAI
05/21/2018

MARCIA B WILLIAMS
05/21/2018

JINA KWAK
05/21/2018

LASHAWN M GRIFFITHS
05/21/2018

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

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

Memorandum

Date: May 14, 2018

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

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

CC: Matthew Falter, PharmD, Team Leader, OPDP

Subject: **NDA 22517**
OPDP labeling comments for NOCDURNA® (desmopressin acetate) sublingual tablets

In response to DBRUP consult request dated March 13, 2018, OPDP has reviewed the proposed product labeling (PI), Medication Guide and carton and container labeling for NOCDURNA® (desmopressin acetate) sublingual tablets.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI accessed from SharePoint on May 11, 2018, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 9, 2018 and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Jina Kwak: 301-796-4809; Jina.Kwak@fda.hhs.gov

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/s/

JINA KWAK
05/14/2018

CLINICAL OUTCOME ASSESSMENT CONSULT REVIEW

CLINICAL OUTCOME ASSESSMENT (COA) TRACKING NUMBER IND/NDA/BLA NUMBER	AT 2015-208 NDA 22517
LETTER DATE/SUBMISSION NUMBER PDUFA GOAL DATE DATE OF CONSULT REQUEST	SDN 38 December 1, 2015
REVIEW DIVISION MEDICAL REVIEWER REVIEW DIVISION PM	Division of Bone, Reproductive and Urologic Products (DBRUP) Roger Wiederhorn, M.D. Nenita Crisostomo
PRIMARY COA REVIEWER SECONDARY COA REVIEWER ASSOCIATE DIRECTOR, COA STAFF (ACTING)	Sarrit M. Kovacs, Ph.D. Selena Daniels, Pharm.D., M.S. Elektra Papadopoulos, M.D., M.P.H.
REVIEW COMPLETION DATE	February 10, 2016
ESTABLISHED NAME TRADE NAME SPONSOR	Desmopressin orally disintegrating tablets Nocdurna Ferring Pharmaceuticals, Inc.
CLINICAL OUTCOME ASSESSMENT TYPE	Patient-reported outcome (PRO)
ENDPOINT(S) CONCEPT(S) MEASURE(S) INDICATION INTENDED POPULATION(S)	Impacts of nocturia Nocturia Impact (NI) Diary Treatment of nocturia due to nocturnal polyuria in adults who awaken two or more times each night to void Adult men and women (≥ 18 years of age) with nocturia due to nocturnal polyuria who awaken two or more times each night to void

Clinical Outcome Assessment Review

Sarrit M. Kovacs, Ph.D.

NDA 22517

Nocturna/desmopressin

Nocturia Impact (NI) Diary

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 22517. The sponsor has asked for guidance from the FDA regarding their proposed plans to “further validate” the patient-reported outcome (PRO), the Nocturia Impact (NI) Diary total score in connection with a future phase 2/3 trial. The sponsor proposes the NI Diary total score as a measurement of the impacts of nocturia for use in adult patients with nocturia due to nocturnal polyuria who awaken two or more times each night to void.

A previous review by COA Staff for this NDA (AT 2015-082; Kovacs) stated the following to be conveyed to the sponsor (the Division summarized these comments in their preliminary comments to the sponsor):

- *As a total score, the NI Diary is broad in its inclusion of a number of feelings and problems, and it is unclear which items may be contributing most to the total score. Some items (e.g., difficulty concentrating) may be more indicative of treatment benefit than other items (e.g., worry, concern).*
- *It would be risky to proceed with including the total score as a key secondary efficacy endpoint given that there are some items that are not expected to be sensitive to treatment effects.*
- *The NI Diary’s ability to detect clinically meaningful change has not yet been established.*
- *It is recommended to include 1) a patient global impression of disease severity (current status, not requiring recall to a previous time point), 2) a patient global impression of change, and 3) the change from baseline in overall NI Diary impact question, as supportive exploratory endpoints to serve as anchor measures in anchor-based method analyses for establishing a clinically meaningful responder definition for the NI Diary total score.*

The Division added the following to their preliminary comments to the sponsor:

“You could minimize your overall risk related to these concerns by conducting further psychometric evaluation of NI Diary items and domains in Phase 2 trials.”

A copy of the final version of the NI Diary from the NI Diary’s development and validation article¹ is included in Appendix A. A copy of the NI Diary that was used in the sponsor’s IMPACT Study 000034 (double-blind, placebo-controlled, randomized, fixed-dose small-sample study) is included in Appendix B. The Patient Global Impression of Improvement (PGI-I) and

¹Holm-Larsen T, Andersson F, van der Meulen E, Yankov V, Rosen RC, Nørgaard JP. The Nocturia Impact Diary: a self-reported impact measure to complement the voiding diary. Value Health. 2014 Sep;17(6):696-706.

Clinical Outcome Assessment Review

Sarrit M. Kovacs, Ph.D.

NDA 22517

Nocturna/desmopressin

Nocturia Impact (NI) Diary

Patient Global Impression of Severity (PGI-S) scales are included in Appendices C and D, respectively.

It is important to note that the two versions are not identical. There are three discrepancies between the two versions of the NI Diary:

1. The final version of Item 8 includes the word “tripping or” before the word “falling”; however, “tripping or” was not included in the version used in the IMPACT Study.
2. The final version of Item 11 includes the word “overnight” as the last word in the item; however, that word was not included in the version used in the IMPACT Study.
3. The final version of Item 12 includes the word “presently” before the word “impact”; however “presently” was not included in the version used in the IMPACT Study.

Given that the developers included the three aforementioned revisions when finalizing the NI Diary, based on qualitative research with patients, we recommend that the final version of the NI Diary be included in the proposed 3-month study rather than the version used in the IMPACT Study. While the sponsor’s study objectives for psychometric evaluation are consistent with the Agency’s expectations, the sponsor should provide more information concerning the psychometric evaluation study (e.g., study timing, study design, study sample size) before the Agency can conclude that their proposed analyses are sufficient.

B. SUGGESTED COMMENTS TO SPONSOR

Please find our suggested comments to the sponsor’s questions below:

FDA general comments to the sponsor regarding their proposed 3-month trial to examine the NI Diary’s psychometric performance:

Based on qualitative research with patients, you made revisions to three items in the NI Diary (Items 8, 11, and 12). We strongly recommend that the final version of the NI Diary, which includes those three revised items, be included in the proposed psychometric evaluation study, rather than including the version that was used in the IMPACT Study. You should submit for our review the final version of the NI Diary that you plan to include in the proposed psychometric evaluation study.

[Internal post-sponsor meeting comments: Ferring confirmed that they will use the final version of the NI Diary and submitted to FDA before the meeting. Ferring stated that they are leaning towards evaluating the NI Diary in a phase 2 trial moving forward.]

Sponsor’s Question 1:

“Does the FDA agree to the two NI Diary-related objectives:

- To assess reliability and validity of the NI Diary.
- To assess the clinical importance of treatment effect on change in NI Diary Total Score.

Clinical Outcome Assessment Review

Sarrit M. Kovacs, Ph.D.

NDA 22517

Nocturna/desmopressin

Nocturia Impact (NI) Diary

and would the FDA consider the described analyses sufficient for final psychometric validation of NI Diary and for establishment of a MCID?”

FDA Response to Question 1:

No, we do not agree. While your study objectives for psychometric evaluation are consistent with our expectations, we require more information concerning the psychometric evaluation study (e.g., study timing, study design, study sample size) before we can conclude that your proposed analyses are sufficient.

We have the following comments and recommendations in regard to your analysis plan for final psychometric validation and establishment of an MCID:

- **You should carefully consider the primary time point for conducting the co-primary analysis. You should select a time point in which you expect peak efficacy as measured by the NI Diary total score in order to appropriately determine the clinically meaningful threshold. You may wish to consider performing secondary analyses using other time points in order to learn more about your instrument and the timing of benefit.**
- **We recommend time frames shorter than one month to assess test-retest reliability (e.g., 7 to 10 days between the two assessments). You should ensure that patients are stable in order to conduct a proper analysis of test-retest reliability. You should provide clear rationale for the assumptions used when defining your analysis population for test-retest reliability.**

[Internal post-sponsor meeting comments: Ferring clarified that they intend to analyze stable patients between the two time points, defining “stable” patients as those having the same number of voids at multiple time points. The Division advised Ferring to provide a definition of what constitutes “stable” in terms of nocturnal voids (e.g., fixed number of voids, average number of voids over the measured time period, range of number of voids, etc.) along with a justification for this definition. Ferring stated they would define their analysis population (i.e., stable patients) for test-retest reliability in their statistical analysis plan (SAP).]

- **You should conduct analyses to evaluate other measurement properties of the NI Diary, including known groups validity (e.g., examine the ability of the NI Diary to distinguish among pre-specified nocturia severity groups) and concurrent validity (e.g., examine the convergent and discriminant validity of the NI Diary Total Score with other relevant/related measures in your trial).**
- **In addition to your proposed analyses to establish a response definition for the NI Diary total score, we recommend that you evaluate responsiveness using cumulative distribution function (CDF) curves, as follows:**
 - a. **A CDF plot of NI Diary (total score) change scores from baseline to Month 3 with separate curves for treatment versus placebo arms**

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- b. A CDF plot of NI Diary (total score) change scores from baseline to Month 3 for all patients (treatment and placebo arms pooled) with separate curves for each PGI-I response option at Month 3
 - c. A CDF plot of NI Diary (total score) change scores from baseline to Month 3 for all patients (treatment and placebo arms pooled) with separate curves for each score change in PGI-S scores between baseline and Month 3 (e.g., +3 points change, +2 points change, +1 point change, 0 point change, -1 point change, -2 points change, -3 point change, etc.)
 - d. A CDF plot of NI Diary (total score) change scores from baseline to Month 3 for all patients (treatment and placebo arms pooled) with separate curves for each score change in NI Diary overall impact score between baseline and Month 3 (e.g., +3 points change, +2 points change, +1 point change, 0 point change, -1 point change, -2 points change, -3 point change, etc.)
- Your proposed ROC analyses are considered exploratory and secondary to the anchor-based method and CDF analyses in determining a clinically meaningful change in the NI Diary total score. At this stage of development, we recommend using the anchor-based approach and CDF plots to help guide you in determining a clinically meaningful threshold. Multiple anchors should be explored to support the threshold.
 - At minimum, you should interview patients at study exit to assess their perception of what constitutes a clinically meaningful change from baseline in NI Diary total score. Optimally, patients would be interviewed at the beginning, middle and end of the trial.

[Internal post-sponsor meeting comments: Ferring clarified that exit interviews are performed at set times in person, but if not available, telephone interviews are conducted by trained interviewers. The Division stated that ideally, exit interviews should be completed in person, by a trained interviewer, with all patients undergoing interview at the end of treatment visit. However, telephone interviews may be acceptable if conducted by a trained interviewer. The Division requested Ferring to submit an exit interview guide for FDA review and comment. Regarding Bullet #2, the Division reminded Ferring to ensure that the patient population for the exit interviews include patients with a broad range of nocturia severity and other relevant demographics (responder definition and status will be unknown at the time of the interview) to provide robust data to help supplement anchor-based and CDF methods to determine a clinically meaningful threshold and generate a responder definition. The Division expressed concern that 20 patients may not be sufficient for this purpose, and further explained that the appropriate sample size would depend on appropriate diversity of the sample participants and consistency of response.]

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- **You should provide the schedule of study assessments and the order of questionnaire administration at the time of assessment. It is important that you specify at what time points (e.g., study visits) patients will complete the NI Diary, PGI-I, and PGI-S. We recommend that the NI Diary and PGI-S be completed at the same time points and that the PGI-I and PGI-S are administered to patients after they complete the NI Diary (e.g., that the anchors are measured after all other COAs).**
- **You should examine the performance of individual items to ensure that no one item, or few items, is driving the total score. We agree with your proposal to confirm the unidimensionality of the NI Diary and also encourage you to explore potential domains.**
- **For regulatory purposes, we are more interested in what constitutes a clinically meaningful change in your scale versus what is a “minimally” clinically meaningful difference (i.e., MCID). We recommend that you consider a clinically meaningful threshold to define treatment success, and reach agreement with the Agency on this threshold. Additionally, you will need to provide a justification for this threshold. You have proposed to include three anchor measures (PGI-I, PGI-S, and NI Diary overall impact score) to determine a clinically meaningful change in the NI Diary total score from baseline. Please confirm that “the three diaries before the End-of-Trial Visit” that you plan to use for these analyses are in fact the diaries from three consecutive days immediately prior to the final visit. Please also confirm that the three consecutive diaries before the baseline visit will be used to analyze change-from-baseline scores for the PGIS and the NI Diary overall impact score anchor measures.**

[Internal post-sponsor meeting comments: Ferring agreed to collect the data for the three anchors (PGI-I, PGI-S, and NI Diary overall impact score) at the same time points as the NI Diary, e.g., at three consecutive days prior to baseline and each endpoint visit. They plan to do the anchor analysis on PGI-I and PGI-S both using the 3-day average but also using each day separately (to maintain the simplicity and the straight forward interpretation of the scales). The Division stated that the SAP requires further detail (e.g., handling missing data, how data will be combined and which pairs of data will be used [e.g., -3 day NI Diary data at baseline compared with -3 day NI Diary data at end of treatment time point]). Ferring will provide a more detailed SAP for FDA review and comment. The Division noted that PGI-I data becomes less reliable as you move farther away from baseline to later time points, due to patients having to recall longer periods of time. The Division also recommended that Ferring should analyze the NI Diary data using both raw scores and transformed (0 to 100) scores, as raw scores may be more useful.]

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- **You should provide a more detailed statistical analysis plan, including your scoring algorithm and plans for analysis of the NI Diary data.**
[Internal COA Staff comment: We defer to OB for final determination of whether the sponsor's plan and our proposed additional analyses are adequate.]
- **Ultimately, the adequacy of a COA is a review issue. The results of the described analyses may lead to additional questions about the psychometric validity of the NI Diary and additional considerations about what constitutes a clinically meaningful change.**

Sponsor's Question 2:

"Does the FDA accept the proposed split into different classes of response for the 3 anchors?"

FDA Response to Question 2:

At this stage of development, it is premature to define responder categories because the responder definition is unknown. Instead, we recommend that you define your clinical responder (anchor) groups based on the following changes (see below) and then analyze your data to determine what constitutes a clinically meaningful change:

- **Marked improvement : ≥ 2 -point decrease**
- **Minimal improvement: 1-point decrease**
- **No Change: same score as baseline**
- **Worsening: ≥ 1 -point increase *or* decrease, depending on anchor measure scoring**

The above recommendation may be useful for scores with simple categorical responses. If the average of 3 days of categorical responses will be used, the set of definitions should take the continuous nature of the data into account (e.g., the change in the 3 day average may be 1.7). Analyses that focus more on how to define or validate previous definitions of a responder may be more appropriate at this stage of instrument development. Regardless, the use of only three classes of response (responder, stable, non-responder) appears to be premature at this time.

Because the PGI-I has a balanced response scale (e.g., an equal number of favorable and unfavorable response choices), you should consider recoding the response options from +3 to -3 rather than the current codes of 0 to 6. For instance, the middle response option of "no change" would be coded as a "0."

[Internal COA Staff comment: We defer to OB for final determination of whether the sponsor's plan is adequate.]

In regard to the "normal" response item for the PGI-S ("Check the one number that best describes how your urinary symptoms are now on a 4-point scale as: "normal" [1], "mild" [2], "moderate" [3], or "severe" [4]), we have the following concerns:

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- “Normal” may be misinterpreted at baseline. A patient may erroneously choose the response item “normal” because his “severe” symptoms are “normal” for him.
- “Normal” may adversely affect the assessment of change in severity over time. A patient who erroneously assumes that “normal” means the current state of his symptoms may have difficulty choosing the appropriate response option in post-baseline PGI-S assessments.
- Most PGI-S measures use “none” for the least severe response option.

For these reasons, you should consider changing “normal” to “none” for the PGI-S scale.

[Internal post-sponsor meeting comments: Ferring requested clarification on the acceptability of their proposed anchor measures, PGI-I and PGI-S, due to the circulation of numerous versions. The Division stated their residual concerns regarding some language in the proposed PGI-I and PGI-S anchors, including the terms “urinary tract” and “normal,” which may not be defined the same way by all patients. The Division expressed concern that “normal” is subject to misinterpretation and “urinary tract” is highly technical and not quite clear. The Division requested that Ferring submit a proposal that would address this concern. The Division encouraged Ferring to research the literature for different potential versions of the PGI-I and PGI-S.]

The Division added that Phase 2 represents an opportune time to explore and test a variety of endpoints and measures, including new or modified anchor measures. Ferring expressed their understanding that the anchor measures need to be well understood and relevant to patients. Ferring asked the following question: “Considering the validity of the PGI-I and PGI-S scales is well-documented in the literature, would the Agency require additional qualitative research if Ferring modified the anchor measures, for example, if Ferring changed ‘normal’ to ‘none’, and revised ‘urinary tract’? If so, would this research need to be conducted prior to the Phase 2 study?”

The Division responded that additional qualitative research is not necessary and that Ferring should explore the existing qualitative data to determine what words and what terms patients use to refer to their condition. The Division reiterated that the proposed anchor measures are acceptable; however, Ferring should consider utilizing their Phase 2 trial as an opportunity to test additional anchor measures that may be better and more effective in Phase 3. Ferring expressed their understanding and will incorporate the FDA’s recommendations.]

Sponsor’s Question 3:

“Does the FDA agree with using all data, without adjustment for treatment, in analyzing the reliability of the NI Diary?”

FDA Response to Question 3:

We recommend analyzing the data in several ways: pooled and by each separate treatment arm (treatment, placebo).

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[Internal COA Staff comment: We defer to DBRUP and OB to tailor recommendations depending on whether this will be a phase 2 or 3 trial.]

Sponsor's Question 4:

“Does the FDA consider a cross-sectional analysis of the NI Diary Total Score at Month 3, as coprimary analysis in a Phase 3 trial, appropriate considering efficacy in voids will be evaluated using a repeated measures model to take the longitudinal effect into account?”

FDA Response to Question 4:

We need more details concerning your proposed cross-sectional analysis of the NI Diary Total Score at Month 3. We remind you that longitudinal information is typically of higher relevance than analysis at a single time point.

[Internal COA Staff comment: We defer to DBRUP and OB.]

Sponsor's Question 5:

“Does the FDA accept the proposed sensitivity analyses to address missing data?”

FDA Response to Question 5:

[Internal COA Staff comment: We defer to DBRUP and OB.]

Sponsor's Question 6:

Given that the suggested validation and establishment of a MCID can be achieved in a phase 2 study, as co-primary endpoint in conjunction with mean change in nocturnal voids, would the agency prefer to see:

a) Change from Baseline in NI Diary Total Score at Month 3?

or

b) NI Diary Responders, defined as subjects achieving the MCID, at Month 3?”

FDA Response to Question 6:

[Internal COA Staff comment: We defer to DBRUP.]

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C. CLINICAL OUTCOME ASSESSMENT REVIEW

Materials reviewed:

- Minutes from September 2015 sponsor meeting
- Most recent previous COA Staff review (AT 2015-082; Kovacs)
- Sponsor's Type A meeting briefing document (Dated December 10, 2015)
- Sponsor's synopsis of statistical analysis related to the Nocturia Impact Diary document (Appendix 6.1 to the sponsor's December 10, 2015 briefing document)

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APPENDIX A –NOCTURIA IMPACT (NI) DIARY FROM HOLM-LARSEN ET AL., 2014 PAPER

(Copy obtained from Supplemental Materials linked to Holm-Larsen et al., 2014 paper website: <http://www.sciencedirect.com/science/article/pii/S1098301514018919>)

NOCTURIA IMPACT DIARY[®]

This nocturia (getting up to void at night) diary will assess the daily impact of nocturia on your everyday life. Please answer the questions in the late afternoon or evening and use the scale from 'not at all' to 'a great deal':

Thinking over the day, to what extent...	0) Not at all	1) Slightly	2) Moderately	3) Quite a bit	4) A great deal
1) Was it difficult to concentrate?	0) ____	1) ____	2) ____	3) ____	4) ____
2) Did you feel low in energy and/or tired?	0) ____	1) ____	2) ____	3) ____	4) ____
3) Were you unable to be productive at work or complete your personal, daily activities?	0) ____	1) ____	2) ____	3) ____	4) ____
4) Did you avoid participating in activities that you enjoy?	0) ____	1) ____	2) ____	3) ____	4) ____
5) Did you feel irritable or moody?	0) ____	1) ____	2) ____	3) ____	4) ____
6) Did you limit your fluid intake?	0) ____	1) ____	2) ____	3) ____	4) ____
Thinking about last night, to what extent					
	0) Not at all	1) Slightly	2) Moderately	3) Quite a bit	4) A great deal
7) Did you lie awake without being able to return to sleep after getting up to use the bathroom at night?	0) ____	1) ____	2) ____	3) ____	4) ____
8) Were you worried about tripping or falling?	0) ____	1) ____	2) ____	3) ____	4) ____
9) Did you feel you got too little sleep?	0) ____	1) ____	2) ____	3) ____	4) ____
Overall, to what extent...					
	0) Not at all	1) Slightly	2) Moderately	3) Quite a bit	4) A great deal
10) Do you worry that the nocturia will get worse in the future?	0) ____	1) ____	2) ____	3) ____	4) ____
11) Are you concerned with where the bathroom is when away from home overnight?	0) ____	1) ____	2) ____	3) ____	4) ____
12) Does nocturia presently impact your life?	0) ____	1) ____	2) ____	3) ____	4) ____

Nocturia Impact Diary[®] is protected by international copyright / copyright registration, with all rights reserved to Ferring Pharmaceuticals A/S. Do not use without permission. For information on, or permission to use Nocturia Impact Diary[®], please contact MAPI Research Trust.

NID - United States/English - MAPI Institute.
ID7222 / Ni-Diary_AU2.0_eng-US01.doc

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APPENDIX B – VERSION OF NI DIARY USED IN IMPACT STUDY 000034

Day 2 Day-Time		
Protocol: FE992026 000034	A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY, INVESTIGATING THE IMPACT BURDEN OF NOCTURIA USING THE NOCTURIA IMPACT DIARY	
Screening #:	Subject #:	Module/Tab: DIARY

DAY 2 DAY-TIME (DIARY)

SCREENING(COLLECTED AT VISIT 2) (DAY 2 DAY-TIME)

Not Done, please provide an explanation:

Time You Woke Up	<input type="text"/> (24-hour clock, hhmm)
Time of completion	<input type="text"/> (24-hour clock, hhmm)

Nocturia Impact Diary Afternoon/Evening	
This nocturia (getting up to void at night) diary will assess the daily impact of nocturia on your everyday life. Please answer the questions in the late afternoon or evening and use the scale from 'not at all' to 'a great deal':	
Thinking over the day, to what extent...	
1. Was it difficult to concentrate?	<input type="radio"/> Not at all <input type="radio"/> Slightly <input type="radio"/> Moderately <input type="radio"/> Quite a bit <input type="radio"/> A great deal
2. Did you feel low in energy and/or tired?	<input type="radio"/> Not at all <input type="radio"/> Slightly <input type="radio"/> Moderately <input type="radio"/> Quite a bit <input type="radio"/> A great deal
3. Were you unable to be productive at work or complete your personal, daily activities?	<input type="radio"/> Not at all <input type="radio"/> Slightly <input type="radio"/> Moderately <input type="radio"/> Quite a bit <input type="radio"/> A great deal
4. Did you avoid participating in activities that you enjoy?	<input type="radio"/> Not at all <input type="radio"/> Slightly <input type="radio"/> Moderately <input type="radio"/> Quite a bit <input type="radio"/> A great deal
5. Did you feel irritable or moody?	<input type="radio"/> Not at all <input type="radio"/> Slightly <input type="radio"/> Moderately <input type="radio"/> Quite a bit <input type="radio"/> A great deal
6. Did you limit your fluid intake?	<input type="radio"/> Not at all <input type="radio"/> Slightly <input type="radio"/> Moderately <input type="radio"/> Quite a bit <input type="radio"/> A great deal
Thinking about last night, to what extent...	
7. Did you lay awake without being able to return to sleep after getting up to use the bathroom at night?	<input type="radio"/> Not at all <input type="radio"/> Slightly <input type="radio"/> Moderately <input type="radio"/> Quite a bit

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	<input type="radio"/> A great deal
8. Were you worried about falling?	<input type="radio"/> Not at all <input type="radio"/> Slightly <input type="radio"/> Moderately <input type="radio"/> Quite a bit <input type="radio"/> A great deal
Overall, to what extent...	
9. Did you feel you got too little sleep?	<input type="radio"/> Not at all <input type="radio"/> Slightly <input type="radio"/> Moderately <input type="radio"/> Quite a bit <input type="radio"/> A great deal
10. Do you worry that the nocturia will get worse in the future?	<input type="radio"/> Not at all <input type="radio"/> Slightly <input type="radio"/> Moderately <input type="radio"/> Quite a bit <input type="radio"/> A great deal
11. Are you concerned with where the bathroom is when away from home?	<input type="radio"/> Not at all <input type="radio"/> Slightly <input type="radio"/> Moderately <input type="radio"/> Quite a bit <input type="radio"/> A great deal
12. Does nocturia impact your life?	<input type="radio"/> Not at all <input type="radio"/> Slightly <input type="radio"/> Moderately <input type="radio"/> Quite a bit <input type="radio"/> A great deal

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**APPENDIX C - PATIENT GLOBAL IMPRESSION OF IMPROVEMENT
(PGI-I) SCALE**

Table I. Patient Global Impression of Improvement
(PGI-I) Scale

Check the one number that best describes how your urinary tract condition is now, compared with how it was before you began taking medication in this study.

1. Very much better
 2. Much better
 3. A little better
 4. No change
 5. A little worse
 6. Much worse
 7. Very much worse
-

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**APPENDIX D - PATIENT GLOBAL IMPRESSION OF SEVERITY (PGI-S)
SCALE**

Table II. Patient Global Impression of Severity (PGI-S)
Scale

Check the one number that best describes how your urinary tract condition is now.

1. Normal
 2. Mild
 3. Moderate
 4. Severe
-

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/s/

SARRIT M KOVACS
02/10/2016

SELENA R DANIELS
02/10/2016

ELEKTRA J PAPADOPOULOS
02/20/2016

CLINICAL OUTCOME ASSESSMENT CONSULT REVIEW

CLINICAL OUTCOME ASSESSMENT (COA) TRACKING NUMBER	AT 2015-082
IND/NDA/BLA NUMBER	NDA 22517
LETTER DATE/SUBMISSION NUMBER	SDN 35
PDUFA GOAL DATE	
DATE OF CONSULT REQUEST	May 28, 2015
REVIEW DIVISION	Division of Bone, Reproductive and Urologic Products (DBRUP)
MEDICAL REVIEWER	Roger Wiederhorn, M.D.
REVIEW DIVISION PM	Nenita Crisostomo
PRIMARY COA REVIEWER	Sarrit Kovacs, Ph.D.
SECONDARY COA REVIEWER	
ASSOCIATE DIRECTOR, COA STAFF (ACTING)	Elektra Papadopoulos, M.D., M.P.H.
REVIEW COMPLETION DATE	September 9, 2015
ESTABLISHED NAME	Nocturna
TRADE NAME	Desmopressin
APPLICANT	Ferring Pharmaceuticals, Inc.
CLINICAL OUTCOME ASSESSMENT TYPE	Patient-reported outcome (PRO)
ENDPOINT(S) CONCEPT(S)	Impacts of nocturia
MEASURE(S)	Nocturia Impact (NI) Diary
	(b) (4)
INDICATION	Treatment of nocturia due to nocturnal polyuria in adults who awaken two or more times each night to void
INTENDED POPULATION(S)	Adult men and women (≥ 18 years of age) with nocturia due to nocturnal polyuria who awaken two or more times each night to void
NOTE:	The information provided by the applicant for a full review of the instruments, other than for the NI Diary, was insufficient.

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/s/

SARRIT M KOVACS
09/09/2015

ELEKTRA J PAPADOPOULOS
09/13/2015

**CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA
DPP CONSULT # 11528**

Consultant Reviewer:	Paul J. Andreason, M.D. Medical Officer Division of Psychiatry Products
Consultation Requestor:	Nenita Crisostomo, Project Manager Division Of Bone, Reproductive and Urologic Products 301-796-0875
Subject of Request:	Type A Meeting Request /Meeting Package NDA 22-517
Date of Request:	27 May 2015
Desired Completion Date:	20 July 2015

I. Background

DPP was initially consulted on this NDA by the Division of Metabolic and Endocrine Products (DMEP). DMEP listed the following comments: Please provide clinical consultative (sleep) input to DMEP for the review of the July 31, 2014 resubmission (response to Complete Response letter dated January 30, 2013) in preparation for the Advisory Committee meeting scheduled for **January 12, 2015**.

On July 31, 2014, the sponsor, Ferring Pharmaceuticals, Inc., submitted a Complete Response resubmission (S-030) to NDA 22,517. Under this 505(b)(2) NDA, the sponsor is seeking an indication for the treatment of nocturia for their product, Nocurna (desmopressin) orally disintegrating tablets, 25 mcg and 100 mcg. This was the third review cycle for this application. On 12 January 2015 an Advisory Committee Meeting took place where a recommendation for a third Complete Response was made (non-approval).

Desmopressin is currently indicated for the treatment of central diabetes insipidus and primary nocturnal enuresis, and is available for injection, for administration via rhinal tube, and as oral tablets or nasal spray. Current labeling describes a dose range for adults and children from 0.05 mg to 1.2 mg daily, typically in divided doses, with an optimal dose range from 0.1 mg to 0.8 mg daily. Desmopressin is contraindicated in patients with moderate to severe renal impairment (defined as a creatinine clearance below 50ml/min), and in patients with hyponatremia or a history of hyponatremia. Its label includes warnings related to elevations in blood pressure and severe allergic reactions, as well as advice to monitor fluid intake. Associated adverse events include headache and abdominal pain.

NDA 22,517 was initially submitted in June, 2009. Three review cycles have resulted in Complete Response actions, each followed by End of Review meetings during which the sponsor attempted to identify a path forward for this products' development program. From a clinical perspective, FDA identified marginal efficacy at 50 and 75 mcg doses, but unacceptably high risk of hyponatremia at the more clearly effective dose of 100 mcg. The End of Review meeting minutes from the second review cycle (May, 2013) note several times that the placebo-subtracted difference is relatively small, the risk

of severe hyponatremia cannot be entirely eliminated in clinical practice, and that similar efficacy can be achieved with behavioral and lifestyle modifications at virtually no safety risk. The May, 2013 meeting minutes also state: The FDA said it would review any new sleep data that the applicant might have along with any relevant information from the literature that might support the clinical relevance of the improvement in sleep seen in patients treated with Nocodurna. However, such literature has to be specific to the situation seen in the clinical trial.

In February, 2014, FDA and Ferring discussed Ferring's Complete Response resubmission via teleconference. At that time, the FDA provided review questions for the sponsor to address in the resubmission.

Among those questions, FDA asked the sponsor to provide literature support for the expected clinical benefit of the placebo-subtracted increase in time to first awakening which was observed in the clinical trials, **as well as "other impacts on lifestyle or health"** that the sponsor could provide. The Division of Psychiatry Products (DPP) was consulted on September 19, 2014 to comment on the sponsor's responses to these questions.

The sponsor's third submission did not provide new clinical trial data. Rather, the sponsor provided post-hoc analyses of existing trial data in the context of selected literature, ostensibly contributing additional "benefit" considerations to the benefit-risk evaluation. In the Complete Response Resubmission, the sponsor made the argument that sleep disturbance was a major cause of the morbidity associated with nocturia, and that even 39-49 minutes (as observed in studies CS40 and CS41) of additional sleep prior to first awakening (first uninterrupted sleep period, FUSP) could be considered clinically relevant due to its association with normal duration and quality of sleep and increased protection of slow wave sleep (SWS).

The sponsor reached this conclusion by drawing data from several sources:

- Phase 3 trial CS29—In this study, the Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality. Higher scores on the PSQI indicate lower subjective sleep quality. Improvements in FUSP were associated with improvements in (i.e., lower) PSQI scores. A 60-minute increase in FUSP was associated with significant improvement in 6 of the 7 PSQI subscales. Thus, the sponsor suggests that increases in FUSP can be used to indicate deeper, longer, and better quality sleep.
- The sponsor also suggests that increases in FUSP can result in more SWS. SWS occurs predominantly in the first 3-4 hours of sleep; therefore, if an individual can sleep for a longer period of time early in the night, that person will experience more SWS.
- The sponsor goes on to cite evidence that sleep, and slow wave sleep (SWS) in particular, are associated with endocrine and metabolic processes, including changes in blood pressure, heart rate, growth hormone, cortisol, insulin sensitivity and glucose tolerance.

Thus, if Nocturna could increase FUSP, a patient might experience more SWS, and might, in turn, avoid or mitigate some of the physiologic consequences of chronic sleep disturbance. The sponsor asserted that “in about a third of nocturia episodes, bladder signaling awakens nocturia patients specifically during deep sleep, thus interrupting SWS directly.” This assertion was based on a study of 20 patients with benign prostatic hypertrophy. During that study, 14 patients experienced nocturia, with a total of 23 nocturia episodes. Seven of those episodes (30%) occurred during deep sleep (by polysomnography).

Previously DPP suggested that the sponsor might be overgeneralizing the results of this small study. The sponsor further referenced conference proceedings and a published abstract describing a study of 17 older Japanese adults using portable electroencephalography to assess sleep. Based on this data, the sponsor stated that waking for the first void within the first two sleep cycles was associated with a significantly shorter SWS sleep compared with those with FUSP duration of more than two sleep cycles.

Phase 3 trials CS40 and CS41—FUSP > 4 hours (i.e., longer than two sleep cycles) is associated with improvements in ratings of Nocturia related quality of life (N-QoL). Subjects who had a FUSP of <4 hours at baseline and FUSP consistently ≥ 4 hours at Month 1 and Month 3 had significantly better N-QoL scores compared with those who did not consistently experience a FUSP ≥ 4 hours during the trial ($p < 0.0001$). In addition, Nocturna-treated patients were 2.2 times more likely to have a FUSP ≥ 4 hours in CS40 and CS41.

With regard to presenting data on “other impacts on lifestyle or health,” the sponsor previously asserted that “The true clinical impact of nocturia is manifested by adverse effects on sleep and overall quality of life. Much of this impact is attributable to chronic sleep disruption. Relatively small reductions of nighttime voids, therefore, have significant and widespread impact on nocturia related morbidities.” To support this statement, the sponsor presented additional details related to the already noted physiologic consequences of chronic sleep disturbance, and the impact of nocturia on a number of factors related to quality of life.

The most recent FDA Complete Response Letter of January 30, 2015 (Reference ID: 3695148) to NDA 022517 FDA does not mention that the sponsor is required to document improvement in factors related to “quality of life”.

The sponsor requests this meeting in order to discuss the design of new phase three trials.

II. Specific Consultative Questions:

Division of Bone, Reproductive and Urologic Products (DBRUP), requested DPP presence at the End of Review Internal and Industry Meetings as requested by Ferring Pharmaceuticals, Inc. to discuss NDA 22517 NOCDURNA, post Complete Response action (CR on 1/30/15). The meeting request and the Meeting Information Package are submitted in EDR:\\CDSESUB1\evsprod\NDA022517\0032. DBRUP requests DPP input to questions 8, 9 and 10.

(b) (4)

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/s/

PAUL J ANDREASON
06/08/2015

JING ZHANG
06/08/2015

MITCHELL V Mathis
06/08/2015

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

Drug Utilization Review

Date: May 18, 2015

Reviewer: Justin Mathew, Pharm.D., Drug Use Data Analyst
Division of Epidemiology II (DEPI II)

Deputy Director
For Drug Utilization: Grace Chai, Pharm.D., LCDR USPHS
Division of Epidemiology II (DEPI II)

Director: Judy Staffa, Ph.D., R.Ph.
Division of Epidemiology II (DEPI II)

Drug Name(s): Nocurna (desmopressin)

Application Type/Number: 22517

Applicant/Sponsor: Ferring Pharmaceuticals INC

OSE RCM #: 2014-2631

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

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EXECUTIVE SUMMARY

This review analyzes the drug utilization patterns for oral and nasal formulations of desmopressin from year 2004 through 2013. These analyses were conducted in support of an advisory committee meeting held by Division of Metabolism and Endocrinology Products (DMEP) on January 12, 2015 to discuss the New Drug Application (NDA-22517) of Nocdurna[®] (desmopressin) oral disintegrating tablets (ODT).

In U.S. outpatient retail pharmacy settings, the nationally estimated number of patients who received a dispensed prescription for oral and nasal formulations of desmopressi (b) (4)

[REDACTED]

1 INTRODUCTION

1.1 BACKGROUND

The Division of Metabolism and Endocrinology Products (DMEP) conducted an advisory committee meeting on January 12, 2015 to discuss the New Drug Application (NDA-22517) of Nocdurna[®] (desmopressin) oral disintegrating tablets (ODT) submitted by Ferring Pharmaceuticals INC. Nocdurna[®] is intended for the treatment of nocturia due to nocturnal polyuria in adults who awaken two or more times each night to void.

If approved, Nocdurna[®] would be marketed as 25mg and 100mg strength oral disintegrating tablets. However, DMEP is concerned with the possibility of Nocdurna[®], at these strengths, causing hyponatremia especially in the elderly population of 65 years and older. In support of the advisory committee meeting, the Division of Epidemiology II was requested to provide the drug utilization patterns for currently marketed oral and nasal formulations of desmopressin with a focus on patients 65 years and older

1.1 PRODUCTS INCLUDED

Desmopressin is currently indicated for¹:

- Oral Formulation: Central diabetes insipidus; Primary nocturnal enuresis
 - Available Strengths: 0.1mg; 0.2mg

¹ Desmopressin: Drug Facts and Comparisons [online]. 2014. St. Louis, MO: Wolters Kluwer Health, Inc; Accessed January 22, 2015 <http://online.factsandcomparisons.com/Monodisp.aspx?monoid=fandc-hcp12480&book=DFC>

- Nasal Formulation: Central diabetes insipidus; Hemophilia A; von Willebrand disease; off-label use for nocturnal polyuria
 - Available Strengths: 0.01%; 0.1mg/mL; 1.5mg/mL
- Injection Formulation: Central diabetes insipidus; Hemophilia A; von Willebrand disease
 - Available Strengths: 4mcg/mL

The oral formulations (0.1mg and 0.2mg) and nasal formulations (0.01% and 0.1mg/mL) were included in this analysis of desmopressin for indication of primary nocturnal enuresis or off-label use of nocturnal polyuria. The injection formulation (4mcg/mL) was not included in this analysis since it is not indicated for primary enuresis while the nasal formulation with the strength of 1.5mg/mL is too large of a dose for off label use of nocturnal polyuria.

2 METHODS & MATERIALS

2.1 DETERMINING SETTINGS OF CARE

The IMS Health, IMS National Sales Perspective™ was used to determine the various retail and non-retail channels of distribution for desmopressin. Sales data for year 2013 indicated the (b)(4)

As a result, only outpatient retail pharmacy utilization patterns were examined in this review. Retail pharmacies include chain stores, independent pharmacies, and food store pharmacies. Non-retail and mail-order/specialty settings were not included in this analysis.

2.2 DATA SOURCES USED

Proprietary drug utilization databases were used to conduct this analysis (see Appendix 2 for full database description).

The IMS Health, Total Patient Tracker (TPT) was used to obtain the nationally estimated number of patients who received a dispensed prescription for oral and nasal formulations of desmopressin from U.S. outpatient retail pharmacies for January 2004 through December 2013.

The IMS Health, National Prescription Audit (NPA) was used to obtain the nationally estimated number of prescriptions dispensed for oral and nasal formulations of desmopressin stratified by patient age and prescriber specialty from U.S. outpatient retail pharmacies for 2013.

Diagnoses associated with the use of oral and nasal formulations of desmopressin based on office-based physician survey data in the U.S. were obtained from Encuity Research, LLC., Treatment Answers™ with Pain Panel database, for January 2004 through December 2013, aggregated.

3 RESULTS

3.1 PATIENT DATA

² IMS Health, National Prescription Audit (NPA). Year 2013. Extracted December 2014 File: IMS NSP, TPT, NPA 2014-2631_Desmopressin AC data.xlsx

Figure 1 and Table 1 in Appendix 1 provide the nationally estimated number of unique patients who received a dispensed prescription for oral and nasal formulations of desmopressin from U.S. outpatient retail pharmacies from 2004 through 2013, stratified by age. (b) (4)

Table 2 in Appendix 1 provides the nationally estimated number of unique patients who received a dispensed prescription for desmopressin, stratified by formulation and patient sex, among the 65 year and older population. In year 2013, (b) (4)

3.2 PRESCRIPTION DATA

Table 3 in Appendix 1 provides the top 10 physician specialties of prescriptions dispensed for oral and nasal formulations of desmopressin from U.S. outpatient retail pharmacies. During 2013, (b) (4)

3.3 DIAGNOSES DATA

Table 4 in Appendix 1 shows the diagnoses associated with the use of oral and nasal formulations of desmopressin, with a focus on patients aged 65 years and older, during the cumulative time period from January 2004 through December 2013. Diagnoses expressed in terms of *drug use mentions*³ were coded according to the International Classification of Diseases (ICD-9-CM) and 95% confidence intervals were calculated for the estimates.

(b) (4)

4 DISCUSSION

³ The term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

The overall findings from this review illustrate that the total use of oral and nasal desmopressin from outpatient retail settings (b) (4)

Findings from this review should be interpreted in the context of the known limitations of the databases used. Based on the IMS Health, IMS National Sales Perspectives™, sales data for year 2013 indicated that (b) (4)

. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer to various channels of distribution.

We focused our analyses on only the outpatient retail pharmacy settings, therefore these estimates may not apply to other settings of care, such as mail-order/specialty pharmacies, clinics, and hospitals, in which these products are used. The estimates provided are national estimates, but no statistical tests were performed to determine statistically significant changes over time or between products. Therefore, all changes over time or between products should be considered approximate, and may be due to random error.

Indications for use were obtained using a monthly survey of 3,200 office-based physicians. Although these data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, physician survey data are best used to identify the typical uses for the products in clinical practice, and outpatient prescription data are best used to evaluate utilization trends over time. Results should not be overstated when nationally projected estimates of annual uses or mentions fall below 100,000 as the sample size is very small with correspondingly large confidence intervals.

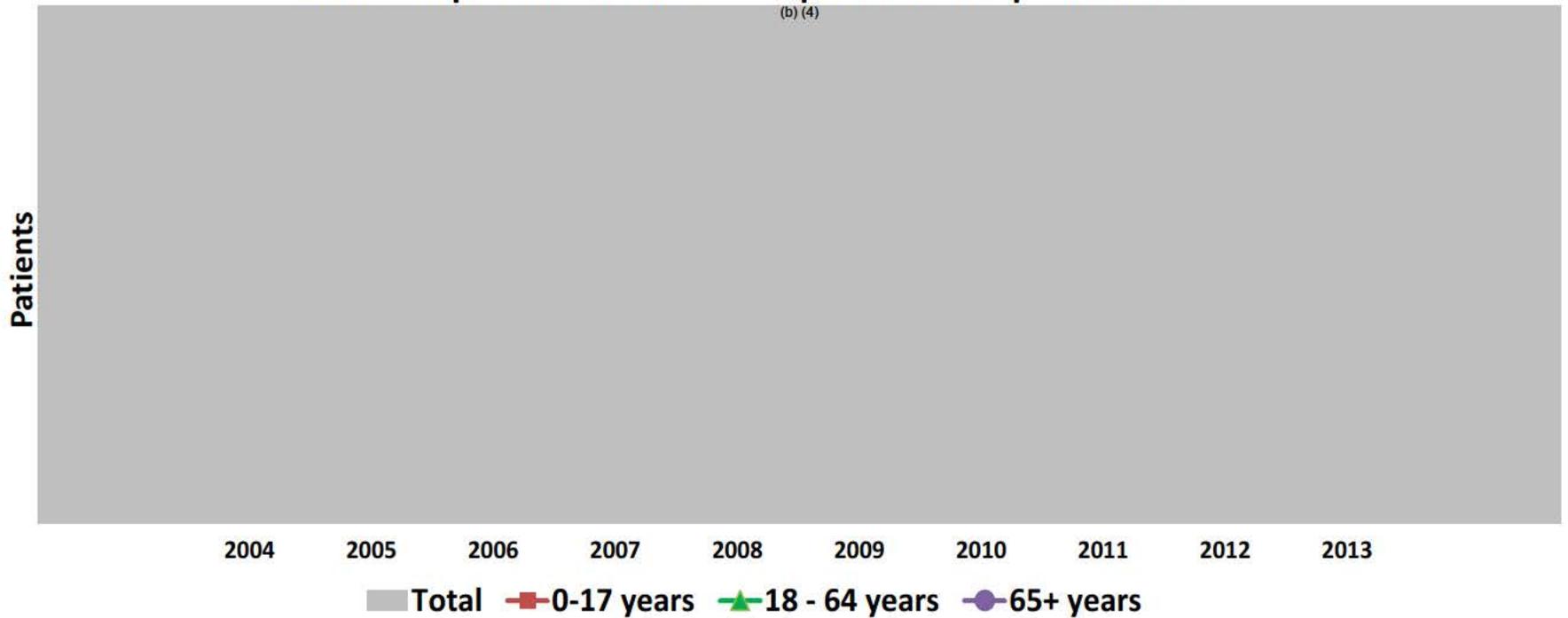
5 CONCLUSION

Overall, the use of desmopressin (b) (4)

APPENDIX 1: Figures & Tables.

Figure 1.

Nationally estimated number of patients who received a dispensed prescription for desmopressin* from U.S. outpatient retail pharmacies



* Desmopressin Included In Analysis: Oral Solids 0.1mg and 0.2mg and Nasal Spray 0.01mg or 10mcg

IMS Health: Total Patient Tracker (TPT). Jan. 2004 through Dec. 2013. Extracted Dec. 2014. File: 2014-2631 TPT Desmopressin AC..

Table 1

Nationally Estimated Number of Patients Who Received a Dispensed Prescription for Desmopressin* Statified by Patient Age, Dispensed Through U.S. Outpatient Retail Pharmacies, Years 2004-2013

	2004		2005		2006		2007		2008	
	Patients		Patients		Patients		Patients		Patients	
	(N)	%Share								
Desmopressin	(b) (4)									
0-17 years	(b) (4)									
18-64 years	(b) (4)									
65+ years	(b) (4)									
Unknown Age	(b) (4)									
	2009		2010		2011		2012		2013	
	Patients		Patients		Patients		Patients		Patients	
	(N)	%Share								
Desmopressin	(b) (4)									
0-17 years	(b) (4)									
18-64 years	(b) (4)									
65+ years	(b) (4)									
Unknown Age	(b) (4)									

Due to the possibility of double counting patients who are receiving treatments over multiple periods in the study, unique patient counts may not be added across age bands and time

* Desmopressin Included In Analysis: Oral Solids 0.1mg and 0.2mg and Nasal Spray 0.01mg or 10mcg

IMS Health: Total Patient Tracker (TPT). Jan. 2004 through Dec. 2013. Extracted Dec. 2014. File: IMS NSP, TPT, NPA 2014-2631_Desmopressin AC data.xlsx

TABLE 2.

**Nationally Estimated Number of Patients Aged 65+ Who Received a Dispensed Prescription for Desmopressin*
Stratified by Patient Sex and Product Formulation, From U.S. Outpatient Retail Pharmacies For Year 2013**

	Year 2013							
	Total		Male			Female		
	Patients (N)	%Share	Patients (N)	%Share	Horz. %Share	Patients (N)	%Share	Horz. %Share
Desmopressin*	(b) (4)							
Oral Formulation	(b) (4)							
Nasal Formulation	(b) (4)							

Due to the possibility of double counting patients who are receiving treatments over multiple periods in the study, unique patient counts may not be added across product formulations

* Desmopressin Included In Analysis: Oral Solids 0.1mg and 0.2mg and Nasal Spray 0.01mg or 10mcg

IMS Health: Total Patient Tracker (TPT). Jan. 2004 through Dec. 2013. Extracted Dec. 2014. File: IMS NSP ,TPT, NPA, 2014-2631 _Desmopressin AC data.xlsx

TABLE 3.

Prescribing Specialties By The Nationally Estimated Number of Prescriptions For Oral & Nasal Desmopressin Dispensed To Patients Aged 65+ Years From U.S. Outpatient Retail Pharmacies

	Year 2013	
	Total Rxs (N)	% Share
Patients 65+ Years: Oral and Nasal Desmopressin	(b) (4)	100.0%
(b) (4)	(b) (4)	(b) (4)
All Others	(b) (4)	(b) (4)

IMS Health: National Prescription Audit (NPA). Jan. 2013 through Dec. 2013. Extracted Dec. 2014. File: NPA Desmopressin AC data.xlsx

TABLE 4.

Top Diagnoses Associated with the Use of Oral and Nasal Desmopressin, Stratified by Patient Age, Based on U.S. Office-Based Physician Surveys, from January 2004 to December 2013, Cumulative

January 2004 to December 2013			
	Uses (N)	95% Confidence Interval	Share (%)
Desmopressin acetate	(b) (4)	(b) (4)	100.0%
0-17 years			(b) (4)
18-64 years			
65+ years			
Unspecified	(b) (4)		

Source: Encuity Research, LLC, Treatment Answers (TM). January 2004 - December 2013 Extracted December 2014. File: Enquity 2014-2631 Desmopressin AC

APPENDIX 1: Drug Use Database Descriptions.

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS Health, National Prescription Audit

The National Prescription Audit (NPA™) has been the industry standard source of national prescription activity since 1952. NPA measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions in the United States. The NPA audit measures both what is prescribed by the physician and what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies.

IMS, Vector One®: Total Patient Tracker (TPT)

The IMS, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time.

TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

Encuity Research, LLC., Physician Drug & Diagnosis Audit (PDDA)

Encuity Research, LLC., TreatmentAnswers with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

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/s/

JUSTIN A MATHEW
05/18/2015

GRACE CHAI
05/18/2015

JUDY A STAFFA
05/18/2015

STUDY ENDPOINT CONSULT REVIEW

STUDY ENDPOINTS TRACKING NUMBER	2014-134
IND/NDA/BLA NUMBER	NDA 022517
LETTER DATE/SUBMISSION NUMBER	SDN 30
PDUFA GOAL DATE	January 31, 2015
DATE OF CONSULT REQUEST	August 21, 2014
REVIEW DIVISION	Division of Metabolism and Endocrinology Products (DMEP)
MEDICAL REVIEWER	William Lubas, M.D., Ph.D. (Clinical TL: Dragos Roman, M.D.)
REVIEW DIVISION PM	Jennifer Johnson
STUDY ENDPOINTS REVIEWER(S) ASSOCIATE DIRECTOR, STUDY ENDPOINTS (ACTING)	Sarrit Kovacs, Ph.D. Elektra Papadopoulos, M.D., M.P.H.
REVIEW COMPLETION DATE	January 23, 2015
ESTABLISHED NAME	Desmopressin orally disintegrating sublingual tablets
TRADE NAME	Nocurna
APPLICANT	Ferring Pharmaceuticals, Inc.
CLINICAL OUTCOME ASSESSMENT TYPE	Patient-reported outcome
ENDPOINT(S) CONCEPT(S)	Intensity of nocturia impacts
MEASURE(S)	Nocturia Impact (NI) Diary; Nocturia Quality-of-Life (NQoL) questionnaire
INDICATION	Treatment of Nocturia
INTENDED POPULATION(S)	Adult males or females (≥ 20 years of age) with at least 2 nocturnal voids every night in a consecutive 3-day period as documented in the diary during the screening period.
NOTE	This abbreviated review is in response to DMEP's request for SEALD input in preparation for an advisory committee meeting for this application. Please see list of previous SEALD reviews for this NDA in Section B.

Study Endpoints Review

Sarrit Kovacs, Ph.D.

NDA 022517

Nocturna

Nocturia Impact (NI) Diary and Nocturia Quality-of-Life (NQoL) questionnaire

A. EXECUTIVE SUMMARY

This Study Endpoints review is provided as a response to a request for consultation by the Division of Metabolism and Endocrinology Products (DMEP) regarding NDA 022517. The applicant (in dialogue with FDA) developed the Nocturia Impact (NI) Diary based on the existing instrument, Nocturia Quality-of-Life (NQoL) questionnaire, that was used in both phase 3 trials (CS40 and CS41). Several changes were made in the development of the NI Diary to address the limitations of the NQoL. These limitations include the relatively long recall period (2 weeks) of the NQoL, which is problematic for distinguishing treatment benefit in drug development trials where a patient's condition fluctuates, as can occur in patients with nocturia. A comparison of the NQoL and the NI diary is appended.

The NI Diary was included in a one-month long phase 3b extension study (IMPACT Trial; CS000034) that enrolled a subgroup of adult patients with nocturia who had completed CS40 and CS41). CS000034 was small (n=56) and exploratory in nature. Its primary objective was to assess the psychometric properties of the NI Diary. Given its exploratory nature, no conclusions of effectiveness can be made using the NI Diary in CS000034. Hence, the NI Diary results cannot serve as a basis for labeling claims.

The NQoL was used in Studies CS40 and CS41. However, the analyses conducted by the applicant with the NQoL were also post hoc and exploratory per discussion with the clinical reviewer, Dr. Lubas (December 5, 2015).

The review concludes that the clinical trial evidence submitted by the applicant is inadequate to support labeling claims on the basis of the NI Diary or NQoL because of the exploratory nature of the data. Therefore, these clinical trial results do not meet standards for inclusion in labeling claims. However, the NI Diary was developed specifically for use in clinical trials and may be able to support labeling claims if it demonstrates a clinically meaningful and statistically significant treatment effect in adequate and well-controlled trials.

Study Endpoints Review

Sarrit Kovacs, Ph.D.

NDA 022517

Nocturna

Nocturia Impact (NI) Diary and Nocturia Quality-of-Life (NQoL) questionnaire

B. ABBREVIATED STUDY ENDPOINT REVIEW

The NQoL and the NI Diary were reviewed in multiple previous Study Endpoints reviews, including the following:

- NQoL (Trentacosti; August 31, 2010)
- NQoL and NI Diary (Stansbury; September 27, 2012)
- NQoL and NI Diary (Stansbury Addendum; January 3, 2013)
- NQoL and NI Diary (Stansbury; May 2, 2013)

Both instruments were paper-based measures and were administered in English only. A history of the development of the NI Diary and its comparison with the NQoL are appended.

Briefly, the NI Diary produces a single overall score. The majority of the items of the NI Diary measure sleep impacts of nocturia; therefore, the overall score produced by NI Diary instrument would most accurately be described as such. The NQoL produces two scores: (a) the Sleep/Energy score and (b) the Bother/Concern score.

The NI Diary items reflect patient input and many of its items are derived from the NQoL. We note that a subset of the NI Diary's items may be less relevant to assess in a drug treatment trial (e.g., "Do you worry that the nocturia will get worse in the future?"). There are also several inconsistencies among versions within the sponsor's submissions (in PRO Dossier, conceptual framework, item comparison table, and CS000034 clinical trial protocol/CRF). More specifically, there is different wording across versions for Item 8 (additional words "tripping or") and/or Item 11 (additional word "overnight"). Despite these findings, there are no apparent concerns that are of the magnitude that would preclude inclusion in labeling of clinically meaningful and statistically robust clinical trial data derived using this instrument.

The following information regarding the NI Diary and NQoL can be found in the appendices.

Appendix A: NQoL Conceptual Framework

Appendix B: NI Diary Conceptual Framework

Appendix C: NI Diary Scoring

Appendix D: Comparison of the Items in the NI Diary and NQoL

Appendix E: Nocturia Quality-of-Life (NQoL)

Appendix F: Nocturia Impact Diary (NI Diary)

Appendix G: Development Process of the NI Diary

Study Endpoints Review

Sarrit Kovacs, Ph.D.

NDA 022517

Nocturna

Nocturia Impact (NI) Diary and Nocturia Quality-of-Life (NQoL) questionnaire

APPENDIX A - NQoL CONCEPTUAL FRAMEWORK

Table 1. Conceptual Framework of N-QoL

SLEEP/ENERGY DOMAIN
1. Has made it difficult for me to concentrate the next day
2. Has made me feel generally low in energy the next day
3. Has required me to nap during the day
4. Has made me less productive the next day
5. Has caused me to participate less in activities I enjoy
7. Has made it difficult for me to get enough sleep at night

BOTHER/CONCERN DOMAIN
6. Has caused me to be careful about when or how much I drink
8. Concerned that I am disturbing others in the house because of having to get up at night to urinate
9. Preoccupied about having to get up at night to urinate
10. Worried that this condition will get worse in the future
11. Worried that there is no effective treatment for this condition (having to get up at night to urinate)
12. Overall how bothersome has having to get up at night to urinate been during the past 2 weeks?

Note: This conceptual framework was reproduced from a previous Study Endpoints review based on a submission from the applicant.

Study Endpoints Review

Sarrit Kovacs, Ph.D.

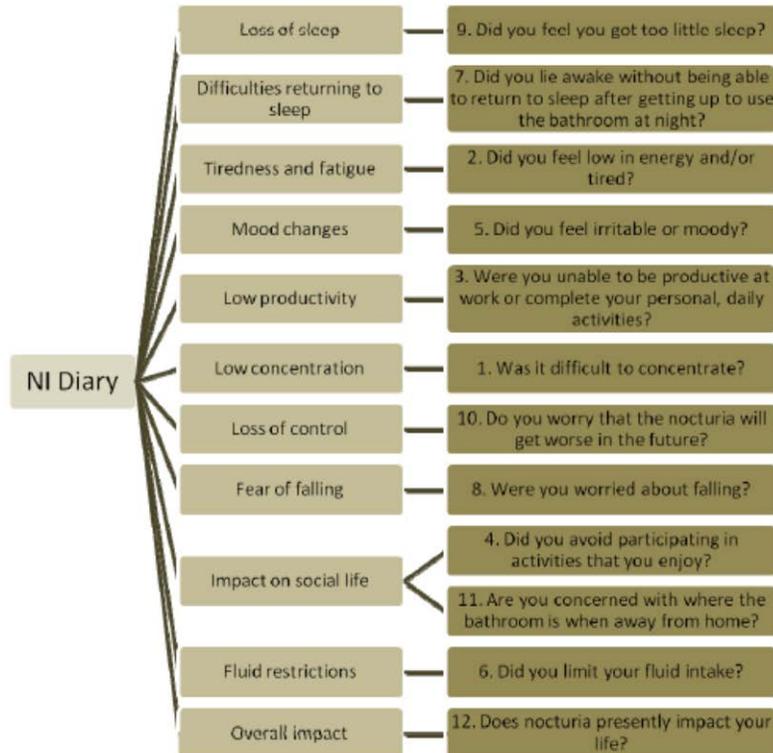
NDA 022517

Nocturna

Nocturia Impact (NI) Diary and Nocturia Quality-of-Life (NQoL) questionnaire

APPENDIX B - NI DIARY CONCEPTUAL FRAMEWORK

The Conceptual framework of the NI Diary summarizes the knowledge about impact of nocturia from content validity studies and assessments in clinical trials conducted by Ferring as well as independent sources.



Reviewer's comment: This figure was reproduced from the applicant's submission. However, in contrast to the figure, it is our understanding that the "overall impact" item (Item 12) is not included in the total NI Diary score.

Study Endpoints Review

Sarrit Kovacs, Ph.D.

NDA 022517

Nocturna

Nocturia Impact (NI) Diary and Nocturia Quality-of-Life (NQoL) questionnaire

APPENDIX C - NI DIARY SCORING

9.6.2 Definitions of the NI Total Score and Overall Impact Score

The NI diary is a 12-item instrument consisting of 11 core items and an overall impact question (Q12). Responses are scored from 0 (lowest) to 4 (highest). The NI total score is defined as the sum of the 11 core items scores.

The analysis of the overall impact question (Q12) and the NI total score will be based on a standardized scale from 0 (lowest) to 100 (highest), i.e. the raw scores are standardized as follows:

$$\text{Transformed score} = \frac{\text{The sum of the component items score} * 100}{\text{Maximum possible raw score}}$$

The NI total score will be analyzable only if all 11 items (Q1-Q11) have non-missing responses. Otherwise, it will be defined as missing. Missing values will not be imputed. The average over the 3-day diary period for the overall impact score and the NI total score will be used for each visit.

From the applicant's PRO Dossier (page 128 of 574)

Study Endpoints Review

Sarrit Kovacs, Ph.D.

NDA 022517

Nocturna

Nocturia Impact (NI) Diary and Nocturia Quality-of-Life (NQoL) questionnaire

APPENDIX D - COMPARISON OF ITEMS IN NI DIARY AND NQoL

Desmopressin, FE 992026, FE 999912

Orally Disintegrating Tablet

Response to: Teleconference between FDA and Ferring

18 February 2014

Date: 15 July 2014

E-Regulatory Authorities Correspondence-17328; Ver.

1.0

Page 65 of 137

Table 25 Comparison of the Items in the NI Diary and N-QoL

NI Diary	N-QoL Questionnaire
Thinking over the day, to what extent:	Over the past 2 weeks, having to get up at night to urinate:
1. Was it difficult to concentrate?	1. Has made it difficult for me to concentrate the next day
2. Did you feel low in energy and/or tired?	2. Has made me feel generally low in energy the next day
3. Were you unable to be productive at work or complete your personal, daily activities?	4. Has made me less productive the next day
4. Did you avoid participating in activities that you enjoy?	5. Has caused me to participate less in activities I enjoy
5. Did you feel irritable or moody?	None
6. Did you limit your fluid intake?	6. Has caused me to be careful when or how much I drink
Thinking about last night, to what extent:	
7. Did you lie awake without being able to return to sleep after getting up to use the bathroom at night?	None
8. Were you worried about tripping or falling?	None
9. Did you feel you got too little sleep?	7. Has made it difficult for me to get enough sleep at night
Overall, to what extent:	Over the past 2 weeks, I have been:
10. Do you worry that the nocturia will get worse in the future?	10. Worried that this condition will get worse in the future
11. Are you concerned with where the bathroom is when away from home overnight?	None
12. Does nocturia presently impact your life?	13. Overall I would rate my quality of life to be...

Source: [Impact 000034 CTR](#)

Reviewer's comments: While this table was reproduced from the sponsor's submission, we noted that Item 11 does not share the same wording with the instrument appended. The version used for the table above included the additional word "overnight" in Item 11 as well as the additional words "tripping or" in Item 8.

Study Endpoints Review

Sarrit Kovacs, Ph.D.

NDA 022517

Nocturna

Nocturia Impact (NI) Diary and Nocturia Quality-of-Life (NQoL) questionnaire

APPENDIX E - NOCTURIA QUALITY-OF-LIFE (NQOL)

Protocol: FE992026 CS40	A MULTI-CENTRE, RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP TRIAL TO INVESTIGATE THE EFFICACY AND SAFETY OF DESMOPRESSIN ORALLY DISINTEGRATING TABLET FOR THE TREATMENT OF NOCTURIA IN ADULT FEMALES
Screening #:	Module/Tab: VISIT 2

NOCTURIA QUALITY OF LIFE (VISIT 2)

Not Done, please provide an explanation:

Over the past 2 weeks, having to get up at night to urinate	
1. Has made it difficult for me to concentrate the next day	<input type="radio"/> Every day <input type="radio"/> Most days <input type="radio"/> Some days <input type="radio"/> Rarely <input type="radio"/> Never
2. Has made me feel generally low in energy the next day	<input type="radio"/> Every day <input type="radio"/> Most days <input type="radio"/> Some days <input type="radio"/> Rarely <input type="radio"/> Never
3. Has required me to nap during the day	<input type="radio"/> Every day <input type="radio"/> Most days <input type="radio"/> Some days <input type="radio"/> Rarely <input type="radio"/> Never
4. Has made me less productive the next day	<input type="radio"/> Every day <input type="radio"/> Most days <input type="radio"/> Some days <input type="radio"/> Rarely <input type="radio"/> Never
5. Has caused me to participate less in activities I enjoy	<input type="radio"/> Extremely <input type="radio"/> Quite a bit <input type="radio"/> Moderately <input type="radio"/> A little bit <input type="radio"/> Not at all
6. Has caused me to be careful when or how much I drink	<input type="radio"/> All the time <input type="radio"/> Most of the time <input type="radio"/> Some of the time <input type="radio"/> Rarely <input type="radio"/> Never
7. Has made it difficult for me to get enough sleep at night	<input type="radio"/> Every night <input type="radio"/> Most nights <input type="radio"/> Some nights <input type="radio"/> Rarely <input type="radio"/> Never
Over the past 2 weeks I have been	
8. Concerned that I am disturbing others in the house because of having to get up at night to urinate	<input type="radio"/> Extremely <input type="radio"/> Quite a bit <input type="radio"/> Moderately <input type="radio"/> A little bit <input type="radio"/> Not at all
	<input type="radio"/> All the time <input type="radio"/> Most of the time

Study Endpoints Review

Sarrit Kovacs, Ph.D.

NDA 022517

Nocturna

Nocturia Impact (NI) Diary and Nocturia Quality-of-Life (NQoL) questionnaire

9. Preoccupied about having to get up at night to urinate	<input type="radio"/> Some of the time <input type="radio"/> Rarely <input type="radio"/> Never
10. Worried that this condition will get worse in the future	<input type="radio"/> Extremely <input type="radio"/> Quite a bit <input type="radio"/> Moderately <input type="radio"/> A little bit <input type="radio"/> Not at all
11. Worried that there is no effective treatment for this condition (having to get up at night to urinate)	<input type="radio"/> Extremely <input type="radio"/> Quite a bit <input type="radio"/> Moderately <input type="radio"/> A little bit <input type="radio"/> Not at all
12. Overall, how bothersome has having to get up at night to urinate been during the past 2 weeks?	<input type="radio"/> Not at all <input type="radio"/> A little bit <input type="radio"/> Moderately <input type="radio"/> Quite a bit <input type="radio"/> Extremely
13. Overall I would rate my quality of life to be..	<input type="radio"/> Very good <input type="radio"/> Good <input type="radio"/> Fair <input type="radio"/> Poor <input type="radio"/> Very poor

Study Endpoints Review

Sarrit Kovacs, Ph.D.

NDA 022517

Nocturna

Nocturia Impact (NI) Diary and Nocturia Quality-of-Life (NQoL) questionnaire

APPENDIX F - NOCTURIA IMPACT (NI) DIARY

Day 2 Day-Time		
Protocol: FE992026 000034	A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY, INVESTIGATING THE IMPACT BURDEN OF NOCTURIA USING THE NOCTURIA IMPACT DIARY	
Screening #:	Subject #:	Module/Tab: DIARY

DAY 2 DAY-TIME (DIARY)

SCREENING(COLLECTED AT VISIT 2) (DAY 2 DAY-TIME)

Not Done, please provide an explanation:

Time You Woke Up	<input type="text"/> (24-hour clock, hhmm)
Time of completion	<input type="text"/> (24-hour clock, hhmm)

Nocturia Impact Diary Afternoon/Evening	
This nocturia (getting up to void at night) diary will assess the daily impact of nocturia on your everyday life. Please answer the questions in the late afternoon or evening and use the scale from 'not at all' to 'a great deal':	
Thinking over the day, to what extent...	
1. Was it difficult to concentrate?	<input type="radio"/> Not at all <input type="radio"/> Slightly <input type="radio"/> Moderately <input type="radio"/> Quite a bit <input type="radio"/> A great deal
2. Did you feel low in energy and/or tired?	<input type="radio"/> Not at all <input type="radio"/> Slightly <input type="radio"/> Moderately <input type="radio"/> Quite a bit <input type="radio"/> A great deal
3. Were you unable to be productive at work or complete your personal, daily activities?	<input type="radio"/> Not at all <input type="radio"/> Slightly <input type="radio"/> Moderately <input type="radio"/> Quite a bit <input type="radio"/> A great deal
4. Did you avoid participating in activities that you enjoy?	<input type="radio"/> Not at all <input type="radio"/> Slightly <input type="radio"/> Moderately <input type="radio"/> Quite a bit <input type="radio"/> A great deal
5. Did you feel irritable or moody?	<input type="radio"/> Not at all <input type="radio"/> Slightly <input type="radio"/> Moderately <input type="radio"/> Quite a bit <input type="radio"/> A great deal
6. Did you limit your fluid intake?	<input type="radio"/> Not at all <input type="radio"/> Slightly <input type="radio"/> Moderately <input type="radio"/> Quite a bit <input type="radio"/> A great deal
Thinking about last night, to what extent...	
7. Did you lay awake without being able to return to sleep after getting up to use the bathroom at night?	<input type="radio"/> Not at all <input type="radio"/> Slightly <input type="radio"/> Moderately <input type="radio"/> Quite a bit

Study Endpoints Review

Sarrit Kovacs, Ph.D.

NDA 022517

Nocturna

Nocturia Impact (NI) Diary and Nocturia Quality-of-Life (NQoL) questionnaire

	<input type="radio"/> A great deal
8. Were you worried about falling?	<input type="radio"/> Not at all <input type="radio"/> Slightly <input type="radio"/> Moderately <input type="radio"/> Quite a bit <input type="radio"/> A great deal
Overall, to what extent...	
9. Did you feel you got too little sleep?	<input type="radio"/> Not at all <input type="radio"/> Slightly <input type="radio"/> Moderately <input type="radio"/> Quite a bit <input type="radio"/> A great deal
10. Do you worry that the nocturia will get worse in the future?	<input type="radio"/> Not at all <input type="radio"/> Slightly <input type="radio"/> Moderately <input type="radio"/> Quite a bit <input type="radio"/> A great deal
11. Are you concerned with where the bathroom is when away from home?	<input type="radio"/> Not at all <input type="radio"/> Slightly <input type="radio"/> Moderately <input type="radio"/> Quite a bit <input type="radio"/> A great deal
12. Does nocturia impact your life?	<input type="radio"/> Not at all <input type="radio"/> Slightly <input type="radio"/> Moderately <input type="radio"/> Quite a bit <input type="radio"/> A great deal

Study Endpoints Review

Sarrit Kovacs, Ph.D.

NDA 022517

Nocturna

Nocturia Impact (NI) Diary and Nocturia Quality-of-Life (NQoL) questionnaire

APPENDIX G - DEVELOPMENT PROCESS OF THE NI DIARY

Development process of the Nocturia Impact Diary	Development steps	FDA comments	Changes made	Description of study	Output	Documentation
1	Review of qualitative, patient reported, item elicitation or cognitive debriefing studies.	Step 1 in the rapid revision process agreed by FDA and Ferring at <i>Guidance meeting minutes Nocturna IND (065890) from the July 20, 2011 meeting</i>	NA	NA	Comprehensive list of concepts of relevance for nocturia patients	PRO dossier Chapter 5 – specifically 5E
2	Condensation of list of concepts into draft questionnaire and adjustment of N-QoL into diary with response: ‘a great deal’ and ‘not at all’ as ends of item scaling.	Step 2 in the rapid revision process agreed by FDA and Ferring at <i>Guidance meeting minutes Nocturna IND (065890) from the July 20, 2011 meeting</i>	NA	NA	Nocturia Impact Draft 1 diary with 14 questions and 4 domains	PRO dossier Chapter 1B for questionnaire and 5C for overview of domains
3	Conduct of a cognitive debriefing study confirming the selected item pool.	Step 3 in the rapid revision process agreed by FDA and Ferring at <i>Guidance meeting minutes Nocturna IND (065890) from the July 20, 2011 meeting</i>	NA	Qualitative focus group study including 24 nocturia patients	Nocturia Impact Draft 2 diary with 12 items and 4 domains	PRO dossier chapter 5C and Appendix E
4	Proposed psychometric protocol and SAP of trial 000034	A. <i>Discourage several domains</i> B. <i>Include Rasch analysis</i> C. <i>Include Cohen’s D</i>	1) Rasch analysis was done in cross sectional data from the 24		Nocturia Impact Draft 3 diary with 11 items and 1 domain + 1 global	Appendix 3 in the study protocol in the NDA:

	was sent to FDA for review.	D. <i>Make sure that it is possible to identify patients with respect to prior randomization</i> E. <i>Specific suggestions to item 10, 6, 12, 11 and 8</i>	cognitive debriefing patients (response to A and B) 2) Changes were incorporated in SAP (response to A, B, C and D) 3) Adaptations were made in the diary (response to E)		item (based on preliminary Rasch analysis and FDA advice)	Nocturia Impact Draft 2 diary
5	IMPACT study (with FDA comments included).	NA	Based on the Rasch analysis 1 domain was kept. Linguistic change was made to item 12	Placebo controlled RCT	Nocturia Impact Diary with 11 items and 1 domain + a global domain	PRO dossier Chapter 1 and Appendix B
6	Scoring algorithm and suggestion of clinical relevance was developed.	NA	NA	NA	Scoring algorithm and first suggestions to a minimal clinical relevant scoring range	PRO dossier Chapters 1C and 7

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/s/

SARRIT M KOVACS
01/23/2015

ELEKTRA J PAPADOPOULOS
01/23/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)**

Epidemiology: Review of Post-Marketing Study Protocol

Date: December 12, 2014

Reviewer: Patricia L. Bright, MSPH, PhD,
Epidemiologist,
Division of Epidemiology 1 (DEPI-1),
Office of Pharmacovigilance and Epidemiology (OPE),
Office of Surveillance and Epidemiology (OSE)

Team Leader Diane K. Wysowski, MPH, PhD,
Epidemiology Team Leader, DEPI-1, OPE, OSE

Associate Division Director: Simone Pinheiro, ScD, MSc
Associate Division Director, DEPI-1, OPE, OSE

Drug Name: Nocdurna (desmopressin) Orally Disintegrating Sublingual
Tablets

Subject Review of the Sponsor's Protocol "(b) (4)"
[Redacted]

Application Type/Number: NDA 022517

Applicant/sponsor: Ferring Pharmaceuticals Inc.

OSE RCM #: 2014-2096

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/s/

PATRICIA L BRIGHT
12/12/2014

DIANE K WYSOWSKI
12/12/2014

SIMONE P PINHEIRO
12/12/2014

NDA: 022517

Division of Bone, Reproductive and Urologic Products

Consultation for NDA 022517 Tracking # 68

DATES: Consult requested: September 9, 2014
 Date of review: December 8, 2014

FROM: Roger Wiederhorn MD, Medical Officer, Division of Bone,
 Reproductive and Urologic Products (DBRUP)

 Mark S. Hirsch MD, Medical Team Leader, DBRUP

 Hylton V. Joffe MD, MMSc, Division Director, DBRUP

TO: Jennifer Johnson, RPM, Division of Metabolic and Endocrine
 Products (DMEP)

SPONSOR: Ferring Pharmaceuticals

DRUG CLASS: 8-arginine vasopressin analogue

TRADE NAME: NOCDURNA

FORMULATION Oral disintegrating tablets

DOSE: 25 µg (for females) and 50 µg (for males) once daily

RELATED IND: 065890

DEVELOPMENT INDICATION: The treatment of nocturia due to nocturnal polyuria in adults who awaken two or more times each night to void

CONSULT QUESTIONS or REASON for CONSULTATION: Provide urology consultative input to DMEP for the review of the July resubmission in preparation for the Advisory Committee (AC) meeting scheduled for January 12, 2015.

DOCUMENTS REVIEWED:

- NDA 022517 SN 0027 Complete Response (CR)
- Minutes of meeting June 5, 2013
- Minutes of meeting December 18, 2013 (in CR)

- Dispute Appeal Denied Letter January 15, 2014
- CSR CS29 (in CR)
- CSR CS31 (in CR)
- CSR CS40 (in CR)
- CSR CS41 (in CR)

1. Consultant's Summary Assessment and Recommendations

We have the following three comments from the urologic perspective:

1. The demonstrated effect of NOCDURNA on the frequency of nocturia in patients with nocturnal polyuria is small when compared to placebo. The clinical meaningfulness of this small effect is not interpretable in the absence of a validated measure of the clinical benefit of reduction of nocturia episodes.
2. In the pivotal studies, homogenous urologic populations were not studied, making the efficacy study results difficult to interpret. Based on the Sponsor's proposed target patient group (nocturia secondary to nocturnal polyuria), patients eligible for Nocturna studies should have had: 1) overproduction of urine at night (nocturnal polyuria), 2) a normal capacity bladder, and 3) little or no symptoms of the two most commonly occurring lower urinary tract voiding dysfunctions, overactive bladder (OAB) and benign prostatic hypertrophy (BPH). Included in the completed studies were patients with lower urinary tract symptoms (LUTS) due to BPH and OAB. In addition, patients with small bladder capacities were neither identified nor eliminated. Responders to lifestyle modification during the run-in period were also not eliminated. Elimination of these subgroups would have allowed for a urologically homogenous study population, free of confounding intrinsic urologic factors that may reasonably be expected to have independent effects on nighttime voids, the primary efficacy endpoint. By grouping these disparate conditions into one trial, no or minimal treatment effects in some populations may have masked clinically meaningful benefits seen in other populations, yielding the observed overall small treatment effect of unknown clinical relevance.

We do not believe that a *post hoc* re-analysis of existing data can resolve these issues. Our overall conclusion is that a new study should be performed incorporating the eligibility criteria recommendations shown in our Overall Comments section (see below). Enrichment of the population by additional modifications to the entry criteria is also recommended in order to maximize the chance of discerning a clinically meaningful treatment effect.

3. Hyponatremia is a significant safety concern. It would appear that a large segment of the target population (patients with nocturia secondary to nocturnal polyuria) is over 65 years of age. This is also the age group of patients who had a disproportionate incidence of hyponatremia due to Nocturna. While it may be ultimately possible to label this risk

with appropriate monitoring, additional information should be presented clarifying the hyponatremia risk, especially in regard to potential of hyponatremia at times distant from initiating therapy, the increased risk in geriatric patients, and the justification for proposed monitoring.

We offer suggestions to correct these deficiencies in our detailed **Overall Comments** section.

2. Background

Ferring is developing desmopressin for the treatment of nocturia due to nocturnal polyuria in adults who awaken two or more times each night to void. The first review of the application resulted in a Complete Response (CR) action. There was a high incidence of hyponatremia that outweighed any perceived benefit of reducing the frequency of nocturnal voids. Post-hoc analyses of different subgroups at different time points suggested differential efficacy by gender at lower doses than those used (100 mcg daily). The Sponsor was instructed to conduct a clinical trial of lower dosing regimens to confirm safe and effective treatment of adult nocturia.

Subsequently, two studies, CS40 and CS41, which were the foundation for providing efficacy information for NDA 022517, were conducted. Both were similarly-designed, placebo-controlled studies. CS40 provided data for female subjects using a dose of 25 mcg per day and CS41 provided data for male subjects using a dose of 75 or 50 mcg a day. Both studies planned comparisons of desmopressin to placebo based on results for two co-primary efficacy endpoints, change from baseline in the average number of nocturnal voids over 3 months (across 4 time points), and 33% responder status (e.g., reduction of nocturnal voids by 33%) over 3 months. Subjects were instructed in behavior and lifestyle modification (e.g., limit fluid intake at bedtime, avoid drinks that may have a diuretic effect, etc.) at the beginning of each trial. From these results, DMEP determined that the treatment effect demonstrated in study CS40 was modest (e.g., for study CS40, the mean effect size was -0.24 voids/night as compared to placebo, which was less than half the target effect size used for the sample size calculation [-0.50 voids/night] and smaller than the mean placebo change from baseline of -1.23 voids/night). The large change in placebo from baseline that was demonstrated was believed to be likely due to behavioral modification instructions given to subjects. Study CS41 demonstrated statistically significant differences on both co-primary endpoints that were unaltered by sensitivity analyses. A placebo subtracted difference of approximately 0.4 voids per night was demonstrated, which DMEP also determined to be a modest treatment effect. The results of these studies were submitted as part of a second cycle complete response submitted July 17, 2013.

The clinical effect demonstrated in the populations studied (in CS40 and CS41) is smaller than the Sponsor's expectations. To our knowledge, there is no validated measure of meaningful clinical benefit for nocturia. The effect size demonstrated was approximately half the amount used for power calculations for Study CS40 and results in this study were not robust to sensitivity analyses. Further, DMEP was not convinced of the clinical meaningfulness of a mean reduction of 0.4 voids/night (2.8 per week) in males and 0.22 voids/night (1.5 per week) in females (all relative to placebo) in a group of patients with approximately 2.8 voids per night (20 nocturnal voids per week) prior to initiation of treatment. In DMEP's estimation, the numerical changes in frequency of nighttime voids observed in studies CS40 and CS41 were not supported

by evidence of clinical benefit from patient reported outcomes (none of which have been considered validated as fit for purpose in the context of use), which demonstrated inconsistent and unconvincing results. DMEP stated that additional evidence of clinical benefit, such as improvement in health-related quality of life, was necessary. The Sponsor chose to use parameters measuring the quality of sleep as related to the frequency of nocturia in support of clinical benefit. As part of the Complete Response, an “*Expert Report: The Clinical Benefit of Sleep Improvements in Nocturia Patients using NOCDURNA*” was submitted. The proposed measures of sleep improvements are, as yet, not validated to indicate a significant clinical benefit of sleep improvement.

In CS40, three women (2.2%) receiving desmopressin 25 mcg versus none of the placebo patients had serum sodium levels between 126 and 129 mmol/L. In study CS41, severe hyponatremia (serum sodium \leq 125 mmol/L) was seen in two men (1.7%) receiving desmopressin 50 mcg and four men (3.3%) receiving 75 mcg versus none of placebo subjects.

On August 14, 2013, DMEP sent an **ACKNOWLEDGE INCOMPLETE RESPONSE** letter to the Sponsor. DMEP did not agree that the information included in the Complete Response submission demonstrated that the duration of sleep extension observed in the NOCDURNA Phase 3 clinical program can be linked to a clear reduction in morbidity and mortality, as the Sponsor suggested. Therefore, DMEP did not consider this submission to be a Complete Response. DMEP stated that an additional clinical study to demonstrate clinically meaningful impact of NOCDURNA on reducing the frequency of nocturnal voids is necessary.

A request for formal dispute resolution (FDRR) was received November 21, 2013. The Sponsor requested that NDA 022517 be approved for marketing on the basis of CS40 and CS41. The Sponsor also requested that an additional clinical study to demonstrate clinically meaningful impact of NOCDURNA on reducing nocturnal voids be considered unnecessary. Both requests were denied. It was suggested that one path forward might consist of the Sponsor submitting their most recent proposed CR response (and any new data considered appropriate), for presentation before an AC meeting. DMEP would then consider the new information provided in the application along with discussions of the advisory panel members in reaching an action decision.

DBRUP has been asked to provide urologic consultative input to DMEP for the review of the resubmission.

3. Consultant’s Analysis

Overall, from the urologic perspective, we have comments on three specific areas: 1) the small size of the observed treatment effect, 2) the urological heterogeneity of the study population, and 3) the significant risk of hyponatremia.

3.1 Small Size of the Observed Treatment Effect

We agree with DMEP that the small placebo-subtracted treatment effect and the lack of a satisfactory measure of meaningful clinical benefit preclude an adequate assessment of clinical efficacy for NOCDURNA. Reference is made to the efficacy data summarized in Section 2 (Background) of this memo and in DMEP's previous and current reviews.

3.2 *Urological Heterogeneity of the Study Population*

From a urologic perspective, an appropriate population was not studied for the proposed indication of treatment (nocturia due to nocturnal polyuria in adults who awaken two or more times each night to void). The population was too heterogeneous in regard to urologic background conditions. The presence of differing intrinsic urological factors, some of them latent (e.g., diminished bladder capacity), makes interpretation of the overall efficacy results difficult. A more homogenous population should have been studied: patients with overproduction of urine at night, a normal capacity bladder, and little or no symptoms of OAB or BPH. This was not the case in the previously performed pivotal studies submitted to this NDA.

In addition, we offer the following comments on improving the key inclusion criteria:

- The inclusion criteria for Studies CS-40 and CS-41 required at least 2 nocturnal voids every night in a consecutive 3-day period during screening, with no requirement for nocturnal polyuria documentation. From a urological perspective, nocturnal polyuria should be documented at baseline and the requirement for at least 2 nocturnal voids every night should be increased to at least 3 nocturnal voids every night. This increase will enrich the population and may identify a patient population in whom a more convincing demonstration of clinical benefit may be discerned, potentially improving the benefit/risk assessment. In addition, using the current criterion of at least 2 nocturnal voids, **approximately 50% of all adults ≥ 65 years of age** would be eligible for treatment with Nocdurna. Such potential widespread use, if the drug were to be approved, is of concern to us.
- Although documentation of nocturnal polyuria was not required at screening, the Sponsor states that 90% of study subjects with at least 2 nocturnal voids had nocturnal polyuria, as defined by a ratio of nocturnal urine volume/24-hour urine volume of $\geq 33\%$. From a urological perspective, the 33% cut-point for nocturnal urine volume relative to daily urine volume (nocturnal polyuria) is too low to identify the population that would likely be helped most by NOCDURNA. We recommend increasing this cut-point to $\geq 40\%$.

From the urological perspective, we have the following additional comments:

Nocturia may be attributed to: 1) nocturnal overproduction of urine (nocturnal polyuria), 2) diminished nocturnal bladder capacity (NBC), or 3) to a combination of both. Unfortunately, diminished NBC was not taken into consideration in the design of the Nocdurna studies. Based on available evidence, nocturia due to diminished NBC will not necessarily improve when there is a reduction in urine volume. Thus, we postulate that nocturia results in the Nocdurna trials may have been confounded by diminished NBC.

In a highly relevant published article (*Neurology and Neurodynamics, Vol. 18, pg. 559-565, 1999*), Drs. Jeffrey Weiss and Jerry Blaivas described three different nocturia-related indices:

- 1) Nocturnal Polyuria index (NPI): nocturnal urine volume divided by 24-hour urine volume,
- 2) Nocturia index (Ni): nocturnal urine volume divided by “functional bladder capacity” (FBC), defined as the volume of the single largest void derived from a 24-hour bladder diary (the maximal capacity), and
- 3) Nocturnal Bladder Capacity index (NBCi): the actual number of nightly voids (“ANV”) minus the predicted number of nightly voids (“PNV”). PNV is calculated as $Ni - 1$. The greater the difference between the actual and predicted nightly voids, the larger the NBCi, and the lower the nocturnal bladder capacity.

The authors state that NBCi is highly predictive of bothersome nocturia in adult men. For example, if the NBCi result is high (> 2.0), the odds of reporting severe bother on the nocturia question of the American Urological Association Symptom Score (AUA-SS) is approximately 4 times higher than if the NBCi result is low (≤ 2.0). Therefore, nocturnal bladder capacity is a key factor that must be considered when assessing nocturia in adult men.

Nocturnal urine production is also an important factor in nocturia. The authors propose that an $Ni > 1.5$ may be used as a practical discriminant indicating that the etiology of nocturia is more likely to be related to nocturnal urine overproduction.

The authors state that using the Ni and NBCi together allows a quantitative assessment of the relative contributions of nocturnal urine overproduction and diminished nocturnal bladder capacity (NBC) in identifying the etiology of nocturia in male patients.

In the absence of any analysis of nocturnal bladder capacity, a latent variable that we consider crucial to nocturia, the interpretation of the results of Studies CS40 and CS41, are confounded (see our explanation above). In addition, we believe that other factors (see below) should have been taken into consideration when designing the Nocturna pivotal trials.

Based on these concerns, we recommend that a new study be performed with Nocturna in patients with simple overproduction of nocturnal urine that includes features to interpret nocturnal bladder capacity as well as other known factors that affect nocturia. For example, patients with small bladder capacities should be excluded from future studies. Patients with bothersome OAB and BPH should also be excluded. By excluding these disparate conditions in the trial, the true treatment effects of Nocturna in patients with simple overproduction of nocturnal urine may be more readily discerned.

In light of this overall conclusion and recommendation, we have made proposals for new studies (see Section 4 of this memo). The intent of our recommendations is to define a homogenous study population that has simple overproduction of urine at night with normal bladder capacities and free from bothersome OAB and BPH. Patients with OAB and BPH should be evaluated in separate studies. For example, in addition to our previously stated concerns, a study evaluating the treatment of nocturia in patients with BPH or OAB would also need to have different

inclusion/exclusion criteria compared to the treatment of nocturia due to other conditions. Similarly, we would want to know how the drug affects other endpoints that are typically studied for these conditions (e.g., the International Prostate Symptom Score for BPH, and daytime frequency and urge urinary incontinence episodes for OAB). Given these types of considerations, we advise separate investigations of the product in the BPH and OAB target populations. Studies in the various separate target populations would likely involve patients using medications that could affect bladder dynamics, and this would need to be accounted for in the study designs.

3.3 Significant Risk of Hyponatremia

Our review supports the contention that hyponatremia is a concern with Nocdurna.

In the long-term Study CS31, the incidences of markedly abnormal serum sodium (≤ 130 mmol/L) were dose-related, as follows: for the 25 μg dose 8/218 (3.7%), for the 50 μg dose 19/201 (9.5%), and for placebo 0 (0.0%).

In addition, we note that the incidence of markedly abnormal serum sodium in patients taking Nocdurna for 96-108 weeks was 0.2% with a prevalence of 0.4%. There are no long-term data available for placebo patients since placebo exposure was limited to 4-12 weeks.

It is notable that many of the patients who had markedly abnormal changes in sodium were noted on subsequent testing to no longer have serum sodium ≤ 130 mmol/L. However, it is not clear how long such changes persisted in these patients. In addition, the time period at which patients are at risk of markedly abnormal serum sodium following initiation of Nocdurna remains unclear. Therefore, until data are submitted and reviewed that addresses these concerns, we believe that monitoring of serum sodium at regular intervals should occur for the entire time a patient is taking NOCDURNA. Abnormal values should be closely monitored to document the time course of their resolution.

We further note that Nocdurna-associated hyponatremia was increased in patients over 65 years of age compared to younger patients, and that geriatric patients are also more likely to report nocturia. We note that in countries where Nocdurna has been approved, the drug is not recommended for use in patients greater than 65 years of age. This situation presents a major safety consideration that ought to be deliberated by the panelists on the upcoming advisory committee meeting.

4. Consultant's Recommendations

To reiterate, we have concerns in three main areas: 1) the small size of the observed treatment effect, 2) the urological heterogeneity of the study population, and 3) the significant risk of hyponatremia.

4.1 Re: Small Size of the Observed Treatment Effect

We agree with DMEP that the small placebo-subtracted treatment effect and the lack of a satisfactory measure of meaningful clinical benefit preclude an adequate assessment of clinical efficacy for NOCDURNA. In our opinion, it is currently unknown as to what constitutes clinically meaningful benefit in the treatment of nocturia. Additional investigations in this area,

with specific explorations of what constitutes meaningful benefit to nocturia patients, would be appropriate prior to deciding upon endpoints for Phase 3 studies.

4.2 Re: Urological Heterogeneity of the Study Population

For the proposed indication, a homogenous population should be studied that has simple overproduction of urine at night, a normal capacity bladder, and no bothersome lower urinary tract symptoms due to OAB or BPH. The following are proposals for eligibility criteria in a new study

For study inclusion

- Nocturnal frequency ≥ 3 . [*Enriching the population may identify patients who will have a more pronounced treatment effect and a population with an improved risk: benefit ratio.*]
- Documentation of nocturnal polyuria with $\geq 40\%$ of 24 hour urinary volume produced at night [*Enriching the population may identify patients who will have a more pronounced treatment effect and a population with an improved risk: benefit ratio.*]
- Patients who have normal bladder capacity. One approach could be to use Nocturnal Bladder Capacity index (NBCi) of ≤ 2.0 [*This criterion ensures that nocturia is not likely to be related to abnormally low bladder capacity.*]
- Patients likely to have nocturnal urine overproduction. One approach could be to use Nocturia Index (Ni) > 1.5 .
- Mean 24 hour urine volume not less than 1700 mL [*Lower than normal daily urine production may mask or decrease nocturia symptoms.*]
- Men should have an AUA-SS score of ≤ 7 for questions 1 through 6 (nocturia question excluded) [*This is to ensure that BPH is not a significant factor in nocturia frequency*]

For study exclusion

- Exclude patients using anticholinergics for OAB, and alpha blockers or daily PDE5i medications for BPH. [*All of these medications may influence the frequency of nocturia. If it is desirable to study nocturia in BPH patients, this study should be performed in a separate protocol and for a separate indication.*]
- Exclude patients who, after a placebo run-in period of 21 days (which includes lifestyle modification), no longer meet study entry criteria. [*This is another effective enrichment strategy.*]
- Exclude patients with > 8 daytime voids, ≥ 1 daily urgency episode, or ≥ 1 daily urge incontinence episode at screening. [*The potential shift of free water clearance from night to daytime could unmask OAB symptoms. If it is desirable to study OAB patients, this study should be performed in a separate protocol and for a separate indication.*]

Concern regarding widespread use

- Based on the eligibility criteria used in the Sponsor's completed trials (at least 2 nocturnal voids every night, nocturnal polyuria with $\geq 33\%$ of 24 hour urinary volume produced at night, etc) approximately 50% of all adults ≥ 65 years of age would be eligible for treatment. Such widespread use, especially in a vulnerable population, if the drug were approved, would be concerning.

4.3 Re: Significant Risk of Hyponatremia

Most serious adverse drug reactions (SADRs) for Nocdurna were reported in connection with hyponatremia. Most SADRs in adults over 65 years of age were reported in connection with hyponatremia. Markedly abnormal serum sodium was a dose-related phenomenon, even at the to-be-marketed doses. Markedly abnormal serum sodium was generally, but not always, reported within approximately 1 month of initiating treatment. However, there were infrequent reports of markedly abnormal serum sodium occurring out to 2 years.

The following questions concerning hyponatremia should be considered by the AC panelists:

- Will the use of NOCDURNA be restricted to patients ≤ 65 years of age?
- What serum sodium monitoring strategy is optimal? Should patients be monitored for serum sodium for as long as they take NOCDURNA, when should they be monitored in relation to dose, and how frequently should serum sodium be measured?
- In Studies CS 29 and CS 31, in patients with markedly decreased serum sodium (<130 mmol/L):
 - Was the markedly abnormal serum sodium result verified with repeat serum sodium determination(s)? If so when?
 - How long did the markedly abnormal serum sodium persist?
 - Did the occurrence of markedly abnormal serum sodium occur multiple times in the same patient?
 - What interventions, if any, were used to treat the hyponatremia? Were these successful? Did markedly abnormal serum sodium recur after intervention? Was chronic hyponatremia reported, and if so, how was chronic hyponatremia defined?

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/s/

A R WIEDERHORN
12/10/2014

MARK S HIRSCH
12/10/2014
I concur.

HYLTON V JOFFE
12/10/2014

**CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA
DPP CONSULT # 11482**

Consultant Reviewer: Tiffany R. Farchione, M.D.
Medical Officer
Division of Psychiatry Products

Consultation Requestor: Jennifer Johnson
Regulatory Project Manager
Division of Metabolic and Endocrine Products

Subject of Request: NDA 22517/Complete Response resubmission

Date of Request: September 19, 2014

Desired Completion Date: November 21, 2014

I. Background

On July 31, 2014, the sponsor, Ferring Pharmaceuticals, Inc., submitted a Complete Response resubmission (S-030) to NDA 22,517. Under this 505(b)(2) NDA, the sponsor is seeking an indication for the treatment of nocturia for their product, Nocdurna (desmopressin) orally disintegrating tablets, 25 mcg and 100 mcg. This is the third review cycle for this application.

Desmopressin is currently indicated for the treatment of central diabetes insipidus and primary nocturnal enuresis, and is available for injection, for administration via rhinal tube, and as oral tablets or nasal spray. Current labeling describes a dose range for adults and children from 0.05 mg to 1.2 mg daily, typically in divided doses, with an optimal dose range from 0.1 mg to 0.8 mg daily. Desmopressin is contraindicated in patients with moderate to severe renal impairment (defined as a creatinine clearance below 50ml/min), and in patients with hyponatremia or a history of hyponatremia. Its label includes warnings related to elevations in blood pressure and severe allergic reactions, as well as advice to monitor fluid intake. Associated adverse events include headache and abdominal pain.

NDA 22,517 was initially submitted in June, 2009. Two review cycles have resulted in Complete Response actions, each followed by End of Review meetings during which the sponsor attempted to identify a path forward for this products' development program. From a clinical perspective, FDA identified marginal efficacy at 50 and 75 mcg doses, but unacceptably high risk of hyponatremia at the more clearly effective dose of 100 mcg. The End of Review meeting minutes from the second review cycle (May, 2013) note several times that the placebo-subtracted difference is relatively small, the risk of severe hyponatremia cannot be entirely eliminated in clinical practice, and that similar efficacy can be achieved with behavioral and lifestyle modifications at virtually no safety risk. The May, 2013 meeting minutes also state:

The FDA said it would review any new sleep data that the applicant might have along with any relevant information from the literature that might support the clinical relevance of the improvement in sleep seen in patients treated with Nocdurna. However, such literature has to be specific to the situation seen in the clinical trial.

In February, 2014, FDA and Ferring discussed Ferring's Complete Response resubmission via teleconference. At that time, the FDA provided review questions for the sponsor to address in the

resubmission. Among those questions, FDA asked the sponsor to provide literature support for the expected clinical benefit of the placebo-subtracted increase in time to first awakening which was observed in the clinical trials, as well as “other impacts on lifestyle or health” that the sponsor could provide. The Division of Psychiatry Products (DPP) was consulted on September 19, 2014 to comment on the sponsor’s responses to these questions. The review in section II below is focused on this question, and does not address other aspects of the submission.

II. Review of Complete Response Resubmission

In the Complete Response Resubmission, the sponsor makes the argument that sleep disturbance is a major cause of the morbidity associated with nocturia, and that even 39-49 minutes (as observed in studies CS40 and CS41) of additional sleep prior to first awakening (first uninterrupted sleep period, FUSP) can be considered clinically relevant due to its association with normal duration and quality of sleep and increased protection of slow wave sleep (SWS).

The sponsor reached this conclusion by drawing data from several sources:

- Phase 3 trial CS29—In this study, the Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality. Higher scores on the PSQI indicate lower subjective sleep quality. Improvements in FUSP were associated with improvements in (i.e., lower) PSQI scores. A 60-minute increase in FUSP was associated with significant improvement in 6 of the 7 PSQI subscales. Thus, the sponsor suggests that increases in FUSP can be used to indicate deeper, longer, and better quality sleep.
- The sponsor also suggests that increases in FUSP can result in more SWS. SWS occurs predominantly in the first 3-4 hours of sleep; therefore, if an individual can sleep for a longer period of time early in the night, that person will experience more SWS.
- The sponsor goes on to cite evidence that sleep, and slow wave sleep (SWS) in particular, are associated with endocrine and metabolic processes, including changes in blood pressure, heart rate, growth hormone, cortisol, insulin sensitivity and glucose tolerance. Thus, if Nocturna can increase FUSP, a patient may experience more SWS, and may, in turn, avoid or mitigate some of the physiologic consequences of chronic sleep disturbance.
- The sponsor asserts that “in about a third of nocturia episodes, bladder signaling awakens nocturia patients specifically during deep sleep, thus interrupting SWS directly.” This assertion is based on a study of 20 patients with benign prostatic hypertrophy. During that study, 14 patients experienced nocturia, with a total of 23 nocturia episodes. Seven of those episodes (30%) occurred during deep sleep (by polysomnography). In this reviewer’s opinion, it appears that the sponsor may be overgeneralizing the results of this small study.
- The sponsor further references conference proceedings and a published abstract describing a study of 17 older Japanese adults using portable electroencephalography to assess sleep. Based on this data, the sponsor states that waking for the first void within the first two sleep cycles was associated with a significantly shorter SWS sleep compared with those with a FUSP duration of more than two sleep cycles.
- Phase 3 trials CS40 and CS41—FUSP \geq 4 hours (i.e., longer than two sleep cycles) is associated with improvements in ratings of Nocturia related quality of life (N-QoL). Subjects who had a FUSP of <4 hours at baseline and FUSP consistently \geq 4 hours at Month 1 and Month 3 had significantly better N-QoL scores compared with those who

did not consistently experience a FUSP ≥ 4 hours during the trial ($p < 0.0001$). In addition, Nocturna-treated patients were 2.2 times more likely to have a FUSP ≥ 4 hours in CS40 and CS41.

With regard to presenting data on “other impacts on lifestyle or health,” the sponsor asserts the following:

The true clinical impact of nocturia is manifested by adverse effects on sleep and overall quality of life. Much of this impact is attributable to chronic sleep disruption. Relatively small reductions of nighttime voids, therefore, have significant and widespread impact on nocturia related morbidities.

To support this statement, the sponsor presents additional details related to the already noted physiologic consequences of chronic sleep disturbance, and the impact of nocturia on a number of factors related to quality of life.

It is important to note that the sponsor’s submission does not provide new clinical trial data. Rather, the sponsor provides post-hoc analyses of existing trial data in the context of selected literature, ostensibly contributing additional “benefit” considerations to the benefit-risk evaluation.

III. Consult Questions

In their initial consult request, DMEP listed the following comments:

Please provide clinical consultative (sleep) input to DMEP for the review of the July 31, 2014 resubmission (response to Complete Response letter dated January 30, 2013) in preparation for the Advisory Committee meeting scheduled for **January 12, 2015**. Specifically, please comment on the sponsor’s response to our Question 11 Clinical Significance of Nocturia, Question 11a: Nocturia and Sleep Quality (Response 12.1); and the subsection “Sleep Disruption: Function and Physiology” under Question 11c: Nocturia and Health related Quality of Life (Response 12.3). The response document is located in Module 1 of the NDA resubmission, and the relevant questions cited above begin on page 111. Direct link to EDR submission:
<\\CDSESUB1\evsprod\NDA022517\0027>

The DMEP clinical reviewer is Bill Lubas, and the clinical team leader is Dragos Roman. As we prepare for this AC we are also working closely with our urology colleagues in the Division of Bone, Reproductive and Urologic Products (DBRUP), including: Roger Wiederhorn (clinical reviewer), Mark Hirsch (clinical TL) and Hylton Joffe (division director). We will be sure to invite the assigned reviewer(s) to upcoming meetings and AC practice sessions once a DPP clinical reviewer has been assigned. Many thanks, DMEP clinical team (*Note: the FDA background package is due to ACS on **December 12, 2014**. The PDUFA goal date is January 31, 2015.*)

DPP response:

The sponsor makes an argument that, on face, appears valid. The fact that SWS occurs predominantly in the first few hours of sleep is, indeed, well-established. The literature also suggests that chronic disruption of SWS can negatively impact an individual's general health. However, Nocdurna's impact on SWS was never objectively measured.

The sponsor asserts that improving the FUSP is a proxy measure for improving SWS, yet offers scant evidence to support that claim. Specifically, the sponsor cites a small study using polysomnography and inflates the estimate of nocturia's effect on SWS (30% to "about a third"). Further, the sponsor attempts to connect improvements on the PSQI with "deeper, longer, and better quality sleep;" however, the evidence correlating subjective sleep quality assessments with objective measures of SWS, total sleep time, sleep efficiency, or other sleep parameters is mixed at best.

IV. Conclusions and Recommendations

Although there is some face validity to the sponsor's argument that a placebo-subtracted increase of 39-49 minutes in FUSP may improve health-related quality of life, the means by which that conclusion is reached requires several inferential steps, each based on limited direct evidence. The sponsor is making an argument based on a proxy in the absence of objective evidence. The argument would be more compelling if the sponsor had polysomnographic data to support the claim that improvements in FUSP are related to increases in SWS; even in that case, there would still be an additional inferential leap required before one could conclude that Nocdurna improves health-related quality of life or reduces the risk of long-term consequences of chronic sleep disturbance. Whether these potential benefits impact the overall benefit-risk analyses in a meaningful way will be determined by the primary review division.

If the primary review division chooses to take a Complete Response action and request additional data, it would be useful to include polysomnography (PSG) in any future clinical trials. If the sponsor can objectively demonstrate that patients treated with Nocdurna experience more SWS than placebo-treated patients, then the subjective evidence of improvement (the long-term health and quality of life arguments) may be considered as confirmatory evidence. A trial could include PSG at baseline and endpoint as a secondary outcome measure. From that data, one could directly measure the time spent in SWS during the FUSP, as well as total SWS during the entire sleep episode.

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Tiffany R Farchione, M.D.

Cc: HFD-130
/Farchione
/Mathis
/Berman
/David

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/s/

TIFFANY R FARCHIONE
12/03/2014

MITCHELL V Mathis
12/04/2014

LABEL AND LABELING REVIEW

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 10, 2014
Requesting Office or Division: Division of Metabolic and Endocrinology Products (DMEP)
Application Type and Number: NDA 22517
Product Name and Strength: Nocdurna (desmopressin) orally disintegrating sublingual tablets, 25 mcg and 50 mcg
Product Type: Single ingredient
Rx or OTC: Rx
Applicant/Sponsor Name: Ferring Pharmaceuticals, Inc.
Submission Date: July 31, 2014
OSE RCM #: 2014-1544
DMEPA Primary Reviewer: Sarah K. Vee, PharmD
DMEPA Team Leader: Yelena Maslov, PharmD

1 REASON FOR REVIEW

Division of Metabolic and Endocrinology Products requested that DMEPA review the proposed blister label, carton and insert labeling for Nocurna (NDA 22517) for areas of vulnerability that could lead to medication errors.

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
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	N/A
ISMP Newsletters	N/A
Other	N/A
Labels and Labeling	D

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant revised the blister label and carton labeling according to our recommendations from our previous review except for one item (See Section 4.1). We find the revisions acceptable.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the revised container label and carton labeling are acceptable except for the color for the 50 mg strength statement.

4.1 RECOMMENDATIONS FOR FERRING

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

1. The use of the same color font for the proprietary name and the product's strength (50 mg) minimizes the prominence of the proprietary name and the strength. Therefore, we recommend that you revise the color fonts used for the strengths, so that they do not overlap with the color fonts of the proprietary name and with each other.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Nocdurna that Ferring Pharmaceuticals submitted on July 31, 2014.

Table 2. Relevant Product Information for Nocdurna	
Initial Approval Date	N/A
Active Ingredient	Desmopressin acetate
Indication	for treatment of nocturia due to nocturnal polyuria in adults who awaken two or more times each night to void
Route of Administration	Sublingual
Dosage Form	Orally disintegrating sublingual tablets
Strength	25 mcg, 50 mcg
Dose and Frequency	1 tablet at bedtime (25 mcg for women, 50 mcg for men)
How Supplied	Blisterpacks (3 x 10 or 2 x 4) in cartons
Storage	(b) (4) excursions permitted to 15° – 30°C (50° – 86°F). Keep in original package to protect from moisture and light. Use immediately upon opening individual tablet blister.
Container Closure	The primary packaging consists of a blister pack with (b) (4) ten (b) (4) cavities containing the orally disintegrating tablets. Blister packs are packed in paper cartons.

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on October 24, 2014 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter²

Date Range	August 1, 2012 to October 24, 2014
Product	Desmopressin [active ingredient] Desmopressin acetate [active ingredient]
Event (MedDRA Terms)	Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Quality Issues (NEC)[HLT] Product Physical Issues (HLT) Route of Administration: BUCCAL; ORAL; SULINGUAL

B.2 Results

Our search resulted in zero cases.

B.3 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:drive on August 19, 2014 using the terms, Nocdurna to identify reviews previously performed by DMEPA.

C.2 Results

Our search identified two previous reviews¹, and we confirmed that our previous recommendations were implemented.

¹ Vee, S. Label and Labeling Review for Nocduna (NDA 22517). 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); 2012 Dec 6. 32 p. OSE RCM No.: 2012-1748.

Toombs, L. Label and Labeling Review for Nocduna (NDA 22517). 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); 2010 Apr 15. 32 p. OSE RCM No.: 2009-1554.

APPENDIX D. LABELS AND LABELING

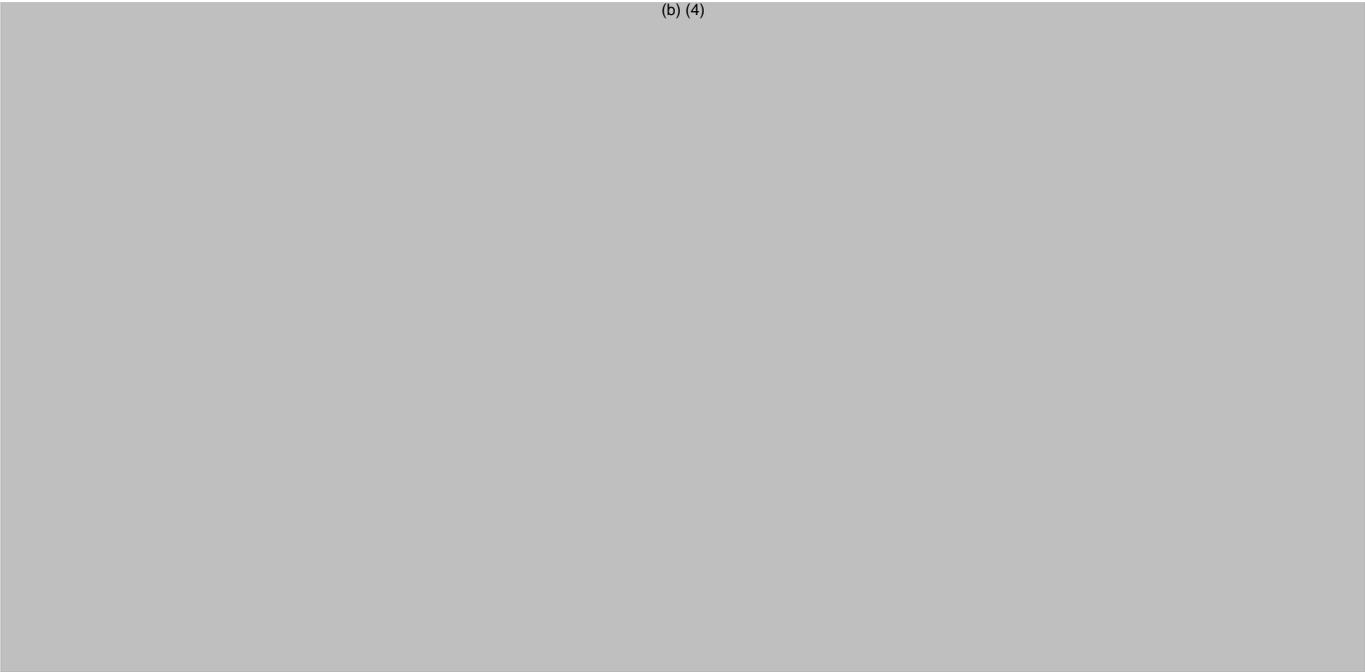
D.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,² along with postmarket medication error data, we reviewed the following Nocdurna labels and labeling submitted by Ferring on July 31, 2014.

- Trade Blistercard label
- Trade Carton labeling
- Professional Sample Blistercards
- Professional Sample Carton Labeling

D.2 Label and Labeling Images

(b) (4)



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

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/s/

SARAH K VEE
11/10/2014

YELENA L MASLOV
11/12/2014

STUDY ENDPOINT CONSULT REVIEW

SEALD TRACKING NUMBER	2013-175
IND/NDA/BLA NUMBER	NDA 022517
LETTER DATE/SUBMISSION NUMBER	SDN 28
PDUFA GOAL DATE	
DATE OF CONSULT REQUEST	December 12, 2013
REVIEW DIVISION	Division of Metabolism and Endocrinology Products (DMEP)
MEDICAL REVIEWER	William Lubas / Dragos Roman
REVIEW DIVISION PM	Jennifer Johnson
SEALD REVIEWER(S)	James P. Stansbury
SEALD ENDPOINTS TEAM LEADER	Elektra J. Papadopoulos
SEALD DIRECTOR	Sandra A. Kweder
REVIEW COMPLETION DATE	February 10, 2014
ESTABLISHED NAME	desmopressin orally disintegrating sublingual tablets
TRADE NAME	Nocturna
SPONSOR/APPLICANT	Ferring Pharmaceuticals, Inc.
CLINICAL OUTCOME ASSESSMENT TYPE	PRO
ENDPOINT(S) CONCEPT(S)	<i>health-related quality of life in nocturia;</i> <i>nocturia impacts</i>
MEASURE(S)	Nocturia Quality of Life (N-QOL) questionnaire; Nocturia Impact (NI) Diary
INDICATION	treatment of nocturia
INTENDED POPULATION(S)	adults with nocturia, with separate dosing for men and women
NOTE	This consultation requested the presence of the SEALD reviewer for internal discussion and at a dispute resolution discussion with the sponsor. Further detail is available under the NDA in DARRTS. See the dispute appeal meeting notes filed January 10, 2014 and the ODE II, Appeal Denied letter filed January 15, 2014. Our review of NDA COA issues is filed May 10, 2013.

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/s/

JAMES P STANSBURY
02/10/2014

ELEKTRA J PAPADOPOULOS
02/11/2014

MEMORANDUM OF CONSULTATION

Date: December 16, 2013

From: Donald McNellis, MD
Medical Officer, Division of Bone, Reproductive and Urologic Products

Suresh Kaul, MD, MPH
Medical Team Leader, Division of Bone, Reproductive and Urologic Products

Christine Nguyen, MD
Deputy Director for Safety, Division of Bone, Reproductive and Urologic Products

To: Sara Stradley, ADRA
Office of Drug Evaluation II

Curtis Rosebraugh M.D., Director
Office of Drug Evaluation II

Subject: The Basis for Approval of Drugs with an Overactive Bladder (OAB) Indication

This memorandum is a reply to your request for consultation regarding the criteria that have been used by DBRUP for the approval of drugs for OAB.

Background

Ferring Pharmaceuticals Inc. has filed a formal dispute resolution request with the Office of Drug Evaluation II. The dispute involves a Complete Response that they received from the Division of Metabolic and Endocrine Products (DMEP) for NDA 22517. This NDA is an application for the use of desmopressin (Nocurna) as a treatment for nocturia. As part of the preparation for this dispute resolution meeting, DBRUP has been asked to provide information to ODE II regarding the criteria that have been used by DBRUP for the approval of medications for the treatment of overactive bladder.

Overactive Bladder Approvals

Approved Drugs

There have been fifteen drugs approved for the treatment of overactive bladder to date. The initial approval occurred in 1953 and the most recent in 2012. The complete list of approved products is shown in Table 1.

Table 1. Approved Drugs for Treatment of OAB

Date of Approval	Brand Name	Active Ingredient	Dose (s)	Sponsor	NDA #
6/28/2012	Myrbetriq	Mirabegron	25 mg, 50 mg	Astellas	202-611
12/7/2011	Gelnique 3%	Oxybutynin 3% gel	84 mg	Antares	202-513
1/27/2009	Gelnique 10%	Oxybutynin 10% gel	100 mg	Watson	022-204
10/31/2008	Toviaz	Fesoterodine fumarate	4 mg, 8 mg	Schwarz	022-030
8/3/2007	Sanctura XR	Tropium chloride	60 mg	Indevus	022-103
12/22/2004	Enblex	Darifenacin hydrobromide	7.5 mg, 15 mg	Pfizer	021-513

11/19/2004	Vesicare	Solifenacin succinate	5 mg, 10 mg	Yamanouchi	021-518
5/28/2004	Sanctura	Trospium chloride	20 mg bid	Indevus	021-595
2/26/2003	Oxytrol patch	Oxybutynin	3.9 mg/day	Watson	021-351
12/22/2000	Detrol LA*	Tolterodine tartrate	4 mg	Pharmacia (Pfizer)	021-228
12/16/1998	Ditropan XL*	Oxybutynin	5 mg, 10 mg	Ortho McNeil	020-897
3/25/1998	Detrol*	Tolterodine tartrate	2 mg, 4 mg	Pharmacia (Pfizer)	020-771
7/16/1975	Ditropan†	Oxybutynin	5 mg, 10 mg	Ortho McNeil	017-577
2/2/1955	Levsin, Cystospaz†	Hyoscyamine sulfate	0.125 mg	Redondo	009-800
4/2/1953	Pro-Banthine†	Propantheline bromide	7.5 mg, 15 mg	Shire	008-732

Trial Designs

The typical trial design for this drug class was a twelve-week randomized double-blind placebo-controlled trial. Most of the trials included more than one dose of the test medication and several included an active comparator. A placebo run-in period was employed in several trials but was not standard. The placebo run-in period was used to exclude dramatic placebo responders, those that no longer met the inclusion criteria.

Baseline symptom entry criteria varied minimally amongst the trials. All but one trial required ≥ 8 voids per day at baseline (or after placebo run-in), the one trial required ≥ 10 voids per day. Most trials required ≥ 7 urgency incontinence episode (UIE) per week (≥ 1 per day). However, Oxytrol required ≥ 10 UIE per week.

The most common primary efficacy endpoint for these trials was change from baseline as compared to placebo for weekly UIE. Many included change in daily urinary frequency as a co-primary endpoint. Vesicare was approved based upon Phase 3 clinical studies with a single primary efficacy endpoint of daily urinary frequency. However, urinary incontinence was a key secondary efficacy variable in the Vesicare trials. All trials also evaluated the change in the average void volume as a key secondary endpoint (except for one trial for which it was a co-primary endpoint).

Table 2 presents a summary of the trial designs.

Table 2. OAB Pivotal Trial Designs

		Placebo Run-in	Entry Criteria	Efficacy Endpoints
Myrbetriq		2 week	≥ 8 voids/day & ≥ 3 urgency/day or UIE/day during 3 day period	Co-Primary Δ in # micturitions/24h Δ in # UIE/ 24h
Gelnique 3%		No	≥ 8 voids/day & ≥ 1 urgency/day ≥ 7 UIE per week	Δ in # UIE/ 24h Secondary Δ in # micturitions/24h
Toviaz	583	2 weeks	≥ 8 voids/day &	Co-Primary
	584	2 weeks	≥ 6 urgency episodes or ≥ 3 UIE per 3 days	Δ in # micturitions/24h Δ in # UIE/ 24h
Sanctura		No	≥ 10 voids/day ≥ 7 UIE per 7 days	Co-Primary Δ in # micturitions/24h Δ in # UIE/ 24h

		Placebo Run-in	Entry Criteria	Efficacy Endpoints
				Δ in Average void vol
Sanctura XR	022	No	≥ 10 voids/day	Co-Primary
	018	No	≥ 3 UIE per 3 days	Δ in # micturitions/24h Δ in # UIE/ 24h
Gelnique 10%		No	≥ 8 voids/day ≥ 4 UIE per 3 days	Δ in # UIE/ 24h Secondary Δ in # micturitions/24h
Oxytrol*		No	≥ 8 voids/day ≥ 10 UIE per week	Δ in # UIE/ 24h Secondary Δ in # micturitions/24h
Enablex	1001	No	≥ 8 voids/day	Δ in # UIE/ week
	1002	2 weeks	≥ 10 & ≤ 100 UIE per 2 weeks	Secondary
	1041	2 weeks	≥ 5 & ≤ 50 UIE/week ≥ 8 voids/day & ≥ 1 urgency/day	Δ in # micturitions/ 24h
Vesicare	CL-018	2 weeks	≥ 8 voids/day ≥ 3 UIE or ≥ 3 urgency per 3 days	Δ in # micturitions/24h Secondary
	CL-015	2 weeks		Δ in # UIE/ 24h
Detrol LA		No	≥ 8 voids/day ≥ 5 UIE per week	Δ in # UIE/ 24h Secondary Δ in # micturitions/ 24h
Ditropan XL		No	≥ 10 voids/day ≥ 10 & ≤ 60 UIE per week	Δ in # UIE/ 24h

* The active comparator was tolterodine 2 mg bid.

† Active comparator was Ditropan IR (no placebo arm).

Results

As shown in Table 2, change in the number of incontinence episodes was the primary or co-primary endpoint in most of the OAB trials. Table 3 presents the change in incontinence results for the drugs approved after 2000.

Table 3. Results for Change in Incontinence Episodes per Week

	Study #	Baseline UIE (mean)	Change for Placebo (mean)	Change for Drug (mean)	Drug Activity Beyond Placebo	P value
Myrbetriq	046	19	-8.2	-11/-10.2 [†]	2.9/2.0 [†]	0.003/0.01 [†]
	047	20.6	-7.9	-10.3/-11.4 [†]	2.4/3.5 [†]	0.026/<0.001 [†]
	074	*	*	-9.5/-9.7 [†]	2.8/2.9 [†]	0.005/0.001 [†]
Gelnique 3%		42	-20	-25	5	0.14
Toviaz	583	21	-6	-13	7	< 0.0001
	584	22	-6	-15	9	< 0.0001
Sanctura		29	-13.5	-16.7	3.2	0.002
Sanctura XR	022	28	-12	-17	5	< 0.001
	018	29	-14	-18	4	0.004
Gelnique 10%		32	-18	-21	3	0.001
Oxytrol (39 cm)		31	-19	-22	3	0.05
Enablex (15 mg)	1001	20	-8.8	-15.1	6.3	0.0002
	1002	*	-5.5	-11	5.5	< 0.0001
	1041	19	-8	-10	2	0.03
Vesicare (10 mg)	018	11	-4.8	-6.3	1.5	0.22
	015	11	-2.7	-6.6	3.9	0.03
Detrol LA		*	*	*	4.8	*
Mean		23.9		-13.6	4	

[†] Myrbetriq 50mg/100mg

* Data unavailable

A simple mean of the trial results shows that on average a subject using the drug experienced 13.6 fewer weekly incontinence episodes (range 6.3 – 25). This was 4 fewer episodes per week (range 1.5 – 9) than the average subject using placebo.

Table 4 presents the results for the change in number of daily micturition episodes during the trials.

Table 4. Results for Change in Number of Daily Micturations

	Study #	Baseline Voids per day (mean)	Change for Placebo (mean)	Change for Drug (mean)	Drug Activity Beyond Placebo	P value
Myrbetriq	046	11.7	-1.34	-1.93/-1.77 [†]	0.6/0.44 [†]	<0.001/0.005 [†]
	047	11.6	-1.05	-1.66/-1.75 [†]	0.61/0.70 [†]	0.026/<0.001 [†]
	074	*	*	-1.65/-1.60 [†]	0.47/0.42 [†]	0.007/0.015 [†]
Gelnique 3%		11.4	-1.93	-2.92	1	0.001
Toviaz	583	11.7	-1	-1.8	0.8	< 0.0006
	584	12.3	-1	-2.1	1.1	< 0.0001
Sanctura		12.8	-1.5	-2.8	1.3	< 0.0001
Sanctura XR	022	13	-2	-2.8	0.8	0.007
	018	12.9	-2.1	-3	0.9	0.0001
Gelnique 10%		12.3	-2.1	-2.7	0.6	0.007
Oxytrol (39 cm)		12.1	-1.7	-2.3	0.6	0.03
Enablex (15 mg)	1001	11.1	-1.6	-2.0	0.4	0.03
	1002	11.2	-1.2	-2.1	0.9	0.007
	1041	10.9	-0.9	-1.9	1	< 0.0001
Vesicare (10 mg)	018	12.1	-1.7	-2.9	1.2	< 0.0001
	015	12.5	-1.6	-2.9	1.3	< 0.0001
Mean		12		-2.2	0.8	

[†] Myrbetriq 50mg/100mg

* Data unavailable

A simple mean of the trial results shows that on an average a subject using the drug saw a reduction in the number of daily voids of 2.2 episodes (range 1.6 – 3). This was 0.8 fewer episodes per day (range 0.4 – 1.3) than the average subject using placebo.

The adverse events seen with the OAB drugs have generally been mild and mainly involve the anticholinergic effects of the drugs. The adverse events that are seen can be adequately handled by appropriate labeling.

Discussion

Overactive bladder is a symptom complex that is defined as urinary urgency, with or without urgency incontinence, usually with urinary frequency, in the absence of other local or metabolic factors that would account for the symptoms. Most trials of drugs for treatment of overactive bladder have focused on urge incontinence episodes as the primary endpoint, because we believe improvement in incontinence episodes has clear significance for the patients. For the most part, change in daily frequency of urination has been a co-primary or secondary endpoint. The change in the average volume voided has also been commonly evaluated as a key secondary endpoint.

DBRUP as of yet has not recognized any Patient Reported Outcome (PRO) instruments as being validated to serve as primary or key secondary endpoints. Various PRO instruments have been used in phase 3 trials, but have not been used as key factors in the approval of these drugs.

As shown in Tables 3 and 4, most of the phase three trials demonstrated statistically significant differences from placebo for both the change in incontinence and the change in daily urinary frequency. While not shown in these Tables, the changes seen in average void volume were similar; there was a small but statistically significant improvement in the drug group as compared to the placebo group.

Therefore, DBRUP has approved OAB drugs based on “modest” but statistically significant changes seen in urinary incontinence and frequency, supported by improvement in average voided volume and based on a known safety profile that could be adequately managed by labeling. In each case, DBRUP considered that the benefits, however modest, offset the safety findings.

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/s/

DONALD R MCNELLIS
12/17/2013

SURESH KAUL
12/17/2013

CHRISTINE P NGUYEN
12/17/2013

STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	AT 2013-053
APPLICATION NUMBER	NDA 022517 (Refer also to IND 65890)
LETTER DATE/SUBMISSION NUMBER	April 11, 2013
PDUFA GOAL DATE	
DATE OF CONSULT REQUEST	April 15, 2013
REVIEW DIVISION	Division of Metabolism and Endocrinology Products (DMEP)
MEDICAL REVIEWER	Bill Lubas
REVIEW DIVISION PM	Jennifer Johnson
SEALD REVIEWER(S)	James P. Stansbury
REVIEW COMPLETION DATE	May 2, 2013
ESTABLISHED NAME	desmopressin orally disintegrating sublingual tablets
TRADE NAME	Nocurna
APPLICANT	Ferring Pharmaceuticals Inc.
ENDPOINT(S) CONCEPT(S)	nocturia impacts
MEASURE(S)	NQoL, NI Diary
CLINICAL OUTCOME ASSESSMENT TYPE	PRO
INDICATION	treatment of nocturia
INTENDED POPULATION(S)	adults with nocturia
NOTE	This abbreviated review includes a summary of issues and response to questions raised by the sponsor in a submission for a Type A, End-of-Review meeting. The sponsor is seeking input following a Complete Response issued January 30, 2013 (2nd review cycle).

SEALD Review

Stansbury

NDA 022517

Nocturna (desmopressin orally disintegrating sublingual tablets)

A. EXECUTIVE SUMMARY

This Study Endpoints and Labeling Development (SEALD) review is provided as a response to a request for consultation by the Division of Metabolism and Endocrinology Products regarding NDA 022517. The sponsor used the Nocturia Quality of Life Questionnaire (NQoL) for the measurement of quality of life in two pivotal trials as a secondary endpoint in adult patients with nocturia.

Following consultation with FDA as these trials were concluding, the sponsor combined insights from the literature and revised NQoL items into the form of a daily diary. The resulting Nocturia Impacts (NI) Diary was examined in cognitive interviews with an appropriate patient population, providing a tool with acceptable content validity in the proposed context of use. The NI Diary was then used in a small continuation study that randomized patients to treatment and placebo, with the primary goal of instrument validation.

Based on reexamination of existing evidence, these comments and discussion for the most part restate previous conclusions regarding trial evidence based on the NQoL and NI Diary.

- NQOL results from sponsor Trials CS40 and CS41 do not provide reliable consistent evidence for a treatment effect on patient-reported health-related quality-of-life (HRQL). Further, the NQoL is not an instrument that FDA views as fit-for-purpose in drug development trials.
- NI Diary results from sponsor Trial 000034 do not provide evidence in support of effectiveness.

There is no new trial evidence provided in the briefing package, although the sponsor has provided an additional pooled, post-hoc analysis from CS 40 and CS 41 intended to demonstrate the relationship between uninterrupted sleep duration and NQoL, awakenings presumably attributable to nocturia.

Finally, we cannot concur with the sponsor regarding secondary and exploratory PRO support for desmopressin treatment in Trials CS40 and CS41. The results were mixed and do not meet the standard for substantial evidence.

B. SUGGESTED RESPONSES TO SPONSOR QUESTIONS

The following are the preliminary meeting comments to the sponsor's questions developed in discussion between SEALD and the Division.

Clinical benefits question #1:

Does the Agency concur that the combined picture of primary, key secondary and key QoL endpoints results confirms the clinical benefit?

SEALD Review

Stansbury

NDA 022517

Nocdurna (desmopressin orally disintegrating sublingual tablets)

No, the N-QoL information is not confirmatory. As FDA noted in various discussions regarding the NQoL, we did not find the instrument fit-for-purpose as a drug-development tool for use in clinical trials. The content validity of the NQoL was observed to be weak due to:

- a long (2-week) recall period
- question framing that asks patients to attribute a general impact to the specific cause of awakening for the purpose of urination
- distal impacts that do not clearly indicate the patient's condition or implicate changes in that condition (e.g., effects on others).

As noted as early as 2007 when considering the application for IND 65890 (see communication detailing meeting of March 26, 2007), we expressed concern that instruments used in pivotal trials for desmopressin provide reproducible and consistent data.

The NQoL results from Trial CS 40 were statistically non-significant. NQoL results from Trial CS 41 were statistically significant but did not have clear clinical meaning due to issues of instrument content. Analyses from the pivotal trials where the NQoL was positioned as a secondary outcome do not provide consistent, reproducible evidence for clinical benefit.

Clinical benefit question #3:

Does the Agency concur that desmopressin increases the first period of undisturbed sleep and that this is relevant for assessing clinical benefit of treating nocturia?

Your finding is based on post-hoc, pooled, analysis and thus would not support a labeling claim.

Clinical benefits question #4:

Ferring acknowledge[s] that the Agency finds that ‘the Nocturnal Impact Diary appears to be an acceptable measure’, but would like to understand why the agency did not allow for a statement in the package insert during labeling negotiations as agreement was reached on all steps in the rapid revision process?

The NI Diary was used with 56 patients in Trial 000032, which reenrolled a subsample of CS 40 and CS 41 patients 30 days after completion. However, there were no results supportive of efficacy seen in Trial 000032. We appreciate that a “Bridging Study” was prepared, attempting to correlate results from the sample using the newer measure with NQoL results. The resulting correlation did not constitute secure evidence of treatment benefit; this was not a pre-planned test of a hypothesis capable of meeting the substantial evidence threshold. Therefore, we are unable to conclude that the NI results were supportive of treatment benefit, and hence they cannot serve as a basis for labeling claims.

Clinical benefits question #5:

Does the Agency concur that a) 7 of the 8 PRO scores supported desmopressin, and b) the WPAI productivity domain remains inconclusive due to the small sample size?

SEALD Review

Stansbury

NDA 022517

Nocturna (desmopressin orally disintegrating sublingual tablets)

Results were ambiguous with 5 of 7 of the supportive outcomes you identify having a non-significant analysis in one of the pivotal trials. FDA has been consistent that apparent 'trend' in secondary and various exploratory outcomes cannot be taken as unambiguous support for treatment benefit. The lack of consistent statistical significance in results, in addition to our reservations about instrument content expressed on multiple occasions, do not allow us to concur.

C. BACKGROUND AND SUMMARY OF ISSUES

Background

SEALD has been consulted 7 times since 2009 on this application, both under IND 65890 and NDA 022517. As noted above in comments to the sponsor from 2007, the Division earlier shared concerns about the PROs used in their clinical development program for this formulation of desmopressin.

In an initial SEALD review for IND 65890 (A.M. Trentacosti, 10/01/2009), it was recommended that the Pittsburgh Sleep Quality Index (PSQI) and the International Consultation on Incontinence Questionnaire for Nocturia (ICIQ-N) were not fit for purpose, while inadequate information about the NQoL had been provided. In separate reviews (A.M. Trentacosti, 08/31/2010a; Trentacosti, 08/31/2010b) of the Protocols for Trial CS 40 and CS41, it was stressed that development of a content valid PRO was desirable, and that the NQoL could not support labeling claims in its present form. SEALD was consulted again in June, 2011 to respond to sponsor questions regarding the NQoL and a potential path forward around the use of PROs (J.P. Stansbury, 07/15/2011). Discussion at the Type C meeting focused on a rapid instrument revision to facilitate development of the NI Diary. In November, 2009 we provided comment on the progress of development of the NI Diary and plans for the validation of the instrument (J.P. Stansbury, 01/06/2012).

Under NDA 022517, SEALD was again consulted to comment on the results from PRO analyses that were part of studies CS40 and CS41, as well as extension study CS000034. That review reaffirmed earlier concerns raised about the NQoL. We also found NQoL results to be contradictory across trials, not meeting standards for substantial evidence, while NI Diary results were inconclusive with respect to effectiveness on the basis of the small study (J.P. Stansbury, 09/27/2012). In an effort to more fully provide consideration to PRO results, we recommended specific post-hoc analyses, received that report and provided review (J.P. Stansbury, 01/07/2013). In that most recent review, we concluded:

NQoL results should not be referenced in product labeling. This review verifies that there is inconsistent evidence in the NQoL results, building on our earlier concerns regarding the instrument's content validity. The cumulative distribution displays provided in the October 15, 2012 submission accentuate the inconsistent NQoL results between treatment and placebo arms between trials.

SEALD Review

Stansbury

NDA 022517

Nocurna (desmopressin orally disintegrating sublingual tablets)

Information submitted to support the current status of the NI Diary suggests that the sponsor is committed to developing a well-defined and reliable instrument for measuring nocturia impacts. Development is not complete, although analyses with small samples indicate the scale will likely perform as a unidimensional measure.

The information provided in support of the development of the Nocturia Impact Diary is useful. However, again we see no evidence of NI Diary support for efficacy in CS000034, and observe that proposed labeling language referring to the NI Diary based on those results is inappropriate.

Additional Analyses

No new data were provided relevant to the consideration of PRO results from Trials CS40, CS41, or CS000034. However, the sponsor provided various re-analyses and data displays with respect to the specific questions raised.

The sponsor posed a question regarding the clinical significance of undisturbed sleep, using pooled post-hoc analyses in a comparison of NQoL scores. First, the sponsor showed the tendency for desmopressin to lead to less sleep interruption (roughly 50% of treatment arm without 1st nocturnal micturition vs. 30% in placebo arm), they then suggested the importance of presumably uninterrupted sleep (actually measuring time to first void) comparing means for the NQoL.

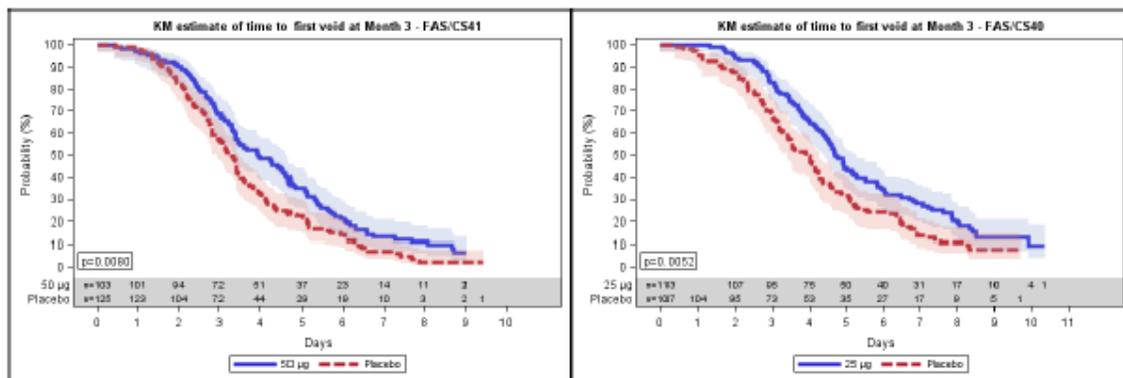


Figure 4 Kaplan-Meier plots illustrating the increase in undisturbed sleep for patients treated with placebo and desmopressin in CS40 and CS41. Patients were censored if they did not have any voids at all during the night (sleep endpoints are based on means across 3 days).

SEALD Review

Stansbury

NDA 022517

Nocturna (desmopression orally disintegrating sublingual tablets)

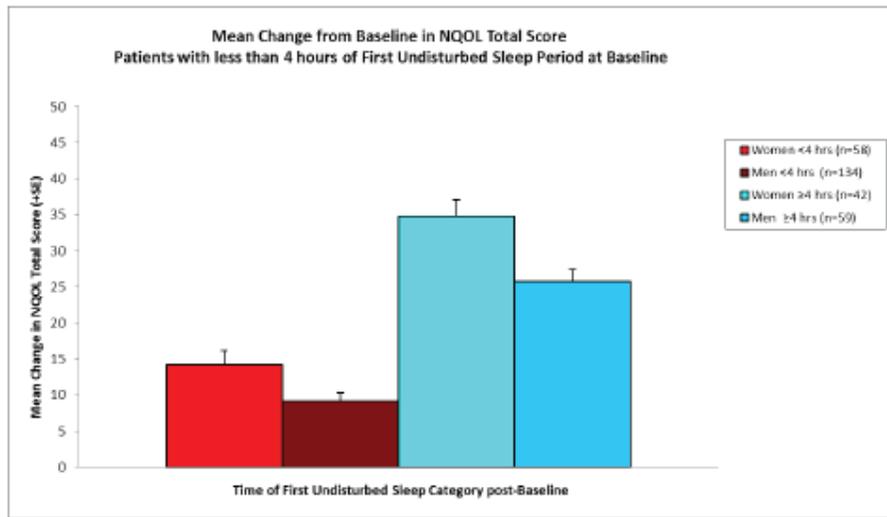


Figure 5 Mean change from baseline in N-QOL total score for men and women with <4 hrs of undisturbed sleep at baseline comparing those who had <4hrs and ≥4 hrs of undisturbed sleep during treatment. P <0.001 for difference in both men and women

Reviewer note: This NQoL analysis does not implicate product efficacy; it compares average NQoL scores by “known-groups” based on patients’ recall of time-to-first-void. It is of course suggestive of a relationship between uninterrupted sleep and patients’ perceptions of nocturia impacts. We advise the sponsor that a post hoc analysis would not support a labeling claim and otherwise defer response to the Division.

The sponsor also presents a Forest Display of PRO results from Trial CS40 and CS41. There is evident trend in the data, although the size of effects and consistency of statistical significance do not meet a standard for substantial evidence.

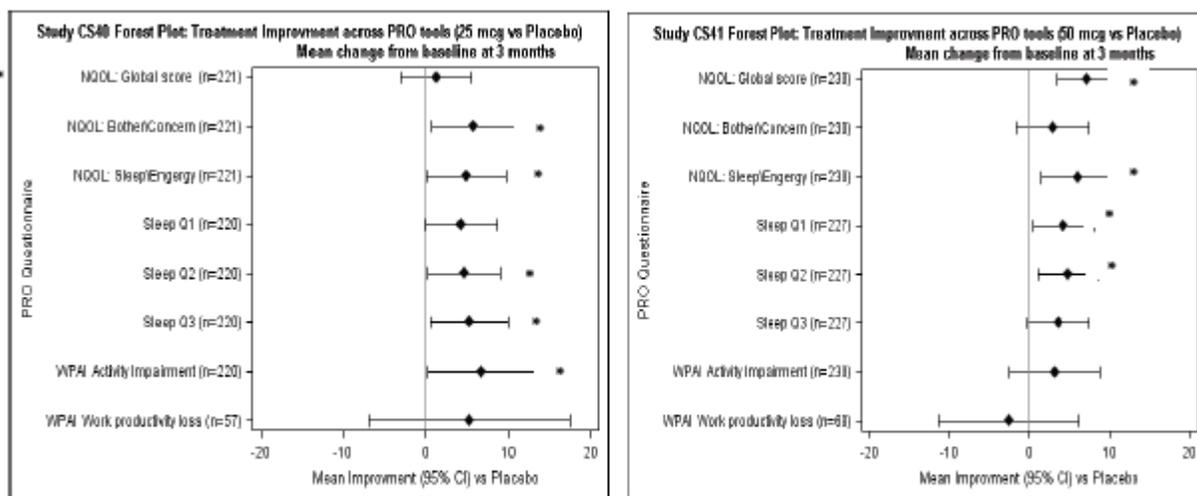


Figure 6 Forest plot of PRO Domain Scores in CS40 and CS41

SEALD Review

Stansbury

NDA 022517

Nocdurna (desmopressin orally disintegrating sublingual tablets)

Reviewer note: The sponsor raises a question as to whether PRO scores supported desmopressin. On the basis of inconsistent statistical significance and the small effects observed, we have not concurred.

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/s/

JAMES P STANSBURY
05/09/2013

LAURIE B BURKE
05/10/2013

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

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

Memorandum

Date: September 19, 2012

To: Jennifer Johnson, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Samuel M. Skariah, Regulatory Review Officer, OPDP
Kendra Y. Jones, Regulatory Review Officer, OPDP

Subject: **NDA #022517 Nocdurna (desmopressin) ODT, 25 mcg, 50 mcg**
OPDP Labeling Review

OPDP acknowledges receipt of your September 19, 2012, consult request for the proposed Package Insert, Carton/Container Labeling, and Medication Guide for Nocdurna (desmopressin) Orally Disintegrating Tablets. Reference is made to the January 30, 2013 complete response letter. As a result, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP requests that DMEP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on these proposed materials.

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/s/

SAMUEL M SKARIAH
03/08/2013

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

PATIENT LABELING REVIEW

Date: January 28, 2013

To: Hylton Joffe, M.D., Director
Division of Reproductive and Urologic Products (DRUP)

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

Melissa Hulett, RN, BSN, MSBA
Team Leader, Patient Labeling Team
Division of Medical Policy Programs

From: Twanda Scales, RN, MSN/Ed.
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name) Nocdurna (desmopressin)

Dosage Form and Route: Oral Disintegrating Tablets

Application Type/Number: NDA 22517

Applicant: Ferring Pharmaceuticals, Inc.

1 INTRODUCTION

On June 19, 2009, Ferring Pharmaceuticals, Inc. (Ferring) submitted for the Agency's review a new drug application (NDA) for NOCDURNA (desmopressin) Orally Disintegrating Tablets, indicated for the treatment of nocturia in adults. On July 30, 2012, Ferring submitted a Complete Response, in response to the Complete Response letter received from the Agency on April 22, 2010.

This review is written in response to a request by the Division of Reproductive and Urologic Products (DRUP) for the Division of Medical Policy Programs (DMPP) to provide a review for the Applicant's proposed MG for NOCDURNA (desmopressin) Orally Disintegrating Tablets.

2 MATERIAL REVIEWED

- Draft NOCDURNA (desmopressin) Orally Disintegrating Tablets (MG) received on July 30, 2012, and received by DMPP on January 24, 2013.
- Draft NOCDURNA (desmopressin) Orally Disintegrating Tablets Prescribing Information (PI) received on July 30, 2012, revised by the Review Division throughout the current review cycle and received by DMPP on January 24, 2013.

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. In our review of the MG the target reading level is at or below an 8th grade 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 APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
01/28/2013

MELISSA I HULETT
01/28/2013

LASHAWN M GRIFFITHS
01/28/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Memo

Date: January 16, 2013

Reviewer: Sarah K. Vee, PharmD
Division of Medication Error Prevention and Analysis

Team Leader Yelena Maslov, PharmD
Division of Medication Error Prevention and Analysis

Drug Name: Nocdurna (Desmopressin) Orally Disintegrating Sublingual
Tablets, 25 mcg and 50 mcg

Application Type/Number: NDA 022517

Applicant/sponsor: Ferring Pharmaceuticals, Inc.

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised container label and carton labeling for Nocdurna (Desmopressin) Orally Disintegrating Sublingual Tablets submitted in response to the Division of Medication Error Prevention and Analysis's (DMEPA's) previous comments to the Applicant in OSE Review #2012-1748, dated December 6, 2012.

2 MATERIAL REVIEWED

The revised container label and carton labeling submitted to the Agency on January 7, 2012 (See Appendices) and OSE Review #2012-1748, dated December 6, 2012, were evaluated to assess whether the revisions adequately address our concerns from a medication error perspective.

3 RECOMMENDATIONS

Please note that all revisions to carton labeling and blister card labels must be done prior to approval of the NDA.

A. *Carton Labeling*

1. We continue to recommend the format below. The format that we recommend is the usual format of how proprietary name, established name, dosage form, and the strength should be presented on labels and labeling. Thus, pharmacists are well aware of where to locate the strength information. Currently, because the strength statement appears next to proprietary name, it can be misinterpreted as part of the proprietary name (i.e. Nocdurna 25 or Nocdurna 50).

Nocdurna

(Desmopressin) Orally Disintegrating Sublingual Tablets

xx mcg

2. Revise the color font of the proprietary name to be the same for both the 25 mcg and 50 mcg strengths, so that it does not overlap with the colors of the strength statements. Currently, the reverse color font of the proprietary name is confusing and may lead to the wrong strength selection. Ensure the color font chosen for the name does NOT overlap with the color fonts chosen for the strength statement.
3. Step #4 of the "How to take Nocdurna": We recommend bolding the entire sentence "Place the tablet under your tongue."
4. The statement "ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide. Do not break open and dispense partial quantities." should be revised to include "Due to space limitation on the blisters, "Orally Disintegrating Sublingual Tablet" has been abbreviated to "ODST"." This statement should be added to clearly state what the new abbreviation "ODST" stands for to avoid confusion and medication errors to read as follows:

ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide. Do not break open and dispense partial quantities. Due to space

limitation on the blisters, "Orally Disintegrating Sublingual Tablet" has been abbreviated to "ODST".

B. *Blister Label*

1. See comment A.1 above
2. Revise the proprietary name to appear in title case (i.e. Nocdurna). Words set in upper and lower case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all-caps.
3. The established name should be placed in parenthesis (Desmopressin).
4. Differentiate the product strengths with color, boxing, or some other means.

If you have further questions or need clarifications, please contact OSE Regulatory Project Manager Ermias Zerislassie at 301-796-0097.

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/s/

SARAH K VEE
01/16/2013

YELENA L MASLOV
01/16/2013

STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	AT 2012-091 (addendum)
APPLICATION NUMBER	NDA 022517
LETTER DATE/SUBMISSION NUMBER	October 15, 2012
PDUFA GOAL DATE	
DATE OF CONSULT REQUEST	September 11, 2012 (follow-up)
REVIEW DIVISION	Division of Metabolism and Endocrinology Products (DMEP)
MEDICAL REVIEWER	Bill Lubas, MD
REVIEW DIVISION PM	Jennifer Johnson
SEALD REVIEWER(S)	James P. Stansbury
REVIEW COMPLETION DATE	January 3, 2013
ESTABLISHED NAME	desmopressin orally disintegrating tablets
TRADE NAME	Nocturna
APPLICANT	Ferring Pharmaceuticals Inc.
ENDPOINT(S) CONCEPT(S)	health-related quality of life
MEASURE(S)	Nocturia Quality of Life (NQoL); Nocturia Impact (NI) Diary
CLINICAL OUTCOME ASSESSMENT TYPE	PROs
INDICATION	nocturia
INTENDED POPULATION(S)	adults with nocturia
NOTE	This summary discusses post hoc analyses provided by the sponsor to aid FDA evaluation of the extent to which NQoL and NI Diary results might be taken as supportive of product efficacy and merit inclusion in product labeling. It provides an addendum to the consult review filed September 27, 2012.

SEALD Review

Stansbury

NDA 022517

Nocdurna (desmopressin orally disintegrating tablets)

A. EXECUTIVE SUMMARY

This addendum to a Study Endpoints and Labeling Development (SEALD) review is provided as a response to a request for consultation by the Division of Metabolism and Endocrine Products regarding NDA 022517. In response to the FDA's request of October, 4, 2012, the sponsor submitted cumulative distribution plots for the Nocturia Quality of Life (NQoL) questionnaire scores from 2 pivotal trials reported earlier. The graphics were provided to aid FDA's determination if NQoL results give evidence of product efficacy or merit inclusion in product labeling. The sponsor also submitted additional analyses detailing development of the NI Diary.

NQoL results should not be referenced in product labeling. This review verifies that there is inconsistent evidence in the NQoL results, building on our earlier concerns regarding the instrument's content validity. The cumulative distribution displays provided in the October 15, 2012 submission accentuate the inconsistent NQoL results between treatment and placebo arms between trials.

Information submitted to support the current status of the NI Diary suggests that the sponsor is committed to developing a well-defined and reliable instrument for measuring nocturia impacts. Development is not complete, although analyses with small samples indicate the scale will likely perform as a unidimensional measure.

The information provided in support of the development of the Nocturia Impact Diary is useful. However, again we see no evidence of NI Diary support for efficacy in CS000034, and observe that proposed labeling language referring to the NI Diary based on those results is inappropriate.

B. REVIEW OF SUPPLEMENTARY SUBMISSION

Background

Earlier SEALD consultations on this application are found under IND 65890 and NDA 022517, with the last review dated September 27, 2012.

The sponsor originally proposed the use of three patient-reported outcome instruments for pivotal trials, including the NQoL, the Pittsburgh Sleep Quality Index (PSQI), and the International Consultation on Incontinence Questionnaire for Nocturia (ICIQ-N). In an initial review under the IND, the PSQI and ICIQ-N were determined not to be measures of nocturia impacts. The reviewer also identified issues related to NQoL content including missing impact domains, inclusion of items unrelated to treatment effect, and the instrument's 2-week recall period (Trentacosti, 10/01/2009).

FDA sent the sponsor a Complete Response (CR) letter on April 22, 2010 for NDA 22517 and a second SEALD consultation was requested in June, 2011 for a Type C meeting request. A publication was provided in the sponsor's submission demonstrating that the NQoL had a basis

SEALD Review

Stansbury

NDA 022517

Nocturna (desmopressin orally disintegrating tablets)

in qualitative research with nocturia patients. However, multiple concerns with instrument content remained, including recall. With the Division's urging, a path forward was found involving a rapid instrument revision process. FDA proposed that the sponsor develop a Nocturia Impact Diary (NI Diary) that could be used in future trials, with a relatively small validation study enrolling patients from the ongoing clinical trials (Stansbury, 07/15/2011).

Per agreement reached in the 2011 meeting, the sponsor submitted a dossier detailing development work on the NI Diary. The work was reviewed by SEALD (Stansbury, 01/06/2012) and the Division as discussed in the July 2011 Type C meeting, with comments provided to the sponsor on 01/20/2012.

In June, 2012 a sponsor submission, summarizing pivotal trials CS40 and CS41 as well as the Nocturia Impact Study CS000034, was aimed at addressing deficiencies outlined in the FDA complete response. SEALD was consulted regarding study results using the Nocturia Quality of Life (NQoL) questionnaire, Work Productivity and Activity Index (WPAI) questionnaire, and Nocturia Impact (NI) Diary (Stansbury, 09/27/2012).

As part of that review, SEALD requested that the sponsor provide a series of cumulative distribution function analyses to complement earlier analyses from studies CS40 and CS41. Additional analyses detailing NI Diary results from CS000034 were also requested. SEALD wished to verify its earlier evaluation of results and provide the basis for feedback on continued development of a well-defined and reliable instrument for use in nocturia trials.

Cumulative Distribution Displays for NQoL Results

NQoL results should not be referenced in product labeling.

Reviewer note: As noted in previous reviews, SEALD has not found the content validity of the NQoL to be strong for use in the context of drug development trials. The "worry" and "concern" items fail as clear effect indicators of treatment benefit and the two-week recall period is less than optimal for efficacy determinations in trial use. Finally, the protocols for studies CS40 and CS41 proposed the NQoL use as an exploratory outcome, rather than clearly placing it in the hierarchy of secondary endpoints.

Despite an optimistic display in one of the sponsor's summary reports, there were inconsistent results from the questionnaire in these two trials. In post-hoc analyses from CS40, the global item showed no significant difference between placebo and treatment and was actually better for placebo on average at Month 1. The adjusted mean total score showed no significant contrast between arms at Month 1, but was significant at Month 3; the fully adjusted longitudinal model for average treatment effect showed a treatment contrast of 3.17 points (of 100) and did not achieve statistical significance. However, the results from CS41 for the global indicator and total score were statistically significant, although treatment contrast was again small with results driven by apparent changes in the sleep/energy domain (Appendix A).

SEALD Review

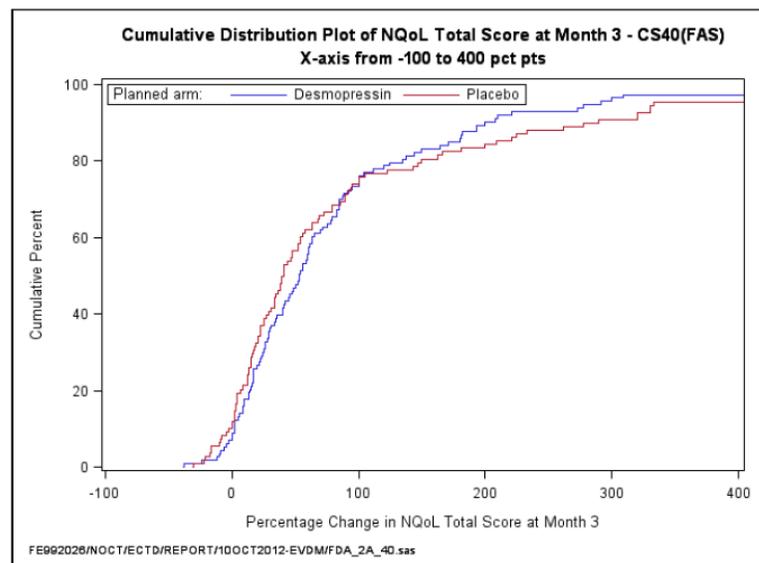
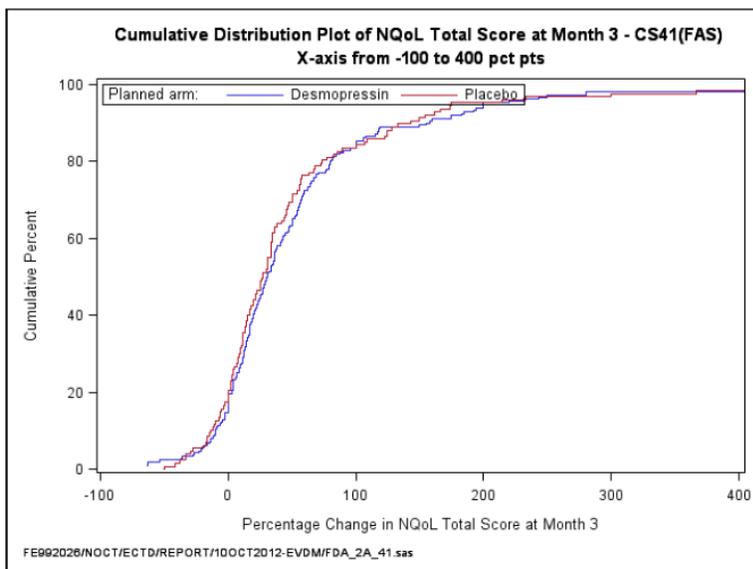
Stansbury

NDA 022517

Nocurna (desmopressin orally disintegrating tablets)

SEALD requested cumulative distribution displays because there was no well-defined threshold for individual clinically meaningful change for the NQoL in nocturia trials. The exemplars below are illustrative of the issues with inferring conclusions of benefit from these results.

The cumulative distribution function curve for an effective treatment measured with a well-defined and reliable instrument would generally be consistently shifted to the left of the curve for placebo in the area above 0 (i.e. greater change reflects improvement) when comparing percentage change in individual scores using the cumulative distribution plots. Despite the results from adjusted models, the score improvements between arms are not consistent or interpretable, showing slight, inconsistent differences in change between treatment and placebo.



SEALD Review

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Nocurna (desmopressin orally disintegrating tablets)

Reviewer note: Across the multiple submitted cdf plots, placebo and treatment cross frequently, while in most cases apparent improvements in total or domain scores appear more likely in the placebo group for changes from baseline less than 100%. Assuming that plot labeling is correct in the sponsor's submission, the results do not show consistent, meaningful improvement in the NQoL results.

NI Diary Development

NI Diary results are not appropriately included in product labeling at this time. However, a table detailing the sponsor's progress in instrument development is found in Appendix B.

Reviewer note: As noted in our previous review, NI Diary results from Study CS000034 were not supportive of labeling claims for efficacy, although the instrument showed promising responsiveness based on comparison with reductions in nocturnal voids. The fact that the NI Diary and the NQoL share a low to moderate correlation with self-reported changes in nocturnal voiding frequency cannot be taken as support for efficacy based on the current results.

The sponsor's work to date shows that the NI Diary will likely provide a useful unidimensional measure of *patient-identified impacts and key concerns in nocturia* in future trials. In the current submission, the sponsor provided rationale for the current form of the instrument. Although the *future worry* item did not scale with the symptoms and impacts items, the sponsor chose to retain the question. The productivity item also misfit, likely due to the unusual framing that may have led respondents to misunderstand the question. This item was also retained, justified by the fact these analyses were preliminary.

Item fit

Item does not fit model if $p < 0.05$

Item	Type	Location	SE	FitResid	DF	ChiSq	DF	Prob
I0001	Poly	1.848	0.291	0.33	18.23	0.622	2	0.732736
I0002	Poly	1.01	0.222	-0.32	18.23	1.275	2	0.52867
I0003	Poly	0.912	0.237	-0.345	18.23	5.324	2	0.069823
I0004	Poly	1.134	0.204	-0.523	18.23	7.337	2	0.025521
I0005	Poly	-0.721	0.192	-0.609	18.23	2.173	2	0.337362
I0006	Poly	-0.656	0.23	0.251	18.23	2.783	2	0.248681
I0007	Poly	-1.194	0.166	0.406	18.23	1.829	2	0.400784
I0008	Poly	-1.213	0.164	0.525	18.23	1.017	2	0.60125
I0009	Poly	-1.309	0.193	0.957	18.23	3.53	2	0.171183
I0010	Poly	-1.167	0.181	1.285	18.23	1.367	2	0.504858
I0011	Poly	3.135	0.354	-0.233	18.23	0.335	2	0.845775
I0012	Poly	-0.43	0.252	0.451	18.23	0.247	2	0.883985
I0013	Poly	-1.348	0.153	0.742	18.23	6.73	2	0.03456

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Nocdurna (desmopressin orally disintegrating tablets)

n=24					
Thinking over the day, to what extent...	1) Not at all	2) Slightly	3) Moderately	4) Quite a bit	5) A great deal
1) Was it difficult to concentrate?	12	8	4	0	0
2) Did you feel low in energy?	12	6	4	2	0
3) Did you feel tired?	9	8	5	2	0
4) Were you unable to be productive?	15	4	2	3	0
5) Did you avoid participating in activities that you enjoy due to nocturia?	15	5	1	2	1
6) Did you feel irritable or moody during the day today?	16	6	1	0	1
7) Did you limit your fluid intake?	10	4	5	2	3
8) Are you preoccupied that night time voiding is a sign of getting older?	10	5	4	2	3
Thinking about last night, to what extent...					
9) Did you lay awake without being able to return to sleep?	4	8	7	3	2
10) Did you feel you got too little sleep?	7	6	5	4	2
11) Were you worried about falling?	22	0	2	0	0
12) Were you worried that you would wake up people in the house?	19	2	2	0	1
Overall, to what extent...					
13) Do you worry that the nocturia will get worse in the future?	9	4	2	4	5
14) Does nocturia impact on your life?	5	3	6	4	6

Reviewer note: Examination of item rating scale performance was not included in this submission nor apparently addressed in the analyses. Respondent use of rating scales often accounts for item misfit. Resolution of potential rating scale problems may improve the measure.

Rating scale analysis and further examination of measurement properties of the 11-item scale with a larger sample should more clearly establish if the instrument performs as a well-defined and reliable measure for use in nocturia trials.

SEALD Review

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Nocdurna (desmopressin orally disintegrating tablets)

C. APPENDICES

Appendix A

Post-hoc Longitudinal Analyses of Treatment Effects

On NQoL Domain Scores—Full Analysis Set

CS40 & CS41

SEALD Review

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NDA 022517

Nocdurna (desmopressin orally disintegrating tablets)

Study CS 40**Table 6.4.1: Post-Hoc Longitudinal Analysis of Treatment effect on NQoL domain scores - Full Analysis Set**

Global Quality of Life

		N	adjusted means	treatment contrast	Comparisons versus placebo		P-value
					95% CI		
				Lower	Upper		
Average Treatment Effect During 3 Months							
	Desmopressin		11.47	0.07	[-3.25;	3.39]	0.9661
	Placebo		11.40				
Full Model - Type 3 test							
	Baseline value						<.0001
	Treatment						0.9661
	Visit						0.0081
	Age (<65, >=65 yrs)						0.5958
	Treatment-by-Visit						0.2589
Adjusting Factors:							
Treatment Comparison by Visit							
1 Month	Desmopressin	126	9.48	-1.12	[-4.68;	2.45]	0.5384
	Placebo	122	10.59				
3 Months	Desmopressin	113	13.47	1.26	[-2.97;	5.49]	0.5579
	Placebo	108	12.21				
Age Strata							
	< 65 years old	136	11.85				0.5958
	>= 65 years old	112	10.94				

Longitudinal analysis of covariance with baseline as a covariate, and age-group (stratification factor in randomization), treatment, visit and treatment-by-visit interaction as factors

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 Nocurna (desmopressin orally disintegrating tablets)

Study CS40

Post-Hoc Longitudinal Analysis of Treatment effect on NQoL domain scores - Full Analysis Set

NQoL Total score

		Comparisons versus placebo					
		N	adjusted means	treatment contrast	95% CI		P-value
					Lower	Upper	

Average Treatment Effect During 3 Months

Desmopressin			24.03	3.17	[-0.87;	7.21]	0.1233
Placebo			20.86				

Full Model - Type 3 test

Baseline value							<.0001
Treatment							0.1233
Visit							<.0001
Age (<65, >=65 yrs)							0.2005
Treatment-by-Visit							0.0389

Adjusting Factors:

Treatment Comparison by Visit

1 Month	Desmopressin	126	20.83	1.01	[-3.48;	5.49]	0.6591
	Placebo	122	19.83				
3 Months	Desmopressin	113	27.24	5.34	[0.76;	9.92]	0.0226
	Placebo	108	21.90				

Age Strata

< 65 years old	136	23.68					0.2005
>= 65 years old	112	21.00					

Longitudinal analysis of covariance with baseline as a covariate, and age-group (stratification factor in randomization), treatment, visit and treatment-by-visit interaction as factors

Study CS 40

Post-Hoc Longitudinal Analysis of Treatment effect on NQoL domain scores - Full Analysis Set

Sub-domain Bother/Concern

	N	adjusted means	Comparisons versus placebo			P-value
			treatment contrast	95% CI		
				Lower	Upper	

Average Treatment Effect During 3 Months

Desmopressin		23.92	3.54	[-0.76;	7.83]	0.1060
Placebo		20.38				

Full Model - Type 3 test

Baseline value						<.0001
Treatment						0.1060
Visit						0.0008
Age (<65, >=65 yrs)						0.3831
Treatment-by-Visit						0.0645

Adjusting Factors:

Treatment Comparison by Visit

1 Month	Desmopressin	126	20.88	1.39	[-3.37;	6.15]	0.5659
	Placebo	122	19.49				
3 Months	Desmopressin	113	26.96	5.69	[0.72;	10.65]	0.0250
	Placebo	108	21.27				

Age Strata

< 65 years old	136	23.06				0.3831
>= 65 years old	112	21.11				

Longitudinal analysis of covariance with baseline as a covariate, and age-group (stratification factor in randomization), treatment, visit and treatment-by-visit interaction as factors

SEALD Review
 Stansbury
 NDA 022517
 NocduRNA (desmopressin orally disintegrating tablets)

Study CS40

Post-Hoc Longitudinal Analysis of Treatment effect on NQoL domain scores - Full Analysis Set

Sub-domain Sleep/Energy

		Comparisons versus placebo					
		N	adjusted means	treatment contrast	95% CI		P-value
					Lower	Upper	

Average Treatment Effect During 3 Months

Desmopressin			24.15	2.74	[-1.57; 7.04]	0.2114
Placebo			21.41			

Full Model - Type 3 test

Baseline value						<.0001
Treatment						0.2114
Visit						<.0001
Age (<65, >=65 yrs)						0.1229
Treatment-by-Visit						0.0610

Adjusting Factors:

Treatment Comparison by Visit

1 Month	Desmopressin	126	20.76	0.57	[-4.32; 5.46]	0.8179
	Placebo	122	20.18			
3 Months	Desmopressin	113	27.53	4.90	[0.06; 9.75]	0.0471
	Placebo	108	22.63			

Age Strata

< 65 years old	136	24.34				0.1229
>= 65 years old	112	20.92				

Longitudinal analysis of covariance with baseline as a covariate, and age-group (stratification factor in randomization), treatment, visit and treatment-by-visit interaction as factors

SEALD Review
 Stansbury
 NDA 022517
 NocduRNA (desmopressin orally disintegrating tablets)

Study CS41

Global Quality of Life

		Comparisons versus placebo				
		N	adjusted means	treatment contrast	95% CI	P-value
Average Treatment Effect During 3 Months						
	75 µg		7.59	3.88 [0.61; 7.14]	0.0201
	50 µg		9.76	6.04 [2.73; 9.36]	0.0004
	Placebo		3.72			

Full Model - Type 3 test

Baseline value	<.0001
Treatment	0.0013
Visit	0.1163
Age (<65, >=65 yrs)	0.0289
Treatment-by-Visit	0.2891

Adjusting Factors:

Treatment Comparison by Visit

1 Month	75 µg	117	6.34	2.40 [-1.47; 6.27]	0.2235
	50 µg	112	8.82	4.88 [0.95; 8.80]	0.0152
	Placebo	137	3.94			
3 Months	75 µg	107	8.84	5.35 [1.61; 9.10]	0.0052
	50 µg	103	10.70	7.21 [3.42; 11.00]	0.0002
	Placebo	127	3.49			

Age Strata

< 65 years old	191	5.33				0.0289
>= 65 years old	175	8.41				

Longitudinal analysis of covariance with baseline as a covariate, and age-group (stratification factor in randomization), treatment, visit and treatment-by-visit interaction as factors

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Nocdurna (desmopressin orally disintegrating tablets)

Study CS41

Post-Hoc Longitudinal Analysis of Treatment effect on NQoL domain scores - Full Analysis Set

NQoL Total score

		Comparisons versus placebo				
		N	adjusted means	treatment contrast	95% CI	P-value
Average Treatment Effect During 3 Months						
	75 µg		16.39	3.69 [0.17; 7.21]	0.0399
	50 µg		17.32	4.62 [1.06; 8.18]	0.0111
	Placebo		12.70			

Full Model - Type 3 test

Baseline value	<.0001
Treatment	0.0238
Visit	0.0119
Age (<65, >=65 yrs)	0.4169
Treatment-by-Visit	0.9300

Adjusting Factors:

Treatment Comparison by Visit

1 Month	75 µg	117	15.58	4.05 [0.29; 7.82]	0.0350
	50 µg	112	16.28	4.75 [0.94; 8.56]	0.0147
	Placebo	137	11.53			
3 Months	75 µg	107	17.20	3.33 [-0.88; 7.54]	0.1209
	50 µg	103	18.37	4.49 [0.24; 8.74]	0.0385
	Placebo	127	13.88			

Age Strata

< 65 years old	191	14.71				0.4169
>= 65 years old	175	15.93				

Longitudinal analysis of covariance with baseline as a covariate, and age-group (stratification factor in randomization), treatment, visit and treatment-by-visit interaction as factors

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Study CS41

Post-Hoc Longitudinal Analysis of Treatment effect on NQoL domain scores - Full Analysis Set

Sub-domain Bother/Concern

		Comparisons versus placebo				
		N	adjusted means	treatment contrast	95% CI	P-value
Average Treatment Effect During 3 Months						
	75 µg		16.12	2.30 [-1.51; 6.12]		0.2361
	50 µg		16.95	3.14 [-0.72; 7.00]		0.1109
	Placebo		13.81			

Full Model - Type 3 test

Baseline value	<.0001
Treatment	0.2455
Visit	0.0100
Age (<65, >=65 yrs)	0.1963
Treatment-by-Visit	0.9054

Adjusting Factors:

Treatment Comparison by Visit

1 Month	75 µg	117	15.21	2.78 [-1.49; 7.06]	0.2013
	50 µg	112	15.78	3.36 [-0.97; 7.68]	0.1281
	Placebo	137	12.42		
3 Months	75 µg	107	17.03	1.82 [-2.62; 6.27]	0.4203
	50 µg	103	18.13	2.92 [-1.58; 7.42]	0.2022
	Placebo	127	15.20		

Age Strata

< 65 years old	191	14.50			0.1963
>= 65 years old	175	16.61			

Longitudinal analysis of covariance with baseline as a covariate, and age-group (stratification factor in randomization), treatment, visit and treatment-by-visit interaction as factors

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 NDA 022517
 Nocodurna (desmopressin orally disintegrating tablets)

Study CS41

Post-Hoc Longitudinal Analysis of Treatment effect on NQoL domain scores - Full Analysis Set

Sub-domain Sleep/Energy

		Comparisons versus placebo				
		N	adjusted means	treatment contrast	95% CI	P-value
Average Treatment Effect During 3 Months						
	75 µg		16.71	5.13 [1.28; 8.99]	0.0091
	50 µg		17.72	6.14 [2.25; 10.04]	0.0021
	Placebo		11.58			

Full Model - Type 3 test

Baseline value	<.0001
Treatment	0.0035
Visit	0.0527
Age (<65, >=65 yrs)	0.8436
Treatment-by-Visit	0.9668

Adjusting Factors:

Treatment Comparison by Visit

1 Month	75 µg	117	16.00	5.40 [1.25; 9.55]	0.0110
	50 µg	112	16.78	6.18 [1.98; 10.38]	0.0041
	Placebo	137	10.60			
3 Months	75 µg	107	17.43	4.87 [0.23; 9.51]	0.0399
	50 µg	103	18.67	6.11 [1.42; 10.80]	0.0108
	Placebo	127	12.56			

Age Strata

< 65 years old	191	14.94				0.8436
>= 65 years old	175	15.27				

Longitudinal analysis of covariance with baseline as a covariate, and age-group (stratification factor in randomization), treatment, visit and treatment-by-visit interaction as factors

SEALD Review

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Nocdurna (desmopressin orally disintegrating tablets)

Appendix B

Development Process of the NI Diary

STUDY ENDPOINT REVIEW

<u>Development process of the Nocturia Impact Diary</u>	Development steps	FDA comments	Changes made	Description of study	Output	Documentation
1	Review of qualitative, patient reported, item elicitation or cognitive debriefing studies.	Step 1 in the rapid revision process agreed by FDA and Ferring at <i>Guidance meeting minutes Nocturna IND (065890) from the July 20, 2011 meeting</i>	NA	NA	Comprehensive list of concepts of relevance for nocturia patients	PRO dossier Chapter 5 – specifically 5E
2	Condensation of list of concepts into draft questionnaire and adjustment of N-QoL into diary with response: ‘a great deal’ and ‘not at all’ as ends of item scaling.	Step 2 in the rapid revision process agreed by FDA and Ferring at <i>Guidance meeting minutes Nocturna IND (065890) from the July 20, 2011 meeting</i>	NA	NA	Nocturia Impact Draft 1 diary with 14 questions and 4 domains	PRO dossier Chapter 1B for questionnaire and 5C for overview of domains
3	Conduct of a cognitive debriefing study confirming the selected item pool.	Step 3 in the rapid revision process agreed by FDA and Ferring at <i>Guidance meeting minutes Nocturna IND (065890) from the July 20, 2011 meeting</i>	NA	Qualitative focus group study including 24 nocturia patients	Nocturia Impact Draft 2 diary with 12 items and 4 domains	PRO dossier chapter 5C and Appendix E
4	Proposed psychometric protocol and SAP of trial 000034	<ul style="list-style-type: none"> A. <i>Discourage several domains</i> B. <i>Include Rasch analysis</i> C. <i>Include Cohen’s D</i> 	1) Rasch analysis was done in cross sectional data from the 24		Nocturia Impact Draft 3 diary with 11 items and 1 domain + 1 global	Appendix 3 in the study protocol in the NDA:

SEALD Review

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Nocdurna (desmopressin orally disintegrating tablets)

	was sent to FDA for review.	<p><i>D. Make sure that it is possible to identify patients with respect to prior randomization</i></p> <p><i>E. Specific suggestions to item 10, 6, 12, 11 and 8</i></p>	<p>cognitive debriefing patients (response to A and B)</p> <p>2) Changes were incorporated in SAP (response to A, B ,C and D)</p> <p>3) Adaptations were made in the diary (response to E)</p>		item (based on preliminary Rasch analysis and FDA advice)	Nocturia Impact Draft 2 diary
5	IMPACT study (with FDA comments included).	NA	Based on the Rasch analysis 1 domain was kept. Linguistic change was made to item 12	Placebo controlled RCT	Nocturia Impact Diary with 11 items and 1 domain + a global domain	PRO dossier Chapter 1 and Appendix B
6	Scoring algorithm and suggestion of clinical relevance was developed.	NA	NA	NA	Scoring algorithm and first suggestions to a minimal clinical relevant scoring range	PRO dossier Chapters 1C and 7

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/s/

JAMES P STANSBURY
01/07/2013

LAURIE B BURKE
01/07/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: December 6, 2012

Reviewer: Sarah K. Vee, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Yelena Maslov, PharmD
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name: Nocdurna (Desmopressin) Orally Disintegrating Sublingual
Tablets, 25 mcg and 50 mcg

Application Type/Number: NDA 022517

Applicant/sponsor: Ferring Pharmaceuticals, Inc.

OSE RCM #: 2012-1748

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1 INTRODUCTION

This review evaluates the proposed blister label, carton and insert labeling for Nocdurna NDA 022517 for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

NDA 22517 was originally submitted on June 22, 2009. However, the Application received a complete response (CR) on April 22, 2010. The Applicant resubmitted this NDA on July 30, 2012. In the resubmission, the Applicant indicated that the dose for men was decreased from 100 mcg to 50 mcg. The updated labels and labeling were submitted on July 30, 2012.

On September 20, 2012, DMEPA sent an email to the CMC reviewer to inquire whether the dosage form for this product could be called a "sublingual tablet" as a stand alone or could it be combined with ODT and be labeled as "orally disintegrating sublingual tablet". The CMC reviewer noted that this issue was discussed during the previous review cycle and that "sublingual" should be added to the name. The CMC reviewer commented that it would be clearest to label this product as "orally disintegrating sublingual tablets" to indicate the dosage form and the route of administration.

1.2 PRODUCT INFORMATION

The following product information is provided in the July 30, 2012 Class 2 resubmission after the CR.

- Active Ingredient: Desmopressin
- Indication of Use: Treatment of nocturia in adults
- Route of Administration: Sublingual
- Dosage Form: Orally disintegrating sublingual tablets
- Strength: 25 mcg and 50 mcg
- Dose and Frequency: 1 tablet once daily 1 hour before bedtime (women: 25 mcg and men: 50 mcg)
- How Supplied: Unit dose blister box of 30 (3 x 10)
- Storage: (b) (4), keep in original packaging to protect from moisture and light. Use immediately upon opening.
- Container and Closure Systems: (b) (4)

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA FAERS database for desmopressin medication error reports. We also reviewed the Nocturna labels and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 1.

Table 1: AERS Search Strategy	
Date	March 24, 2010 (from the date of last search in OSE Review # 2009-1554)
Drug Names	Desmopressin Desmopressin Acetate
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues (HLT) Product Label Issues (HLT) Product Physical Issues (HLT) Product Quality Issues NEC (HLT) Route of Administration: PO;BUCC;ORAL;P.O;PO;SL

The FAERS database searches identified 8 cases (all foreign). Each case was reviewed for relevancy and duplication. After individual review, all 8 reports were not included in the final analysis for the following reasons:

- 2 cases were for a different indication (diabetes insipidus)
- 1 case described an overdose (0.2 mg of desmopressin) for nocturnal enuresis, but the narrative did not indicate root cause (2 duplicate cases).
- 1 case described a lack of effect for an unknown indication
- 1 case described wrong technique error of splitting a DDAVP tablet for financial reasons (1 duplicate case).

2.2 LABELS AND LABELING

Using the principals of Human Factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Blister Labels submitted July 30, 2012 (Appendix B)
- Carton Labeling submitted July 30, 2012 (Appendix C)

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Insert Labeling submitted July 30, 2012 (No image)

2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed Nocdurna label and labeling in OSE Review #2009-1554, dated April 15, 2010. We ensured that our recommendations from that review were still relevant.

3 INTEGRATED SUMMARY OF MEDICATION ERROR ASSESSMENT

Blister packs are appropriate since this product is fragile and sensitive to moisture. The blister pack requires the patient to peel back the label to remove the tablet. Thus, the product package design is appropriate for this product.

We agree with CMC that the dosage form should be orally disintegrating sublingual tablet since this product is an orally disintegrating tablet that is administered sublingually. In order to convey the sublingual administration of this product, labels and labeling will be the most appropriate means of communicating these two characteristics of this product.

4 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. *Carton Labeling and Blister Labels*

We note that the proprietary name is presented in all capital letters. Revise the proprietary name to appear in title case (i.e. Nocdurna). Words set in upper and lower case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all capital letters.

B. *Carton Labeling*

1. Increase the prominence of the established name (which includes dosage form). Ensure that the prominence of the established name is commensurate with the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing feature in accordance with 21 CFR 201.10(g)(2).
2. Relocate the strength to follow the dosage form (see example below).

Nocdurna
(Desmopressin) Orally Disintegrating Sublingual Tablets
xx mcg

3. Revise the statement on the main panel that reads, “30 Tablets” to read “30 Orally Disintegrating Sublingual Tablets”
4. On the back panel, under the Contents section, revise the statement to read, “30 foil blisters, each containing one individually sealed xx mcg orally disintegrating sublingual tablet,…”

5. Revise the color font of the proprietary name to be printed in a single color font. Using two different color fonts for the proprietary name decreases readability of this important information.
6. The use of the same color font for the proprietary name and the product's strengths minimizes the difference between the strengths, which may lead to wrong strength selection errors. Therefore, revise the color fonts used for the strengths, so that they do not overlap with the color fonts of the proprietary name and with each other.
7. Relocate the Medication Guide statement "Each patient is required to receive the enclosed Medication Guide" to the principle display panel (PDP) to increase the prominence of that statement in accordance with 21 CFR 208.24.
8. Minimize or delete the company's name, "Ferring pharmaceuticals", as the company's name is as prominent as the established name of the product; thus, distracting from the most important information on the principle display panel such as proprietary and established names of the product.
9. We request "How to take Nocdurna" steps with illustrations be placed on the back panel of the carton labeling (similar to "How should I take Nocdurna" section of the Medication Guide), so that they are not covered with a pharmacy label. We recommend the addition of these steps with illustrations because this product is orally disintegrating sublingual tablet that is fragile and sensitive to moisture that should be administered sublingually. Therefore, placing instructional steps with illustrations on how to properly handle and administer your product will help to ensure that it is used correctly. This can be achieved by relocating the contents of the back panel to the side panels.

C. *Blister Label*

1. Increase the prominence of the established name (which includes dosage form). Ensure that the prominence of the established name is commensurate with the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing feature in accordance with 21 CFR 201.10(g)(2).
2. Relocate the strength to follow the dosage form (see example below).

Nocdurna
(Desmopressin) Orally Disintegrating Sublingual Tablets
xx mcg

3. Differentiate the product strengths with color, boxing, or some other means.
4. Delete the "Rx Only" statements on individual blister labels.

If you have further questions or need clarifications, please contact Margarita Tossa, project manager, at 301-796-4053.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS)
immediately following this page

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

/s/

SARAH K VEE
12/06/2012

YELENA L MASLOV
12/06/2012

CAROL A HOLQUIST
12/07/2012

STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	AT 2012-091
APPLICATION NUMBER	NDA 022517
LETTER DATE/SUBMISSION NUMBER	SDN 19
PDUFA GOAL DATE	
DATE OF CONSULT REQUEST	September 11, 2012
REVIEW DIVISION	Division of Metabolism and Endocrinology Products (DMEP)
MEDICAL REVIEWER	Bill Lubas, MD
REVIEW DIVISION PM	Jennifer Johnson
SEALD REVIEWER(S)	James P. Stansbury
REVIEW COMPLETION DATE	September 27, 2012
ESTABLISHED NAME	desmopressin orally disintegrating tablets
TRADE NAME	Nocturna
APPLICANT	Ferring Pharmaceuticals Inc.
ENDPOINT(S) CONCEPT(S)	quality of life, work productivity
MEASURE(S)	Nocturia Quality of Life (NQoL), Work Productivity and Activity Index (WPAI); Nocturia Impact (NI) Diary
CLINICAL OUTCOME ASSESSMENT TYPE	PROs
INDICATION	nocturia
INTENDED POPULATION(S)	adults with nocturia
NOTE	This review responds to specific questions from the Division in relation to the use of PRO evidence from 2 pivotal trials and an additional study aimed at examining the measurement properties of a revised instrument. Two of the instruments considered have been reviewed previously, and the third was used in support of an exploratory outcome. Additional background is provided in Section C below.

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Nocturna (desmopressin orally disintegrating tablets)

A. EXECUTIVE SUMMARY

This Study Endpoints and Labeling Development (SEALD) review is provided as a response to a request for consultation by the Division of Metabolism and Endocrine Products regarding NDA 022517. The sponsor used the Nocturia Quality of Life (NQoL) questionnaire in 2 pivotal trials for the measurement of health-related quality of life as a secondary endpoint. The sponsor also used the Work Productivity and Activity Index (WPAI) as an exploratory endpoint.

The review concludes that neither the NQoL nor the WPAI results from Trials CS 40 and CS 41 should be used for labeling claims. As we have noted in previous evaluations, the content validity (meanings, item framings, and item attributes) of the NQoL and recall period are problematic for distinguishing treatment benefit in drug development trials. Further, both instruments were originally proposed and evaluated as exploratory endpoints in the trials. The NQoL analyses showing differences favoring treatment were post hoc, repeat measures analyses of covariance (ANCOVA) adjusted for baseline score, age category, visit and interaction effects. The WPAI addresses issues that fall outside of FDA's regulatory concern with drug efficacy and safety.

The extent to which NQoL results are supportive of the efficacy result for the sponsor's product remains undetermined without further information requested from the sponsor. A global indicator of patient improvement, the last item of the NQoL questionnaire, performed inconsistently in Trials CS40 and CS41, supporting efficacy in the latter while providing no support for that conclusion in the former. Additionally, the CS41 results show a consistent, statistically significant but modest treatment contrast for NQoL and Sleep/Energy domain scores; we have no sense of the clinical meaning of the adjusted average 4-6% differences between treatments and placebo encountered.

Finally, the development of the Nocturia Impact Diary remains a work in process. It is unclear if the sponsor has taken into account FDA recommendations provided in January, 2012 because a copy of the instrument was not provided in the Clinical Trial Report for Trial CS000034. The version of the NI Diary used in the small study showed promising construct validity when compared with change in the self-reported number of nighttime voids ($r = 0.31$). However, there was no evidence of NI Diary support for efficacy in CS000034, recognizing that the study was not sufficiently powered to detect modest clinically meaningful differences like those seen in the pivotal trials.

B. REQUESTS FOR THE SPONSOR

The following request for additional information and analyses may be shared with the sponsor:

To aid our evaluation of the extent to which NQoL results from Trials CS 40 and CS 41 might be supportive of product efficacy, please provide:

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Nocodurna (desmopressin orally disintegrating tablets)

- cumulative distribution plots based on unadjusted NQoL Total Scores (BC+SE), and the two subscale scores. Each figure should show a continuous plot of the percent change in score from baseline on the X-axis against the cumulative percentage of patients experiencing that change on the Y-axis. The figures should show separate lines for treatment (combine doses for a single treatment line in CS 41) and placebo. Also provide comparisons for Month 1 and Month 3 results (a total of 12 figures; 6 per trial based on 3 scores and at 2 time periods).
- a full explanation for the inconsistent performance of the NQoL global indicator, if you can, between the two trials

To aid our evaluation and provide additional feedback for continued development of the NI Diary, please provide:

- a copy of the final version of the NI Diary you used in Trial CS000034. It does not appear to be included as part of your report. It is unclear if you had incorporated FDA suggestions from our communication under IND 065890 of January 21, 2012 or used the existing form of the NI Diary.
- more complete information from a Rasch analysis of the results from Trial 000034. It appears that you have removed the global item in your analysis but this is not clear—the global question should not be part of the NI Diary in further development, unless administered separately as an anchor-based value on which to better select a response threshold. Please:
 - base your Rasch analysis on a single (cross-sectional) administration of the NI Diary, using the same administration across respondents
 - show item rating scale analysis, and make any changes to the scale as indicated should respondents not appear to be using items in ways that were anticipated
 - provide model diagnostics, Rasch item and person parameter estimates, fit statistics for items, and the person-item map along with an explanation
 - proceed with item deletion for misfitting or redundant items, and consider new items if gaps are evident or the apparent floor effects noticed with raw scores is pronounced before using the tool in further trials.
- an anchor-based justification for the selection of a clinically meaningful response definition for the NI Diary. For example, you may explore different levels of decrease in the number of voids (e.g., include 50% or greater in voids and other categorical intervals to compare average percent decrease in the NI Diary score within those categories; additionally compare the global question with scale percent improvement categories for this purpose).
- clarify the rationale for subjects included for analysis and considerable differences in responsiveness seen in the FAS and PP results presented in Tables 6.1.5—6.1.8.

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Nocturna (desmopressin orally disintegrating tablets)

C. REVIEW AND RESPONSE TO DIVISION QUESTIONS

Background

Earlier SEALD consultation on this application is found under IND 65890, with review dated October 1, 2008. The sponsor originally proposed the use of three patient-reported outcome instruments for pivotal trials, including the NQoL, the Pittsburgh Sleep Quality Index (PSQI), and the International Consultation on Incontinence Questionnaire for Nocturia (ICIQ-N). In this initial review, the PSQI and ICIQ-N were determined not to be measures of nocturia impacts. The reviewer also identified issues related to NQoL (Appendix A) content including missing impact domains, inclusion of items unrelated to treatment effect, and the instrument's 2-week recall period (Trenatacosti, 10/01/2009).

A second consultation was requested in June, 2011 following a Type C meeting request. A publication was provided in the sponsor's submission demonstrating that the NQoL had a basis in qualitative research with nocturia patients. However, multiple concerns with instrument content remained, including recall. With the Division's urging, a path forward was found involving a rapid instrument revision process. FDA proposed that the sponsor develop a Nocturia Impact Diary (NI Diary) that could be used in future trials, with a relatively small validation study enrolling patients from the ongoing clinical trials (Stansbury, 07/15/2011).

Per agreement reached in the 2011 meeting, the sponsor submitted a dossier detailing development work on the NI Diary (Appendix B). The work was reviewed by SEALD (Stansbury, 01/06/2012) and the Division as discussed in the July 2011 Type C meeting, with comments provided to the sponsor on 01/20/2012.

In parallel to this work, FDA sent the sponsor a Complete Response (CR) letter on April 22, 2010 for NDA 22517. The current sponsor submission, summarizing pivotal trials CS40 and CS41 as well as the Nocturia Impact Study CS000034, was aimed at addressing deficiencies outlined in that communication. SEALD was consulted regarding study results using the Nocturia Quality of Life (NQoL) questionnaire, Work Productivity and Activity Index (WPAI) (Appendix C) questionnaire, and Nocturia Impact (NI) Diary.

Response to Division Questions

1) Can any of these three questionnaires be used as acceptable validated endpoints and included in labeling? If not, what is your impression of how much we can rely upon this information to support clinical efficacy?

No. Information from these instruments should not be used in labeling claims for the following reasons:

- As noted in at least two reviews, SEALD does not find the content validity of the NQoL to be strong for use in the context of drug development trials. The *worry* and *concern* items fail as clear effect indicators of treatment benefit and the two-week recall period is identified as less than optimal for trial use. The protocols for studies CS40 and CS41

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proposed the NQoL use as an exploratory outcome, rather than clearly placing it use in the hierarchy of secondary endpoints.

- The inconsistent positive results shown for use of the questionnaire in these two trials (see Appendix D) appeared in post-hoc analyses rather than planned statistical procedures. In CS40, the global item shows no significant difference between placebo and treatment and is actually better for placebo on average at Month 1, while the global results show a clear advantage for drug in CS41. The bother/concern domain results show no significant advantage for drug in CS41, with evidence for a significant advantage at 3 months in Trial CS40.
- The demonstration of the NI Diary's measurement properties is not complete. Additionally, the results from CS000034 were not supportive of a conclusion of efficacy using the instrument, recognizing that the study was not powered to test for a modest difference.
- The WPAI was also proposed as an exploratory endpoint in CS40 and CS41. It measures concepts and seeks patient attribution about attributes that are too distal to be clearly indicative of treatment benefit.

It also remains unclear as to whether any of the results may be taken as fully supportive of efficacy at this point. We appreciate the positive NQoL results encountered in CS41, but the inconsistent results for the global indicator and Bother/Concern domain comparing with study CS40 are not encouraging. We have asked the sponsor for additional interpretation. The clinical importance of small observed average differences in scale change scores (2-4%) is unclear, despite the observed statistical significance.

- 2) Please review Study CS000034, the Nocturia Impact Study (using the Nocturia Impact Diary) and comment on whether it supports labeling claims of improvement in sleep-related consequences and the sponsor's claims of improvement based on the NQoL in the pivotal confirmatory trials CS40 and CS41. As the NQoL data are now statistically significant in these new trials, please comment on the reason for the difference between the sponsor's analyses in the earlier trials and the new trials.

NI Diary results from Study CS000034 are not supportive of labeling claims for efficacy, although the instrument shows promising responsiveness based on comparison with reductions in nocturnal voids (Appendix E). The fact that the NI Diary and the NQoL share a low to moderate correlation with self-reported changes in nocturnal voiding frequency in no way implicates support for efficacy, as no comparison between arms is made. The similarity in correlation levels between NI Diary results and NQoL results in Studies CS40 and CS41 are unremarkable given that the NI Diary is a revised instrument that draws on NQoL items.

Reviewer note: The adjusted ANCOVA for CS29 NQoL data are even less consistent than those seen in CS40 and CS41 (see Question 1 above; CS29 statistical table 14.4.6.1.1, p.733). This may reflect the 28-day treatment duration, inclusion of 2 additional groups with what appear to have been sub-therapeutic doses in the analyses, or simply divergent NQoL results. The 3-month results are more informative in the more recent trials.

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D. APPENDICES

Appendix A

The Nocturia Quality of Life (NQoL) Questionnaire

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Nocdurma (desmopressin orally disintegrating tablets)

Ferring - FE992026 CS29
Blank eCRF: QOL Questionnaire

09-May-2007
Forms Version: 1.0.2.2

QOL QUESTIONNAIRE (NQOL)

OVER THE PAST 2 WEEKS , HAVING TO GET UP AT NIGHT TO URINATE...

1. Has made it difficult for me to concentrate the next day

- 0 Every day
- 1 Most days
- 2 Some days
- 3 Rarely
- 4 Never

2. Has made me feel generally low in energy the next day

- 0 Every day
- 1 Most days
- 2 Some days
- 3 Rarely
- 4 Never

3. Has required me to nap during the day

- 0 Every day
- 1 Most days
- 2 Some days
- 3 Rarely
- 4 Never

4. Has made me less productive the next day

- 0 Every day
- 1 Most days
- 2 Some days
- 3 Rarely
- 4 Never

5. Has caused me to participate less in activities I enjoy

- 0 Extremely
- 1 Quite a bit
- 2 Moderately
- 3 A little bit
- 4 Not at all

**Attachment 4
N-QoL Questionnaire**

1 of 3

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Nocdurma (desmopressin orally disintegrating tablets)

Ferring - FE992026 CS29
Blank eCRF: QoL Questionnaire

09-May-2007
Forms Version: 1.0.2.2

6. Has caused me to be careful when or how much I drink

- 0 All the time
- 1 Most of the time
- 2 Some of the time
- 3 Rarely
- 4 Never

7. Has made it difficult for me to get enough sleep at night

- 0 Every night
- 1 Most nights
- 2 Some nights
- 3 Rarely
- 4 Never

OVER THE PAST 2 WEEKS , I HAVE BEEN...

8. Concerned that I am disturbing others in the house because of having to get up at night to urinate

- 0 Extremely
- 1 Quite a bit
- 2 Moderately
- 3 A little bit
- 4 Not at all

9. Preoccupied about having to get up at night to urinate

- 0 All the time
- 1 Most of the time
- 2 Some of the time
- 3 Rarely
- 4 Never

10. Worried that this condition will get worse in the future

- 0 Extremely
- 1 Quite a bit
- 2 Moderately
- 3 A little bit
- 4 Not at all

Attachment 4
N-QoL Questionnaire

2 of 3

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Nocdurna (desmopressin orally disintegrating tablets)

Ferring - FE992026 CS29
Blank eCRF: QOL Questionnaire

09-May-2007
Forms Version: 1.0.2.2

11. Worried that there is no effective treatment for this condition (having to get up at night to urinate)
- 0 Extremely
1 Quite a bit
2 Moderately
3 A little bit
4 Not at all
12. Overall, how bothersome has having to get up at night to urinate been during the past 2 weeks?
- 4 Not at all
3 A little bit
2 Moderately
1 Quite a bit
0 Extremely
13. Overall I would rate my quality of life to be...
- 0 Very Good
1 Good
2 Fair
3 Poor
4 Very Poor

Attachment 4
N-QoL Questionnaire

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Nocdurna (desmopressin orally disintegrating tablets)

Appendix B

The Nocturia Impact Diary (NI Diary)

STUDY ENDPOINT REVIEW

NOCTURIA IMPACT DIARY

This nocturia (getting up to void at night) diary will assess the daily impact of nocturia on your everyday life. Please answer the questions in the late afternoon or evening and use the scale from 'not at all' to 'a great deal':

Thinking over the day, to what extent....	1) Not at all	2) Slightly	3) Moderately	4) Quite a bit	5) A great deal
1) Was it difficult to concentrate?	1) ____	2) ____	3) ____	4) ____	5) ____
2) Did you feel low in energy and/or tired?	1) ____	2) ____	3) ____	4) ____	5) ____
3) Were you unable to be productive at work or complete your personal daily activities?	1) ____	2) ____	3) ____	4) ____	5) ____
4) Did you avoid participating in activities that you enjoy?	1) ____	2) ____	3) ____	4) ____	5) ____
5) Did you limit your fluid intake?	1) ____	2) ____	3) ____	4) ____	5) ____
6) Are you concerned that night time voiding is a sign of getting older?	1) ____	2) ____	3) ____	4) ____	5) ____
<hr/>					
Thinking about last night, to what extent...	1) Not at all	2) Slightly	3) Moderately	4) Quite a bit	5) A great deal
7) Did you lie awake without being able to return to sleep after getting up to use the bathroom at night?	1) ____	2) ____	3) ____	4) ____	5) ____
8) Did you feel you got too little sleep?	1) ____	2) ____	3) ____	4) ____	5) ____
<hr/>					
Overall, to what extent...	1) Not at all	2) Slightly	3) Moderately	4) Quite a bit	5) A great deal
9) Do you worry that the nocturia will get worse in the future?	1) ____	2) ____	3) ____	4) ____	5) ____
10) Are you concerned with where the bathroom is when away from home?	1) ____	2) ____	3) ____	4) ____	5) ____
11) Does nocturia impact your life?	1) ____	2) ____	3) ____	4) ____	5) ____

Appendix C

Work Productivity and Activity Impairment Questionnaire:

Specific Health Problem V2.0 (WPAI:SHP)

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Nocdurna (desmopressin orally disintegrating tablets)

**Work Productivity and Activity Impairment Questionnaire:
Specific Health Problem V2.0 (WPAI:SHP)**

The following questions ask about the effect of your PROBLEM on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your PROBLEM? *Include hours you missed on sick days, times you went in late, left early, etc., because of your PROBLEM. Do not include time you missed to participate in this study.*

_____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

_____ HOURS

4. During the past seven days, how many hours did you actually work?

_____ HOURS *(If "0", skip to question 6.)*

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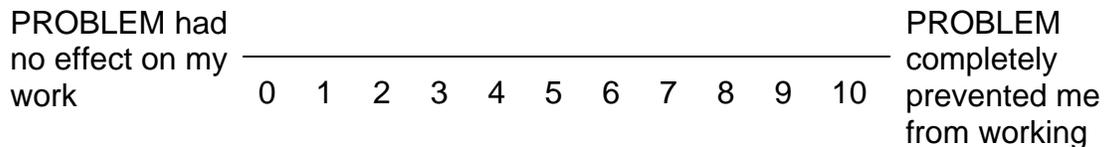
NDA 022517

Nocdurna (desmopressin orally disintegrating tablets)

5. During the past seven days, how much did your PROBLEM affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If PROBLEM affected your work only a little, choose a low number. Choose a high number if PROBLEM affected your work a great deal.

Consider only how much PROBLEM affected productivity while you were working.

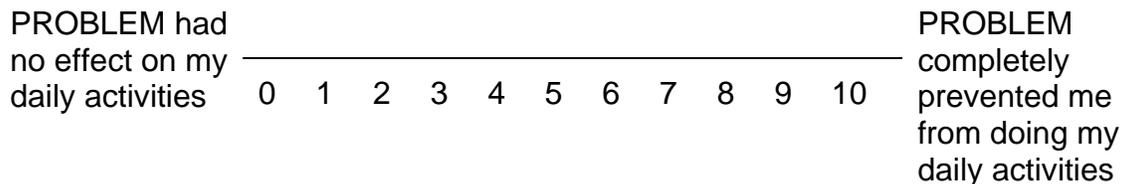


CIRCLE A NUMBER

6. During the past seven days, how much did your PROBLEM affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If PROBLEM affected your activities only a little, choose a low number. Choose a high number if PROBLEM affected your activities a great deal.

Consider only how much PROBLEM affected your ability to do your regular daily activities, other than work at a job.



CIRCLE A NUMBER

WPAI:SHP V2.0 (US English)

Appendix D

Post-hoc Longitudinal Analyses of NQoL Results from Trials CS40 and CS41

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Nocurna (desmopressin orally disintegrating tablets)

Trial CS40

Table 10-24 Adjusted Treatment Differences in Mean Change from Baseline in NQoL Domain Scores by Visit Including Treatment-by-Visit Interaction Term (Full Analysis Set using Repeated Measures ANCOVA)

NQoL Visit	Adjusted Means		Difference in Adjusted Means		
	Desmopressin (N=133)	Placebo (N=128)	Treatment Contrast	95% CI	p-value
Global Quality of Life					
Month 1	9.48	10.59	-1.12	[-4.68, 2.45]	0.5384
Month 3	13.47	12.21	1.26	[-2.97, 5.49]	0.5579
Average effect during 3 months	11.47	11.40	0.07	[-3.25, 3.39]	0.9661
Bother/Concern Domain					
Month 1	20.88	19.49	1.39	[-3.37, 6.15]	0.5659
Month 3	26.96	21.27	5.69	[0.72, 10.65]	0.0250*
Average effect during 3 months	23.92	20.38	3.54	[-0.76, 7.83]	0.1060
Sleep/Energy Domain					
Month 1	20.76	20.18	0.57	[-4.32, 5.46]	0.8179
Month 3	27.53	22.63	4.90	[0.06, 9.75]	0.0471*
Average effect during 3 months	24.15	21.41	2.74	[-1.57, 7.04]	0.2114
Total Score (BC+SE)					
Month 1	20.83	19.83	1.01	[-3.48, 5.49]	0.6591
Month 3	27.24	21.90	5.34	[0.76, 9.92]	0.0226*
Average effect during 3 months	24.03	20.86	3.17	[-0.87, 7.21]	0.1233

* Statistically significant difference versus placebo, $p \leq 0.05$.

Note: All scores are re-scaled to 0-100.

Note: The number of desmopressin and placebo subjects was 126 and 122, respectively, at Month 1 and 113 and 108, respectively, at Month 2.

Cross-reference: [Table 6.4.1]

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Nocurna (desmopressin orally disintegrating tablets)

Trial CS41

Table 10-25 Adjusted Treatment Differences in Mean Change from Baseline in NQoL Domain Scores by Visit Including Treatment-by-Visit Interaction Term (Full Analysis Set using Repeated Measures ANCOVA)

Visit	Treatment	N	Adjusted Mean Change	Difference in Adjusted Means versus Placebo		
				Treatment Contrast	95% CI	p-value
Global Quality of Life						
Month 1	75 µg	117	6.34	2.40	[-1.47, 6.27]	0.2235
	50 µg	112	8.82	4.88	[0.95, 8.80]	0.0152*
	Placebo	137	3.94			
Month 3	75 µg	107	8.84	5.35	[1.61, 9.10]	0.0052*
	50 µg	103	10.70	7.21	[3.42, 11.00]	0.0002*
	Placebo	127	3.49			
Average effect during 3 months	75 µg		7.59	3.88	[0.61, 7.14]	0.0201*
	50 µg		9.76	6.04	[2.73, 9.36]	0.0004*
	Placebo		3.72			
Bother/Concern Domain						
Month 1	75 µg	117	15.21	2.78	[-1.49, 7.06]	0.2013
	50 µg	112	15.78	3.36	[-0.97, 7.68]	0.1281
	Placebo	137	12.42			
Month 3	75 µg	107	17.03	1.82	[-2.62, 6.27]	0.4203
	50 µg	103	18.13	2.92	[-1.58, 7.42]	0.2022
	Placebo	127	15.20			
Average effect during 3 months	75 µg		16.12	2.30	[-1.51, 6.12]	0.2361
	50 µg		16.95	3.14	[-0.72, 7.00]	0.1109
	Placebo		13.81			
Sleep/Energy Domain						
Month 1	75 µg	117	16.00	5.40	[1.25, 9.55]	0.0110*
	50 µg	112	16.78	6.18	[1.98, 10.38]	0.0041*
	Placebo	137	10.60			
Month 3	75 µg	107	17.43	4.87	[0.23, 9.51]	0.0399*
	50 µg	103	18.67	6.11	[1.42, 10.80]	0.0108*
	Placebo	127	12.56			
Average effect during 3 months	75 µg		16.71	5.13	[1.28, 8.99]	0.0091*
	50 µg		17.72	6.14	[2.25, 10.04]	0.0021*
	Placebo		11.58			
NQoL Total Score (BC+SE)						
Month 1	75 µg	117	15.58	4.05	[0.29, 7.82]	0.0350*
	50 µg	112	16.28	4.75	[0.94, 8.56]	0.0147*
	Placebo	137	11.53			
Month 3	75 µg	107	17.20	3.33	[-0.88, 7.54]	0.1209
	50 µg	103	18.37	4.49	[0.24, 8.74]	0.0385*
	Placebo	127	13.88			
Average effect during 3 months	75 µg		16.39	3.69	[0.17, 7.21]	0.0399*
	50 µg		17.32	4.62	[1.06, 8.18]	0.0111*
	Placebo		12.70			

* Statistically significant difference versus placebo, p<0.05.

Note: All scores are re-scaled to 0-100.

Cross-reference: [Table 6.4.1]

Appendix E

Planned NI Diary Analysis

In Support of Efficacy

SEALD Review

Stansbury

NDA 022517

Nocdurma (desmopressin orally disintegrating tablets)

Table 6.1.3: Sensitivity to Responder Status of NI Total Score and items: Change from Baseline to Month 1 - Full Analysis Set

	Non-responder		Responder		Diff.	95% CI	P-value
	Mean Change	N	Mean Change	N			
NI Total*	-2.6	22	-13.3	34	10.7	[2.7;18.8]	0.0099
Q01	-0.1	22	-0.4	34	0.4	[-0.1;0.8]	0.0856
Q02	-0.0	22	-0.6	34	0.6	[0.1;1.0]	0.0214
Q03	-0.2	22	-0.5	34	0.3	[-0.2;0.9]	0.2079
Q04	-0.2	22	-0.5	34	0.3	[-0.1;0.8]	0.1629
Q05	-0.1	22	-0.6	34	0.4	[-0.0;0.9]	0.0622
Q06	-0.1	22	-0.4	34	0.3	[0.0;0.7]	0.0443
Q07	-0.2	22	-0.8	34	0.6	[0.1;1.0]	0.0104
Q08	-0.0	22	-0.3	34	0.3	[-0.1;0.8]	0.1293
Q09	-0.2	22	-0.8	34	0.6	[0.0;1.1]	0.0423
Q10	-0.1	22	-0.5	34	0.4	[0.0;0.8]	0.0329
Q11	0.0	22	-0.5	34	0.5	[0.0;1.0]	0.0408
Overall Q12*	-4.9	22	-4.9	34	-0.0	[-9.6;9.6]	0.9963

Notes:

*Individual period means forms the basis of the analysis

*Please note that the two transformed overall items take values in [0; 100]

*A responder is defined as a subject who experiences a reduction in nocturnal voids from Baseline to the Month 1 visit of $\geq 33\%$.

Table 6.1.5: NI Diary: Treatment Effect Size in Change from Baseline to Month 1 - Full Analysis Set

	Placebo		Desmopressin		Diff.	95% CI	Pooled SD	Cohen's D
	Mean	N	Mean	N				
NI Total*	-9.6	29	-8.5	27	-1.1	[-9.5;7.2]	15.6	-0.07
Q01	-0.3	29	-0.3	27	-0.0	[-0.4;0.4]	0.8	-0.02
Q02	-0.3	29	-0.4	27	0.1	[-0.4;0.6]	0.9	0.09
Q03	-0.5	29	-0.3	27	-0.1	[-0.6;0.4]	1.0	-0.13
Q04	-0.5	29	-0.3	27	-0.2	[-0.7;0.2]	0.8	-0.28
Q05	-0.5	29	-0.3	27	-0.2	[-0.6;0.3]	0.9	-0.20
Q06	-0.3	29	-0.3	27	-0.1	[-0.4;0.3]	0.6	-0.12
Q07	-0.6	29	-0.5	27	-0.1	[-0.5;0.4]	0.9	-0.07
Q08	-0.3	29	-0.1	27	-0.1	[-0.5;0.3]	0.8	-0.13
Q09	-0.6	29	-0.5	27	-0.1	[-0.7;0.4]	1.0	-0.14
Q10	-0.2	29	-0.5	27	0.3	[-0.1;0.7]	0.7	0.41
Q11	-0.2	29	-0.3	27	0.1	[-0.4;0.5]	0.9	0.06
Overall Q12*	-3.2	29	-6.8	27	3.6	[-5.7;12.9]	17.4	0.21

Notes:

*Individual period means forms the basis of the analysis

*Please note that the two transformed overall items take values in [0; 100]

SEALD Review

Stansbury

NDA 022517

Nocdurna (desmopressin orally disintegrating tablets)

Table 6.1.9: Treatment Effect on NI Total Score: Change From Baseline to Month 1 - Full Analysis Set

	N		Effect	95% CI	P-value
Females	26	Desmo. vs. Placebo	3.0	[-6.8;12.8]	0.5310
		Baseline			<.0001
		Age stratum			0.1521
Males	30	Desmo. vs. Placebo	-1.9	[-10.8;7.1]	0.6721
		Baseline			0.0016
		Age stratum			0.1642
All	56	Desmo. vs. Placebo	-0.1	[-6.6;6.3]	0.9647
		Baseline			<.0001
		Age stratum			0.8333

Notes:

*The model is an ANCOVA with covariates Baseline Score, Treatment and Age stratum (<65, >=65).

*NITOT-TOTAL TRANSFORMED NI SCORE

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

/s/

JAMES P STANSBURY
09/27/2012

LAURIE B BURKE
09/27/2012

STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	2010-093
APPLICATION NUMBER	NDA 22517
LETTER DATE/SUBMISSION NUMBER	August 11, 2010
PDUFA GOAL DATE	Industry Meeting September 14, 2010
DATE OF CONSULT REQUEST	August 18, 2010
REVIEW DIVISION	Division of Metabolism and Endocrinology Products (DMEP)
MEDICAL REVIEWER	Bill Lubas
REVIEW DIVISION PM	Jennifer Johnson
SEALD REVIEWER(S)	Ann Marie Trentacosti
REVIEW COMPLETION DATE	August 31, 2010
ESTABLISHED NAME	Desmopressin orally disintegrating tablets
TRADE NAME	Nocturna
APPLICANT	Ferring Pharmaceuticals
ENDPOINT(S) CONCEPT(S)	Health Related Quality of Life in Patients with Nocturia; Sleep Quality
INSTRUMENT(S)	Nocturia-Quality of Life (N-QoL) and Sleep Quality Diary
INDICATION	Treatment of Nocturia
INTENDED POPULATION(S)	Adults with Nocturia

1 EXECUTIVE SUMMARY

This Study Endpoints and Labeling Development (SEALD) review is provided as a response to a request for consultation by the Division of Metabolism and Endocrinology Products (DMEP) regarding Ferring's submission of an End-of-Review Meeting to discuss the deficiencies noted in FDA's Complete Response letter dated April 22, 2010 for NDA 22-517: desmopressin orally disintegrating tablets (Nocturna) for the treatment of nocturia in adults. The meeting package includes Protocol FE 992026 CS41, which was designed to evaluate the safety and efficacy of Nocturna for adult males with nocturia. SEALD has been requested by DMEP to review the proposed secondary efficacy patient reported outcome (PRO) endpoints included in the protocol.

The review concludes that Protocol FE 992026 CS41 is not adequately designed to show a treatment benefit associated with treatment of nocturia with Nocturna.

In order to provide direct evidence of clinical benefit with reduction of nocturnal void frequency, evidence of improvement in the target population defined signs and symptoms of nocturia, through a content valid PRO measure needs to be established. In developing a nocturia PRO sign/symptom measure, it would be important to understand why patients void at night [i.e. bladder pressure, other sleep disturbance, such as insomnia or sleep disturbance by a sleep partner); the frequency and occurrence of symptoms and degree of bother; possible associated night-time and daytime urinary symptoms, as well as other concomitant factors (i.e. caffeinated beverage ingestion before bed)]. Treatment benefit can be established by enrolling patients who have evidence of these signs and symptoms at baseline and show an improvement in these signs and symptoms with treatment. Only after the effect of treatment on the patient defined signs and symptoms of nocturia has been determined can the impacts of nocturia (i.e. sleep disturbance, daytime tiredness, daytime difficulty concentrating and HRQL) associated with nocturia be interpreted.

In addition, the content validity of both proposed secondary efficacy endpoints: the Nocturia-Quality of Life (N-QoL) and Sleep Quality Diary has not been established and the measures therefore cannot adequately support labeling claims.

It is recommended that sponsor use the principles delineated in the "FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims" and develop a measure of the signs and symptoms of nocturia as the primary measure of treatment benefit. A PRO measure of the direct impacts associated with nocturia could be a useful secondary clinical outcome measure in evaluating treatment benefit.

2 SUGGESTED RESPONSES TO SPONSOR QUESTIONS

Proposed responses to questions posed in the briefing package are provided in *italics*.

Question 4: Does the FDA agree to the proposed secondary endpoints and the rank order for the purpose of supporting the clinical efficacy and durability of effect of NOCDURNA™ (desmopressin) orally disintegrating tablets in the male CS41 study?

Response:

We do not agree with the patient-reported outcome secondary endpoints (N-QoL and sleep quality rating scales) as posed (See our response to question 12).

Question 12: Does the FDA accept that the N-QoL is a valid instrument to measure overall nocturia specific quality of life?

Response:

No, we do not agree that the N-QoL or sleep quality rating scale is the most appropriate measures of treatment benefit (the effect of treatment on how a patient survives, feels, or functions). In order to provide direct evidence of clinical benefit with reduction of nocturnal void frequency, it would be necessary to show evidence of improvement in the target population defined signs and symptoms of nocturia with a content valid PRO measure.

Treatment benefit can be evaluated by enrolling patients who have evidence of the relevant signs and symptoms (relevancy depending on the subpopulation enrolled) at baseline and show an improvement in these signs and symptoms with treatment.

Only after the effect of treatment on the patient defined signs and symptoms of nocturia has been determined can the impacts of nocturia (i.e. sleep disturbance, daytime tiredness, and HRQL) be interpreted.

In addition, the content validity of the N-QoL has not been established, as exemplified by the following:

Qualitative data to support the content validity of the N-QoL in males with nocturia has not been submitted. The N-QoL content validity study in females only enrolled 5 subjects and did not provide sufficient evidence that the measure was appropriate, interpretable, and comprehensive for patients. The subject responses suggest that several items may not be clinically relevant to the target population and that patients may not be able to adequately recall their experience over a two week period of time. Items such as, “worried that there is no effective treatment for this condition.”, and “worried that this condition will get worse in the future” are likely to be impacted by patient personality and many other patient attributes besides the frequency of nocturnal voiding and will introduce variability, yield uninterpretable study results, and will likely not support labeling claims. In addition, the N-QoL does not include all of the HRQL domains since it does not measure the emotional impacts of nocturia (as noted in the content validity summary) or the negative aspects of treatment.

STUDY ENDPOINT REVIEW

We recommend that you refer to the “FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims” and develop a measure of the signs and symptoms of nocturia as the primary measure of treatment benefit. A PRO measure of the direct impacts associated with nocturia could be a useful secondary clinical outcome measure in evaluating a treatment response.

Question 13: Does the FDA accept sleep quality rating scale from a diary as an instrument measuring the nocturia specific quality of sleep?

Response:

No, we do not agree. See our response to question 12. In addition, the content validity of the sleep rating scale has not been adequately established. “Quality of sleep” is a complex concept that includes several domains (i.e. feeling rested on waking and motivation to get up in the morning) which cannot be adequately captured by a single item.

3 ENDPOINT REVIEW

On April 22, 2010, DMEP sent a Complete Response to Ferring concerning NDA 22-517: Nocurna (desmopressin) Orally Disintegrating Tablets for the treatment of nocturia in adults. In response to the Complete Response, Ferring plans to conduct two phase 3 studies with Nocurna: one enrolling female patients and one enrolling male patients with nocturia, to confirm that a lower dosing regimen is a safe and effective treatment of adults with nocturia.

In this submission, the sponsor has submitted a briefing package to discuss the deficiencies listed in the April 2010 Complete Response Letter. The package includes a protocol for the phase 3 trial in male nocturia patients entitled: “Protocol FE 992026 CS41: A Multi-centre, Randomised, Double-blind, Placebo-controlled, Parallel, Group Trial to Demonstrate the Efficacy and Safety of Desmopressin Orally Disintegrating Tablet for the Treatment of Nocturia in Adult Males”.

3.1 Instruments

The sponsor has included two PRO measures as secondary endpoints in Protocol FE 992026 CS41: the N-QoL and Sleep Quality instruments.

Nocturia-Quality of Life (N-QoL)

The N-QOL (See Appendix) was developed to measure the impact of nocturia and its treatment on a patient’s quality of life. The instrument includes 13 items, with 12 items directly related to nocturia plus a global quality of life item. An overall score of the 12 nocturia items as well as a measure of the 2 N-QOL domain scores (sleep/energy and bother/concern) can be obtained. Each domain includes 6 items. The global item of life quality is scored separately. All 13 items are scored from 0 to 4, with higher scores indicating better quality of life. The recall period is the past 2 weeks.

In Protocol FE 992026 CS41, the score for each sub-domain will be analyzable only if all six questions have responses. Since the total score is independent of the sub-domain scores, patients can miss up to one question and still have an analyzable total score.

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Summary scores are computed by transforming the raw score onto a standardized scale of 0-100 using the following formula:

$$\text{Transformed Total Score} = \frac{\text{The sum of the component items score}}{\text{Possible raw score range}} * 100$$

Domain scores are transformed using the formula:

$$\text{Transformed Domain Scores} = \frac{\text{The sum of the component items score}}{\text{Possible raw score range}} * 100$$

Sleep Quality

In Study FE 992926 CS41, sleep quality will be assessed by the following sleep diary that will be collected on a daily basis using an electronic data and time stamped.

Rate how refreshed you feel now (after waking):	1= poor.....10=excellent 1 2 3 4 5 6 7 8 9 10 (circle one)
Rate the quality of your sleep last night?	1= poor10=excellent 1 2 3 4 5 6 7 8 9 10 (circle one)

Ferring is planning to explore the clinical benefit of treating nocturia by linking sleep quality/QOL with reduction in frequency of nocturnal voids by using an anchor-based approach based on patient ratings at different periods of time.

Comments: The content validity of this sleep quality measure has not been established. "Quality of sleep" is a complex concept that includes many domains (i.e. feeling rested on waking; feeling alert throughout the day; and motivation to get up in the morning) which cannot be adequately captured by a single item.¹ Therefore a single item cannot effectively capture this complex concept.

3.2 Conceptual Framework

The conceptual framework of the N-QoL includes two sub-domains: sleep/energy and bother/concern, as noted in Table 1. Each sub-domain is made up of 6 items.

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Table 1. Conceptual Framework of N-QoL

SLEEP/ENERGY DOMAIN
1. Has made it difficult for me to concentrate the next day
2. Has made me feel generally low in energy the next day
3. Has required me to nap during the day
4. Has made me less productive the next day
5. Has caused me to participate less in activities I enjoy
7. Has made it difficult for me to get enough sleep at night

BOTHER/CONCERN DOMAIN
6. Has caused me to be careful about when or how much I drink
8. Concerned that I am disturbing others in the house because of having to get up at night to urinate
9. Preoccupied about having to get up at night to urinate
10. Worried that this condition will get worse in the future
11. Worried that there is no effective treatment for this condition (having to get up at night to urinate)
12. Overall how bothersome has having to get up at night to urinate been during the past 2 weeks?

Comments: The sleep/energy domain includes two domains: next day symptoms (items 1-5) and sleep quantity (item 7) at night. These concepts should be measured as separate domains.

The bother/concern domain includes items such as “worried that there is no effective treatment for this condition.”, and “worried that this condition will get worse in the future” that are not measures of treatment impacts of nocturia and cannot effectively support labeling claims.

3.3 Content Validity

The N-QoL’s development included qualitative research only with men with nocturia. In order to justify the content validity of the N-QoL in women with nocturia validity a qualitative study was performed with 5 women with nocturia (defined as 2 nocturnal voids per night). One-on-one interviews were conducted with 4 of the subjects; while 1 subject was interviewed by telephone. A standardized interview guide was used to conduct the interviews. Study participants were asked to complete each item of the N-QoL. After each item was completed, they were asked about the meaning, interpretation, and relevance of each item and the basis for their response. At the end of the interview, participants were asked about any missing content and overall impressions. Finally, participants completed a brief socio-demographic and clinical form.

Table 2 depicts the socio-demographic and clinical characteristics of the subjects

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Table 2. Qualitative Study Socio-Demographics

Age	57	39	66	77	49
Time since onset of symptoms	5+ years	5+ years	5+ years	1-2 years	2-5 years
Currently taking medication for nocturia	Yes	No	Yes	Yes	No
Frequency of getting up during a typical night in the past week	2	2	2	5+	3
Physician rated severity of nocturia	Moderate	Mild	Mild	Severe	Moderate
Patient weight (lbs)	195	150	203	155	185

Comments: Qualitative data to support the content validity of the N-QoL in males with nocturia has not been submitted. It is unlikely that five female subjects could provide an adequate representation of female patients with nocturia.

The content validity report included some direct quotes as well as paraphrased responses to each item of the questionnaire. The following is a sample of a few items and subject responses:

- “Over the past 2 weeks, having to get up at night to urinate has made it difficult for me to concentrate the next day” with the responses of every day, most days, some days, rarely, and never. As noted in the study report, all participants found this item to be clear and easy to understand and complete. All interpreted the item as intended and most found the item to be applicable in their lives. One participant noted some difficulty in responding, because some days are more difficult than others. However, this respondent was “very sure that it’s some days”.

Comments: The respondent’s response suggests that patients may have difficulty recalling their symptoms over a two week period.

- “Over the past 2 weeks, having to get up at night to urinate has made me feel generally low in energy the next day”. Two participants indicated that their lack of energy was not due attributed to lack of sleep.
- “Over the past 2 weeks, having to get up at night to urinate has required me to nap during the day”. Three out of five participants did not find this applicable to them.

Comments: The previous two subject comments suggest that these items may not be pertinent to the target population.

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- “Over the past 2 weeks, I have been preoccupied about having to get up at night to urinate”. The study report noted that “Several participants indicated that while this item was applicable in their lives, their nocturia was not something that they worry about; it is something that they deal with”.

Comments: Noting what “several participants indicated” does not effectively quantify how many subjects endorsed this response.

The content validity summary report noted that overall; the N-QoL “appeared to resonate with females with nocturia. The data suggests that nocturia may have important impacts on daily life, and these impacts may vary in intensity. All participants were able to recall their experiences over the past 2 weeks”. The summary also notes that it would be useful to add an item capturing the emotional impact of the limitations associated with nocturia. In addition, it was recommended that the item, “worried that there is no effective treatment” should be considered for removal since the item was largely not relevant to participants and may be difficult to answer if one is taking medication.

Comments: The qualitative summary does not provide sufficient information to justify the content validity of the N-QoL in females with nocturia for the following reasons:

- *The sponsor did not provide a complete qualitative study report including a copy of the protocol (i.e. inclusion/exclusion criteria and interview guide).*
- *The qualitative study enrolled only 5 subjects. In order to adequately capture the concept of interest a wide range of patients with the condition of interest, including population characteristics such as age, ethnicity, and severity of underlying condition should be enrolled in the study.*
- *Open-ended patient interviews were not used to effectively define the concept of nocturia from the patient’s perspective.*
- *The responses submitted suggest that not all items are clinically important to patients.*
- *The qualitative study did not provide data to suggest that subjects could adequately recall their experiences over a 2 week period. Most of the subject summary responses pertained to what the subject thought about the actual item and not the response options so it is unclear how the study subjects responded to the questions posed. However, one respondent was noted to have difficulty in responding to the question concerning next day concentration because some days she had more difficulty than others.*

In addition, the N-QoL does not include all of the HRQL domains since it does not measure the emotional impacts of nocturia (as noted in the content validity summary) or the negative aspects of treatment.

3.4 Other Measurement Properties

The psychometric properties (excluding content validity) of the N-QoL were assessed using the data from the Phase III trial. In addition to the N-QoL, patients completed the SF-12, Pittsburgh Sleep Quality Index (PSQI), and International Consultation on Incontinence Modular Questionnaire-Nocturia (ICIQ-N) and a sleep and voiding diary. All analyses were conducted on N-QoL data collected at visit 2 (day 1) and visit 7 (day 28).

Comments: The other measurement properties cannot be adequately interpreted unless the content validity of the N-QoL has been established.

3.5 Language Translation and Cultural Adaptation

The sponsor noted that the N-QoL was translated and linguistically validated in US Spanish, Canadian English, and Canadian French.

3.6 Protocol and Analysis Plan

The following is a summary of Protocol FE 992026 CS41 entitled, “A Multi-centre, Randomised, Double-blind, Placebo-controlled, Parallel, Group Trial to Demonstrate the Efficacy and Safety of Desmopressin Orally Disintegrating Tablet for the Treatment of Nocturia in Adult Males”.

Study Objectives:

Primary objective:

To demonstrate the safety and efficacy of desmopressin orally disintegrating tablets against placebo for the treatment of patients with nocturia from Visit 2 (baseline) to the end of trial Visit 9 (three months)

Secondary efficacy objectives (in rank order):

- To demonstrate the efficacy of desmopressin orally disintegrating tablets against placebo for the treatment of patients with nocturia with respect to:
 1. Mean time to first void at Visit 9 (three months)
 2. Proportion of 33% responders at Visit 9 (three months)
 3. Pharmacodynamic response at Visit 9 (three months)
- To document the impact of nocturia on:
 4. Quality of life (QoL) as measured by the Nocturia-Quality of Life (N-QoL)
 5. Sleep quality as measured by the sleep diary

Exploratory efficacy objectives:

- To investigate the onset of effect of desmopressin orally disintegrating tablets against placebo with respect to change in mean number of nocturnal voids, change in mean time to first void, proportion of 33% responders and dynamic response
- To investigate the impact of nocturia on sleep quality, work productivity and QoL

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Study Design:

This is a multi-center, randomized, double-blind, parallel-group clinical trial designed to evaluate the efficacy and safety of desmopressin orally disintegrating tablet as compared to placebo in adult males with nocturia. Eligible subjects will be randomized to one of four treatment groups: desmopressin 50 µg, desmopressin 75 µg, desmopressin 100 µg or placebo. The treatment will be administered orally every night, approximately one hour prior to bedtime, for a period of three months. During this period, records of nocturia and sleep over consecutive three-day periods will be kept on voiding and sleep diaries. Two questionnaires (N-QoL and WPAI) will be completed during the trial in order to evaluate the impacts on QoL and work productivity. Serum sodium level will be monitored since hyponatremia is a potential serious adverse event associated with desmopressin.

Study Enrollment Criteria:

Inclusion Criteria:

1. Written informed consent prior to performance of any trial-related activity
2. Male sex 18 years of age (at the time of written consent) or older
3. At least two nocturnal voids every night in a consecutive three-day period during the screening period

Exclusion Criteria:

1. Evidence of severe daytime voiding dysfunction defined as:
 - Urge urinary incontinence (more than one episode/day in the three-day diary period)
 - Urgency (more than one episode/day in the three-day diary period)
 - Frequency (more than eight daytime voids/day in the three-day diary period)
2. Interstitial cystitis
3. Chronic prostatitis/chronic pelvic pain syndrome (CPPS)
4. Suspicion of bladder outlet obstruction (BOO) or a urine flow of less than 5 mL/s as confirmed by uroflowmetry performed after suspicion of BOO
5. Surgical treatment, including transurethral resection, for BOO or benign prostatic hyperplasia within the past six months
6. Urinary retention or a post void residual volume in excess of 250 mL as confirmed by bladder ultrasound performed after suspicion of urinary retention
7. Habitual or psychogenic polydypsia (fluid intake resulting in a urine production exceeding 40 mL/kg/24 hours)
8. Central or nephrogenic diabetes insipidus
9. Syndrome of inappropriate antidiuretic hormone
10. Current or a history of urologic malignancies e.g. bladder cancer
11. Genito-urinary tract pathology e.g. infection or stone in the bladder and urethra causing symptoms
12. Neurogenic detrusor activity (detrusor overactivity)
13. Suspicion or evidence of cardiac failure
14. Uncontrolled hypertension
15. Uncontrolled diabetes mellitus
16. Hyponatremia:
 - Serum sodium level must be within normal limits
17. Renal insufficiency:

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- Serum creatinine must be within normal limits and estimated glomerular filtration rate must be more than or equal to 50 mL/min
- 18. Hepatic and/or biliary diseases:
 - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels must not be more than twice the upper limit of normal range
 - Total bilirubin level must not be more than 1.5 mg/dL
- 19. History of obstructive sleep apnea
- 20. Previous desmopressin treatment for nocturia
- 21. Treatment with another investigational product within three months prior to screening
- 22. Concomitant treatment with any prohibited medication*
- 23. Known alcohol or substance abuse
- 24. Work or lifestyle that may interfere with regular night-time sleep e.g. shift workers
- 25.. Any other medical condition, laboratory abnormality, psychiatric condition, mental incapacity, or language barrier which, in the judgement of the Investigator, would impair participation in the trial

Primary efficacy endpoint:

Change from baseline (Visit 2) in mean number of nocturnal voids at Visit 9 (three months) as assessed by the three-day sleep and voiding diary. The mean number of voids will be calculated as the average over three consecutive 24-hour periods just prior to the respective visits

Secondary efficacy endpoints (in rank order):

In order to support the efficacy of Nocdurna 25 mcg in this study, the sponsor plans to assess the following secondary endpoints (in rank order):

1. Change from baseline (Visit 2) in mean time to first void at Visit 9 (three months) as assessed by the three-day sleep and voiding diary. The time to first void is defined as the time from going to bed with the intention of sleeping until first void or until waking in the morning in the case where there is no nocturnal void. The mean time to first void will be calculated as the average over three consecutive 24-hour periods just prior to the respective visits
2. 33% responder status at Visit 7 (three months) as assessed by the three-day sleep and voiding diary. A 33% responder is defined as a subject with a decrease of at least 33% in the mean number of nocturnal voids at Visit 9 (three months) relative to baseline (Visit 2)
3. Change from baseline (Visit 2) in mean nocturnal urine volume and mean 24-hour urine volume at Visit 9 (three months) as assessed by the three-day urine volume diary. The nocturnal urine volume will include the volume of the first morning void. The mean urine volumes will be calculated as the average over three consecutive 24-hour periods just prior to the respective visits
4. Change from baseline (Visit 2) in nocturia-specific QoL as assessed by the N-QoL scores at Visit 5 (one month) and Visit 9 (three months). The N-QoL scores will be derived according to the N-QoL scoring manual
5. Change from baseline (Visit 2) in mean quality of sleep as measured by the sleep diary at Visit 4 (one week), Visit 7 (one month), Visit 8 (two months), and Visit 9 (three months)

Comments: The rank order of the PRO efficacy endpoints proposed does not adequately reflect the clinical importance of these endpoints in determining a treatment benefit. The effect of study

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drug on a measure of the signs and symptoms of nocturia would be most important. Once this has been established, then the effect of study drug on the more direct impacts (i.e. difficulty sleeping) should be assessed first in order to adequately evaluate the less direct impacts of treatment (i.e. HRQL).

Explorative efficacy endpoints:

- Change from baseline (Visit 2) in mean number of nocturnal voids at Visit 4 (one week), Visit 7 (one month), and Visit 8 (two months) as assessed by the three-day sleep and voiding diary
- Change from baseline (Visit 2) in mean time to first void at Visit 4 (one week), Visit 7 (one month), and Visit 8 (two months) as assessed by the three-day sleep and voiding diary
- 33% responder status at Visit 4 (one week), Visit 7 (one month), and Visit 8 (two months) as assessed by the three-day sleep and voiding diary
- Change from baseline (Visit 2) in mean nocturnal urine volume and mean 24-hour urine volume at Visit 7 (one month)
- Change from baseline (Visit 2) in work productivity as assessed by the work productivity and
- Activity impairment (WPAI) questionnaire at Visit 9 (three months). The WPAI scores will be derived according to the WPAI scoring manual

Safety endpoints:

- Frequency and severity of adverse events
- Clinically significant changes in laboratory values and vital signs
- Incidence of hyponatremia as measured by serum sodium level throughout the trial
- Fluid intake three days before and three days after initiation of treatment (Visit 1 to Visit 3) as assessed by the three day fluid intake diaries

Statistical Analysis Plan:

The primary analysis is based on the number of nocturnal voids at Visit 9 (three months) compared to baseline. Baseline is defined as the most recent value prior to or at Visit 2. Missing values post baseline will be imputed using last observation carried forward (LOCF) assuming at least one post baseline measurement is available at a visit before the missing observation.

The secondary endpoints aimed at demonstrating further treatment effect will be tested in the following order:

1. Mean time to first void at Visit 9 (three months), which will analyzed by using the same methodology as for the primary endpoint.
2. Proportion of 33% responders at Visit 9 (three months), which will be analyzed using logistic regression with main effects for treatment and the stratification factor (age <65, age ≥65), and a covariate for the baseline mean number of nocturnal voids as independent variables. A 33% responder at Visit 9 is defined as a subject with a decrease of at least 33% in the mean number of nocturnal voids at three months relative to baseline.
3. Pharmacodynamic response at Visit 9 (three months) which will be analyzed by using the same methodology as for the primary endpoint.

Significance on secondary endpoints will only be pursued for the doses that proved to be superior to placebo on the primary endpoint. For the secondary endpoints, the active treatment

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groups will be compared to placebo using a step-down approach from highest dose (100 µg) to lowest dose (50 µg). More specifically, the three secondary endpoints listed above will be tested in order for the highest dose (100 µg) first. If a secondary analysis does not achieve statistical significance at the 5% level, then statistical significance will not be declared for this and the subsequent secondary endpoints, regardless of the observed p-values. If all the three secondary endpoints demonstrate statistical significance in the highest dose compared to placebo, the testing is performed on the second to highest dose, and so on.

If the active treatment dose of 100 µg meets all of the three secondary endpoints listed above, then the endpoints related to documenting the impact of nocturia on QoL and quality of sleep will be tested in the following order:

4. QoL as measured by the N-QoL
5. Sleep quality as measured by the sleep diary

The impact of nocturia on QoL and quality of sleep will be explored by assessing the change in QoL and quality of sleep for all patients, using pooled treatments, compared to changes in key clinical endpoints (i.e., mean number of voids or time to first void).

Comments: In order to provide direct evidence of clinical benefit with reduction of nocturnal void frequency, evidence of improvement in the signs and symptoms of nocturia, as defined the target population through a content valid PRO measure needs to be established. In developing a nocturia PRO sign/symptom measure, it would be important to understand why patients void at night (i.e. bladder pressure or possible sleep disturbance, such as insomnia or sleep disturbance from a partner); the frequency and occurrence of symptoms and degree of bother; possible daytime urinary symptoms or other associated factors (i.e. caffeine ingestion before bed). Treatment benefit can be established by enrolling patients who have evidence of these signs and symptoms at baseline evidence that these signs and symptoms improve with treatment.

Only after the effect of treatment on the specific signs and symptoms of nocturia has been assessed can the impacts of nocturia (i.e. sleep disturbance and HRQL) associated with nocturia be evaluated.

3.7 Key References for Instrument

1. Harvey AG, Stinson K, Whitaker KL, Moskovitz D, Virk H. The subjective meaning of sleep quality: a comparison of individuals with and without insomnia. *Sleep*. 2008; 31:383–93

4 APPENDIX

4.1 N-QoL Questionnaire

OVER THE PAST 2 WEEKS , HAVING TO GET UP AT NIGHT TO URINATE...

1. Has made it difficult for me to concentrate the next day

- 0 Every day
- 1 Most days
- 2 Some days
- 3 Rarely
- 4 Never

2. Has made me feel generally low in energy the next day

- 0 Every day
- 1 Most days
- 2 Some days
- 3 Rarely
- 4 Never

3. Has required me to nap during the day

- 0 Every day
- 1 Most days
- 2 Some days
- 3 Rarely
- 4 Never

4. Has made me less productive the next day

- 0 Every day
- 1 Most days
- 2 Some days
- 3 Rarely
- 4 Never

5. Has caused me to participate less in activities I enjoy

- 0 Extremely
- 1 Quite a bit
- 2 Moderately
- 3 A little bit
- 4 Not at all

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6. Has caused me to be careful when or how much I drink

- 0 All the time
- 1 Most of the time
- 2 Some of the time
- 3 Rarely
- 4 Never

7. Has made it difficult for me to get enough sleep at night

- 0 Every night
- 1 Most nights
- 2 Some nights
- 3 Rarely
- 4 Never

OVER THE PAST 2 WEEKS , I HAVE BEEN...

8. Concerned that I am disturbing others in the house because of having to get up at night to urinate

- 0 Extremely
- 1 Quite a bit
- 2 Moderately
- 3 A little bit
- 4 Not at all

9. Preoccupied about having to get up at night to urinate

- 0 All the time
- 1 Most of the time
- 2 Some of the time
- 3 Rarely
- 4 Never

10. Worried that this condition will get worse in the future

- 0 Extremely
- 1 Quite a bit
- 2 Moderately
- 3 A little bit
- 4 Not at all

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11. Worried that there is no effective treatment for this condition (having to get up at night to urinate)
- 0 Extremely
 - 1 Quite a bit
 - 2 Moderately
 - 3 A little bit
 - 4 Not at all
12. Overall, how bothersome has having to get up at night to urinate been during the past 2 weeks?
- 4 Not at all
 - 3 A little bit
 - 2 Moderately
 - 1 Quite a bit
 - 0 Extremely
13. Overall I would rate my quality of life to be...
- 0 Very Good
 - 1 Good
 - 2 Fair
 - 3 Poor
 - 4 Very Poor

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-65890	ORIG-1	FERRING PHARMACEUTICA LS INC	MINIRIN SL MELT
NDA-22517	GI-1	FERRING PHARMACEUTICA LS INC	NOCDURNA

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/s/

ANN M TRENTACOSTI
08/31/2010

LAURIE B BURKE
08/31/2010

STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	2010-062
APPLICATION NUMBER	IND 65890 SDN 62; NDA 22517
LETTER DATE/SUBMISSION NUMBER	July 16, 2010
PDUFA GOAL DATE	September 2, 2010
DATE OF CONSULT REQUEST	July 22, 2010
REVIEW DIVISION	Division of Metabolism and Endocrinology Products (DMEP)
MEDICAL REVIEWER	Bill Lubas
REVIEW DIVISION PM	Jennifer Johnson
SEALD REVIEWER(S)	Ann Marie Trentacosti
REVIEW COMPLETION DATE	August 31, 2010
ESTABLISHED NAME	Desmopressin orally disintegrating tablets
TRADE NAME	Nocturna
APPLICANT	Ferring Pharmaceuticals
ENDPOINT(S) CONCEPT(S)	Health Related Quality of Life in Patients with Nocturia; Sleep Quality
INSTRUMENT(S)	Nocturia-Quality of Life (N-QoL) and Sleep Quality Diary
INDICATION	Treatment of Nocturia
INTENDED POPULATION(S)	Adults with Nocturia

1 EXECUTIVE SUMMARY

This Study Endpoints and Labeling Development (SEALD) review is provided as a response to a request for consultation by the Division of Metabolism and Endocrinology Products (DMEP) regarding IND 65,890 and Ferring's submission of a Special Protocol Assessment for Protocol FE 992026 CS40 to evaluate the safety and efficacy of Nocdurna (desmopressin) Orally Disintegrating Tablets for adult females with nocturia. SEALD has been requested by DMEP to review the proposed secondary efficacy patient reported outcome (PRO) endpoints included in the protocol.

The review concludes that Protocol FE 992026 CS40 is not adequately designed to show a treatment benefit associated with treatment of nocturia with Nocdurna.

In order to provide direct evidence of clinical benefit with reduction of nocturnal void frequency, the sponsor should provide evidence of improvement in the target population-defined signs and symptoms of nocturia, with a content valid PRO measure. In developing a nocturia PRO sign/symptom measure, it would be important to understand why patients void at night [i.e. bladder pressure, other sleep disturbance, such as insomnia or sleep disturbance by a sleep partner); the frequency and occurrence of symptoms and degree of bother; possible associated night-time and daytime urinary symptoms, as well as other concomitant factors (i.e. caffeinated beverage ingestion before bed)]. Treatment benefit can be established by enrolling patients who have evidence of the relevant signs and symptoms (relevancy depending on the subpopulation enrolled) at baseline and show an improvement in these signs and symptoms with treatment. Only after the effect of treatment on the patient-defined signs and symptoms of nocturia has been determined can the impacts of nocturia (i.e. sleep disturbance, daytime tiredness, daytime difficulty concentrating, and health related quality of life (HRQL) be interpreted.

In addition, the content validity of both proposed secondary efficacy endpoints: the Nocturia-Quality of Life (N-QoL) and Sleep Quality Diary has not been established and the measures therefore cannot adequately support labeling claims.

It is recommended that sponsor use the principles delineated in the "FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims" and develop a measure of the signs and symptoms of nocturia as the primary measure of clinical benefit. A PRO measure of the direct impacts associated with nocturia could be a useful secondary clinical outcome measure in evaluating treatment benefit.

2 SUGGESTED RESPONSES TO SPONSOR QUESTIONS

Proposed responses to questions posed in the briefing package are provided in *italics*.

Question 3: Does FDA agree to the proposed secondary endpoints and the rank order for the purpose of supporting the clinical efficacy and durability of effect of NOCDURNA (Desmopressin) orally disintegrating tablet 25 mcg in this study?

Response:

We do not agree with the patient-reported outcome secondary endpoints (N-QoL and sleep quality rating scales) as posed (See our response to question 6).

Question 6: Does FDA agree that N-QoL and the sleep quality rating scales are acceptable secondary outcome measures?

Response:

No, we do not agree that the N-QoL or sleep quality rating scale is the most appropriate measures of treatment benefit (the effect of treatment on how a patient survives, feels, or functions). In order to provide direct evidence of clinical benefit with reduction of nocturnal void frequency, it would be necessary to show evidence of improvement in the target population defined signs and symptoms of nocturia with a content valid PRO measure.

Treatment benefit can be evaluated by enrolling patients who have evidence of the relevant signs and symptoms (relevancy depending on the subpopulation enrolled) at baseline and show an improvement in these signs and symptoms with treatment.

Only after the effect of treatment on the patient defined signs and symptoms of nocturia has been determined can the impacts of nocturia (i.e. sleep disturbance, daytime tiredness, and HRQL) be interpreted.

In addition, the content validity of the measures of nocturia-related quality of life (N-QoL) and sleep quality (sleep quality rating scale) has not been established, as exemplified by the following:

The N-QoL content validity study only enrolled 5 subjects and did not provide sufficient evidence that the measure was appropriate, interpretable, and comprehensive for patients. The subject responses suggest that several items may not be clinically relevant to the target population and that patients may not be able to adequately recall their experience over a two week period of time. Items such as, “worried that there is no effective treatment for this condition.”, and “worried that this condition will get worse in the future” are likely to be impacted by patient personality and many other patient attributes besides the frequency of nocturnal voiding and will introduce variability, yield uninterpretable study results, and will likely not support labeling claims. In addition, the N-QoL does not include all of the HRQL domains since it does not measure the emotional impacts of nocturia (as noted in the content validity summary) or the negative aspects of treatment.

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Data has not been submitted to suggest that the sleep rating scale quality instrument is appropriate, comprehensible, and interpretable for the target population. “Quality of sleep” is a complex concept that includes several domains (i.e. feeling rested on waking and motivation to get up in the morning) which cannot be adequately captured by a single item.

We recommend that you refer to the “FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims” and develop a measure of the signs and symptoms of nocturia as the primary measure of treatment benefit. A PRO measure of the direct impacts associated with nocturia could be a useful secondary clinical outcome measure in evaluating a treatment response.

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On April 22, 2010, DMEP sent a Complete Response to Ferring concerning NDA 22-517: Nocurna (desmopressin) Orally Disintegrating Tablets for the treatment of nocturia in adults. In response to the Complete Response, Ferring plans to conduct two phase 3 studies with Nocurna: one enrolling female patients and one enrolling male patients with nocturia.

In this submission, the sponsor has submitted a Special Protocol Submission for the phase 3 trial in female nocturia patients entitled: “Protocol FE 992026 CS40: A Multi-centre, Randomised, Double-blind, Placebo-controlled, Parallel, Group Trial to Demonstrate the Efficacy and Safety of Desmopressin Orally Disintegrating Tablet for the Treatment of Nocturia in Adult Females”. The study is designed as a confirmatory study to demonstrate that a lower dose regimen and monitoring scheme are safe and effective in the treatment of nocturia in adult females.

3.1 Instruments

The sponsor has included two PRO measures as secondary endpoints in Protocol FE 992026 CS40: the N-QoL and Sleep Quality instruments.

Nocturia-Quality of Life (N-QoL)

The N-QOL (See Appendix) was developed to measure the impact of nocturia and its treatment on a patient’s quality of life. The instrument includes 13 items, with 12 items directly related to nocturia plus a global quality of life item. An overall score of the 12 nocturia items as well as a measure of the 2 N-QOL domain scores (sleep/energy and bother/concern) can be obtained. Each domain includes 6 items. The global item of life quality is scored separately. All 13 items are scored from 0 to 4, with higher scores indicating better quality of life. The recall period is the past 2 weeks.

In Protocol FE 992026 CS40, the score for each sub-domain will be analyzable only if all six questions have responses. Since the total score is independent of the sub-domain scores, patients can miss up to one question and still have an analyzable total score.

Summary scores are computed by transforming the raw score onto a standardized scale of 0-100 using the following formula:

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$$\text{Transformed Total Score} = \frac{\text{The sum of the component items score}}{\text{Possible raw score range}} * 100$$

Domain scores are transformed using the formula:

$$\text{Transformed Domain Scores} = \frac{\text{The sum of the component items score}}{\text{Possible raw score range}} * 100$$

The N-QoL development was based upon a review of the literature, four focus groups with 7 to 8 men with nocturia, pilot testing with 5 men in the United States, and psychometric evaluation in the United Kingdom. Since the initial qualitative research only enrolled males, additional qualitative research was performed in female subjects with nocturia (see Content Validity section of this review).

Sleep Quality

In Study FE 992926 CS40, sleep quality will be assessed by the following sleep diary that will be collected on a daily basis using an electronic data and time stamped.

Rate how refreshed you feel now (after waking):	1= poor.....10=excellent 1 2 3 4 5 6 7 8 9 10 (circle one)
Rate the quality of your sleep last night?	1= poor10=excellent 1 2 3 4 5 6 7 8 9 10 (circle one)

Ferring is planning to explore the clinical benefit of treating nocturia by linking sleep quality/QOL with reduction in frequency of nocturnal voids by using an anchor-based approach based on patient ratings at different periods of time.

Comments: The content validity of this sleep quality measure has not been established. "Quality of sleep" is a complex concept that includes many domains (i.e. feeling rested on waking; feeling alert throughout the day; and motivation to get up in the morning) which cannot be adequately captured by a single item.¹ Therefore a single item cannot effectively capture this complex concept.

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3.2 Conceptual Framework

The conceptual framework of the N-QoL includes two sub-domains: sleep/energy and bother/concern, as noted in Table 1. Each sub-domain is made up of 6 items.

Table 1. Conceptual Framework of N-QoL

SLEEP/ENERGY DOMAIN
1. Has made it difficult for me to concentrate the next day
2. Has made me feel generally low in energy the next day
3. Has required me to nap during the day
4. Has made me less productive the next day
5. Has caused me to participate less in activities I enjoy
7. Has made it difficult for me to get enough sleep at night

BOTHER/CONCERN DOMAIN
6. Has caused me to be careful about when or how much I drink
8. Concerned that I am disturbing others in the house because of having to get up at night to urinate
9. Preoccupied about having to get up at night to urinate
10. Worried that this condition will get worse in the future
11. Worried that there is no effective treatment for this condition (having to get up at night to urinate)
12. Overall how bothersome has having to get up at night to urinate been during the past 2 weeks?

Comments: The sleep/energy domain includes two domains: next day symptoms (items 1-5) and sleep quantity (item 7) at night. These concepts should be measured as separate domains.

The bother/concern domain includes items such as “worried that there is no effective treatment for this condition.”, and “worried that this condition will get worse in the future” that are not measures of treatment impacts of nocturia and cannot effectively support labeling claims.

3.3 Content Validity

The N-QoL’s development included qualitative research only with men with nocturia. In order to justify the content validity of the N-QoL in women with nocturia validity a qualitative study was performed with 5 women with nocturia (defined as 2 nocturnal voids per night). One-on-one interviews were conducted with 4 of the subjects; while 1 subject was interviewed by telephone. A standardized interview guide was used to conduct the interviews. Study participants were asked to complete each item of the N-QoL. After each item was completed, they were asked

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about the meaning, interpretation, and relevance of each item and the basis for their response. At the end of the interview, participants were asked about any missing content and overall impressions. Finally, participants completed a brief socio-demographic and clinical form.

Table 2 depicts the socio-demographic and clinical characteristics of the subjects

Table 2. Qualitative Study Socio-Demographics

Age	57	39	66	77	49
Time since onset of symptoms	5+ years	5+ years	5+ years	1-2 years	2-5 years
Currently taking medication for nocturia	Yes	No	Yes	Yes	No
Frequency of getting up during a typical night in the past week	2	2	2	5+	3
Physician rated severity of nocturia	Moderate	Mild	Mild	Severe	Moderate
Patient weight (lbs)	195	150	203	155	185

Comments: It is unlikely that five subjects could provide an adequate representation of female patients with nocturia.

The content validity report included some direct quotes as well as paraphrased responses to each item of the questionnaire. The following is a sample of a few items and subject responses:

- “Over the past 2 weeks, having to get up at night to urinate has made it difficult for me to concentrate the next day” with the responses of every day, most days, some days, rarely, and never. As noted in the study report, all participants found this item to be clear and easy to understand and complete. All interpreted the item as intended and most found the item to be applicable in their lives. One participant noted some difficulty in responding, because some days are more difficult than others. However, this respondent was “very sure that it’s some days”.

Comments: The respondent’s response suggests that patients may have difficulty recalling their symptoms over a two week period.

- “Over the past 2 weeks, having to get up at night to urinate has made me feel generally low in energy the next day”. Two participants indicated that their lack of energy was not due attributed to lack of sleep.
- “Over the past 2 weeks, having to get up at night to urinate has required me to nap during the day”. Three out of five participants did not find this applicable to them.

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Comments: The previous two subject comments suggest that these items may not be pertinent to the target population.

- “Over the past 2 weeks, I have been preoccupied about having to get up at night to urinate”. The study report noted that “Several participants indicated that while this item was applicable in their lives, their nocturia was not something that they worry about; it is something that they deal with”.

Comments: Noting what “several participants indicated” does not effectively quantify how many subjects endorsed this response.

The content validity summary report noted that overall; the N-QoL “appeared to resonate with females with nocturia. The data suggests that nocturia may have important impacts on daily life, and these impacts may vary in intensity. All participants were able to recall their experiences over the past 2 weeks”. The summary also notes that it would be useful to add an item capturing the emotional impact of the limitations associated with nocturia. In addition, it was recommended that the item, “worried that there is no effective treatment” should be considered for removal since the item was largely not relevant to participants and may be difficult to answer if one is taking medication.

Comments: The qualitative summary does not provide sufficient information to justify the content validity of the N-QoL in females with nocturia for the following reasons:

- *The sponsor did not provide a complete qualitative study report including a copy of the protocol (i.e. inclusion/exclusion criteria and interview guide).*
- *The qualitative study enrolled only 5 subjects. In order to adequately capture the concept of interest a wide range of patients with the condition of interest, including population characteristics such as age, ethnicity, and severity of underlying condition should be enrolled in the study.*
- *Open-ended patient interviews were not used to effectively define the concept of nocturia from the patient’s perspective.*
- *The responses submitted suggest that not all items are clinically important to patients.*
- *The qualitative study did not provide data to suggest that subjects could adequately recall their experiences over a 2 week period. Most of the subject summary responses pertained to what the subject thought about the actual item and not the response options so it is unclear how the study subjects responded to the questions posed. However, one respondent was noted to have difficulty in responding to the question concerning next day concentration because some days she had more difficulty than others.*

In addition, the N-QoL does not include all of the HRQL domains since it does not measure the emotional impacts of nocturia (as noted in the content validity summary) or the negative aspects of treatment.

3.4 Other Measurement Properties

The psychometric properties (excluding content validity) of the N-QoL were assessed using the data from the Phase III trial. In addition to the N-QoL, patients completed the SF-12, Pittsburgh Sleep Quality Index (PSQI), and International Consultation on Incontinence Modular Questionnaire-Nocturia (ICIQ-N) and a sleep and voiding diary. All analyses were conducted on N-QoL data collected at visit 2 (day 1) and visit 7 (day 28).

Comments: The other measurement properties cannot be adequately interpreted unless the content validity of the N-QoL has been established.

3.5 Language Translation and Cultural Adaptation

The sponsor noted that the N-QoL was translated and linguistically validated in US Spanish, Canadian English, and Canadian French.

3.6 Protocol and Analysis Plan

The following is a summary of Protocol FE 992026 CS40 entitled, “A Multi-centre, Randomised, Double-blind, Placebo-controlled, Parallel, Group Trial to Demonstrate the Efficacy and Safety of Desmopressin Orally Disintegrating Tablet for the Treatment of Nocturia in Adult Females”.

Study Objectives:

Primary objective:

To demonstrate the safety and efficacy of desmopressin orally disintegrating tablets against placebo for the treatment of patients with nocturia from Visit 2 (baseline) to the end of trial Visit 7 (three months)

Secondary efficacy objectives (in rank order):

- To demonstrate the efficacy of desmopressin orally disintegrating tablets against placebo for the treatment of patients with nocturia with respect to:
 1. Mean time to first void at Visit 7 (three months)
 2. Proportion of 33% responders at Visit 7 (three months)
 3. Pharmacodynamic response at Visit 7 (three months)

- To document the impact of nocturia on:
 4. Quality of life (QoL) as measured by the Nocturia-Quality of Life (N-QoL)
 5. Sleep quality as measured by the sleep diary

Exploratory efficacy objectives:

- To investigate the onset of effect of desmopressin orally disintegrating tablets against placebo with respect to change in mean number of nocturnal voids, change in mean time to first void, proportion of 33% responders and dynamic response
- To investigate the impact of nocturia on work productivity and QoL

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Study Design:

This is a multi-center, randomized, double-blind, parallel-group clinical trial designed to evaluate the efficacy and safety of desmopressin orally disintegrating tablet as compared to placebo in adult females with nocturia. Eligible subjects will be randomized to one of two treatment groups: desmopressin 25 µg or placebo. The treatment will be administered orally every night, approximately one hour prior to bedtime, for a period of three months. During this period, records of nocturia and sleep over consecutive three-day periods will be kept on voiding and sleep diaries. Two questionnaires (N-QoL and WPAI) will be completed during the trial in order to evaluate the impacts on QoL and work productivity. Serum sodium level will be monitored since hyponatremia is a potential serious adverse event associated with desmopressin.

Study Enrollment Criteria:

Inclusion Criteria:

1. Written informed consent prior to performance of any trial-related activity
2. Female sex 18 years of age (at the time of written consent) or older
3. At least two nocturnal voids every night in a consecutive three-day period during the screening period

Exclusion Criteria:

1. Evidence of severe daytime voiding dysfunction defined as:
 - Urge urinary incontinence (more than one episode/day in the three-day diary period)
 - Urgency (more than one episode/day in the three-day diary period)
 - Frequency (more than eight daytime voids/day in the three-day diary period)
2. Interstitial cystitis
3. Urinary retention or a post void residual volume in excess of 150 mL as confirmed by bladder ultrasound performed after suspicion of urinary retention
4. Habitual or psychogenic polydypsia (fluid intake resulting in a urine production exceeding 40 mL/kg/24 hours)
5. Central or nephrogenic diabetes insipidus
6. Syndrome of inappropriate antidiuretic hormone
7. Current or a history of urologic malignancies e.g. bladder cancer
8. Genito-urinary tract pathology e.g. infection or stone in the bladder and urethra causing symptoms
9. Neurogenic detrusor activity (detrusor overactivity)
10. Suspicion or evidence of cardiac failure
11. Uncontrolled hypertension
12. Uncontrolled diabetes mellitus
13. Hyponatremia:
 - Serum sodium level must be within normal limits
14. Renal insufficiency:
 - Serum creatinine must be within normal limits and estimated glomerular filtration rate must be more than or equal to 50 mL/min
15. Hepatic and/or biliary diseases:
 - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels must not be more than twice the upper limit of normal range
 - Total bilirubin level must not be more than 1.5 mg/dL

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16. History of obstructive sleep apnea
17. Previous desmopressin treatment for nocturia
18. Treatment with another investigational product within three months prior to screening
19. Concomitant treatment with any prohibited medication*
20. Pregnancy, breastfeeding, or a plan to become pregnant during the period of the clinical trial. Subjects of reproductive age must have documentation of a reliable method of contraception. All pre-and perimenopausal subjects have to perform pregnancy tests. Amenorrhea of more than 12 months duration based on the reported date of the last menstrual period is sufficient documentation of post-menopausal status and does not require a pregnancy test
21. Known alcohol or substance abuse
22. Work or lifestyle that may interfere with regular night-time sleep e.g. shift workers
23. Any other medical condition, laboratory abnormality, psychiatric condition, mental incapacity, or language barrier which, in the judgement of the Investigator, would impair participation in the trial

Primary efficacy endpoint:

Change from baseline (Visit 2) in mean number of nocturnal voids at Visit 7 (three months) as assessed by the three-day sleep and voiding diary. The mean number of voids will be calculated as the average over three consecutive 24-hour periods just prior to the respective visits

Secondary efficacy endpoints (in rank order):

In order to support the efficacy of Nocdurna 25 mcg in this study, the sponsor plans to assess the following secondary endpoints (in rank order):

1. Change from baseline (Visit 2) in mean time to first void at Visit 7 (three months) as assessed by the three-day sleep and voiding diary. The time to first void is defined as the time from going to bed with the intention of sleeping until first void or until waking in the morning in the case where there is no nocturnal void. The mean time to first void will be calculated as the average over three consecutive 24-hour periods just prior to the respective visits
2. 33% responder status at Visit 7 (three months) as assessed by the three-day sleep and voiding diary. A 33% responder is defined as a subject with a decrease of at least 33% in the mean number of nocturnal voids at Visit 7 (three months) relative to baseline (Visit 2)
3. Change from baseline (Visit 2) in mean nocturnal urine volume and mean 24-hour urine volume at Visit 7 (three months) as assessed by the three-day urine volume diary. The nocturnal urine volume will include the volume of the first morning void. The mean urine volumes will be calculated as the average over three consecutive 24-hour periods just prior to the respective visits
4. Change from baseline (Visit 2) in nocturia-specific QoL as assessed by the N-QoL scores at Visit 5 (one month) and Visit 7 (three months). The N-QoL scores will be derived according to the N-QoL scoring manual
5. Change from baseline (Visit 2) in mean quality of sleep as measured by the sleep diary at Visit 4 (one week), Visit 5 (one month), Visit 6 (two months), and Visit 7 (three months)

Comments: The rank order of the PRO efficacy endpoints proposed does not adequately reflect the clinical importance of these endpoints in determining a treatment benefit. The effect of study drug on a measure of the signs and symptoms of nocturia would be most important. Once this

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has been established, then the effect of study drug on the more direct impacts (i.e. difficulty sleeping) should be assessed first in order to adequately evaluate the less direct impacts of treatment (i.e. HRQL).

Explorative efficacy endpoints:

- Change from baseline (Visit 2) in mean number of nocturnal voids at Visit 4 (one week), Visit 5 (one month), and Visit 6 (two months) as assessed by the three-day sleep and voiding diary
- Change from baseline (Visit 2) in mean time to first void at Visit 4 (one week), Visit 5 (one month), and Visit 6 (two months) as assessed by the three-day sleep and voiding diary
- 33% responder status at Visit 4 (one week), Visit 5 (one month), and Visit 6 (two months) as assessed by the three-day sleep and voiding diary
- Change from baseline (Visit 2) in mean nocturnal urine volume and mean 24-hour urine volume at Visit 5 (one month)
- Change from baseline (Visit 2) in work productivity as assessed by the work productivity and
- Activity impairment (WPAI) questionnaire at Visit 7 (three months). The WPAI scores will be derived according to the WPAI scoring manual

Safety endpoints:

- Frequency and severity of adverse events
- Clinically significant changes in laboratory values and vital signs
- Incidence of hyponatremia as measured by serum sodium level throughout the trial
- Fluid intake three days before and three days after initiation of treatment (Visit 1 to Visit 3) as assessed by the three day fluid intake diaries

Statistical Analysis Plan:

The primary analysis is based on the number of nocturnal voids at Visit 7 (three months) compared to baseline. Baseline is defined as the most recent value prior to or at Visit 2. Missing values post baseline will be imputed using last observation carried forward (LOCF) assuming at least one post baseline measurement is available at a visit before the missing observation.

The secondary endpoints aimed at demonstrating further treatment effect will be tested in the following order:

1. Mean time to first void at Visit 7 (three months), which will analyzed by using the same methodology as for the primary endpoint.
2. Proportion of 33% responders at Visit 7 (three months), which will be analyzed using logistic regression with main effects for treatment and the stratification factor (age <65, age ≥65), and a covariate for the baseline mean number of nocturnal voids as independent variables. A 33% responder at Visit 7 is defined as a subject with a decrease of at least 33% in the mean number of nocturnal voids at three months relative to baseline.
3. Pharmacodynamic response at Visit 7 (three months) which will be analyzed by using the same methodology as for the primary endpoint.

If a secondary analysis does not achieve statistical significance at the 5 % level, then statistical significance will not be declared for this and the subsequent secondary endpoints, regardless of the observed p-values.

STUDY ENDPOINT REVIEW

If the 25 µg meets all of the three secondary endpoints listed above, then the endpoints related to documenting the impact of nocturia on QoL and quality of sleep will be tested in the following order:

4. QoL as measured by the N-QoL
5. Sleep quality as measured by the sleep diary

The impact of nocturia on QoL and quality of sleep will be explored by assessing the change in QoL and quality of sleep for all patients, using pooled treatments, compared to changes in key clinical endpoints (i.e., mean number of voids or time to first void).

Comments: In order to provide direct evidence of clinical benefit with reduction of nocturnal void frequency, evidence of improvement in the signs and symptoms of nocturia, as defined the target population through a content valid PRO measure needs to be established. In developing a nocturia PRO sign/symptom measure, it would be important to understand why patients void at night (i.e. bladder pressure or possible sleep disturbance, such as insomnia or sleep disturbance from a partner); the frequency and occurrence of symptoms and degree of bother; possible daytime urinary symptoms or other associated factors (i.e. caffeine ingestion before bed). Treatment benefit can be established by enrolling patients who have evidence of these signs and symptoms at baseline evidence that these signs and symptoms improve with treatment.

Only after the effect of treatment on the specific signs and symptoms of nocturia has been assessed can the impacts of nocturia (i.e. sleep disturbance and HRQL) associated with nocturia be evaluated.

3.7 Key References for Instrument

1. Harvey AG, Stinson K, Whitaker KL, Moskovitz D, Virk H. The subjective meaning of sleep quality: a comparison of individuals with and without insomnia. *Sleep*. 2008; 31:383–93

4 APPENDIX

4.1 N-QoL Questionnaire

OVER THE PAST 2 WEEKS , HAVING TO GET UP AT NIGHT TO URINATE...

1. Has made it difficult for me to concentrate the next day

- 0 Every day
- 1 Most days
- 2 Some days
- 3 Rarely
- 4 Never

2. Has made me feel generally low in energy the next day

- 0 Every day
- 1 Most days
- 2 Some days
- 3 Rarely
- 4 Never

3. Has required me to nap during the day

- 0 Every day
- 1 Most days
- 2 Some days
- 3 Rarely
- 4 Never

4. Has made me less productive the next day

- 0 Every day
- 1 Most days
- 2 Some days
- 3 Rarely
- 4 Never

5. Has caused me to participate less in activities I enjoy

- 0 Extremely
- 1 Quite a bit
- 2 Moderately
- 3 A little bit
- 4 Not at all

STUDY ENDPOINT REVIEW

6. Has caused me to be careful when or how much I drink

- 0 All the time
- 1 Most of the time
- 2 Some of the time
- 3 Rarely
- 4 Never

7. Has made it difficult for me to get enough sleep at night

- 0 Every night
- 1 Most nights
- 2 Some nights
- 3 Rarely
- 4 Never

OVER THE PAST 2 WEEKS , I HAVE BEEN...

8. Concerned that I am disturbing others in the house because of having to get up at night to urinate

- 0 Extremely
- 1 Quite a bit
- 2 Moderately
- 3 A little bit
- 4 Not at all

9. Preoccupied about having to get up at night to urinate

- 0 All the time
- 1 Most of the time
- 2 Some of the time
- 3 Rarely
- 4 Never

10. Worried that this condition will get worse in the future

- 0 Extremely
- 1 Quite a bit
- 2 Moderately
- 3 A little bit
- 4 Not at all

STUDY ENDPOINT REVIEW

11. Worried that there is no effective treatment for this condition (having to get up at night to urinate)
- 0 Extremely
 - 1 Quite a bit
 - 2 Moderately
 - 3 A little bit
 - 4 Not at all
12. Overall, how bothersome has having to get up at night to urinate been during the past 2 weeks?
- 4 Not at all
 - 3 A little bit
 - 2 Moderately
 - 1 Quite a bit
 - 0 Extremely
13. Overall I would rate my quality of life to be...
- 0 Very Good
 - 1 Good
 - 2 Fair
 - 3 Poor
 - 4 Very Poor

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22517	ORIG-1	FERRING PHARMACEUTICA LS INC	NOCDURNA
IND-65890	ORIG-1	FERRING PHARMACEUTICA LS INC	MINIRIN SL MELT

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/s/

ANN M TRENTACOSTI
08/31/2010

LAURIE B BURKE
08/31/2010

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

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

Memorandum

Date: August 27, 2010

To: Jennifer Johnson, Regulatory Project Manager,
Division of Metabolism and Endocrinology Products (DMEP)

From: Samuel Skariah, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Kendra Jones, Regulatory Review Officer
Shefali Doshi, Acting Group Leader, DDMAC
Lisa Hubbard, Professional Group Leader, DDMAC

Subject: NDA 022517

DDMAC labeling comments for Nocdurna[®] (desmopressin)
Orally Disintegrating Tablets

We acknowledge receipt of your March 31, 2010, consult request for the proposed product labeling for Nocdurna, NDA 22-517. Final labeling negotiations were not initiated during this review cycle and a Complete Response letter was issued on April 22, 2010. Therefore, DDMAC will provide comments regarding labeling for this application during a subsequent review cycle. DDMAC requests that DMEP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions, please contact Samuel Skariah at 301.796.2774 or Sam.Skariah@fda.hhs.gov.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22517

ORIG-1

FERRING
PHARMACEUTICA
LS INC

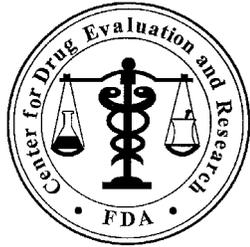
NOCDURNA

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/s/

SAMUEL M SKARIAH

08/27/2010



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: April 15, 2010

To: Mary Parks, MD, Director
Division of Metabolism and Endocrinology Products

Through: Carlos Mena-Grillasca, RPh, Team Leader
Denise Toyer, PharmD, Deputy Director
Division of Medication Error Prevention and Analysis

From: LaToya Shenee' Toombs, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Nocdurna (Desmopressin) Orally Disintegrating Tablets
25 mcg

Application Type/Number: NDA 022517

Applicant: Ferring Pharmaceuticals

OSE RCM #: 2009-1554

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2.1	Adverse Event Reporting System (AERS)	3
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3	RECOMMENDATIONS	3
3.1	Comments to the Division.....	4
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1 INTRODUCTION

This review is written in response to a request from the Division of Metabolism and Endocrinology Products for the Division of Medication Error Prevention and Analysis (DMEPA) to evaluate container labels, carton and insert labeling for areas that could lead to medication errors.

2 METHODS AND RESULTS

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS)

Desmopressin is currently marketed in the United States. Therefore, DMEPA conducted a search of the FDA Adverse Event Reporting System (AERS) database on March 24, 2010 for any medication errors relevant to the labels or labeling of the orally administered desmopressin products, using the following criteria: Active Ingredient “Desmopressin” and “Desmopressin Acetate”, Verbatim term “Desmop%” and the MedDRA reaction terms “Medication Errors” (HGLT) and “Product Quality Issue” (PT). The search was limited to the following routes of administration: buccal, oral and sublingual.

The search resulted in twenty cases, none of which were related to labels or labeling

- Medication errors related to non-oral desmopressin products (n=8).
- Wrong patient, including prescribing to age group not indicated (n=1)
- Pharmaceutical product complaint including lack of efficacy (n=2)
- Intentional overdose (n=3)
- Adverse event (n=1)
- Dose omission, including patient taking doses as needed versus prescribed routine administration (n=1)
- Wrong frequency due to caregiver misinterpretation (n=1)

Three (n=3) of the twenty cases involved improper dose (See Appendix C). The first case describes a patient self-titrating the daily dose, the second case describes a patient who was administered 22 tablets (6 mg) in three days. The final case describes improper dosing due to the pharmacy. However due to lack of information, causality could not be determined in all three cases.

2.2 LABELS AND LABELING

DMEPA used Failure Mode and Effects Analysis (FMEA)¹ in our evaluation of the container labels and carton labeling submitted June 19, 2009 and insert labeling submitted on January 11, 2010 (see Appendices A and B). However, since the Division is not recommending approval of the 100 mcg dose in men, DMEPA will not analyze labels and labeling pertaining to the 100 mcg strength.

3 RECOMMENDATIONS

Our evaluation noted areas where information on the container labels and carton labeling can be improved to minimize medication errors. We provide comments to the Division, including recommendations for the insert labeling, in Section 3.1 for discussion at the labeling meetings. We provide recommendations for the container labels and carton labeling in Section 3.2 that aim at reducing the risk of medication errors. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Margarita Tossa, OSE Project Manager, at 301-796-4053.

3.1 COMMENTS TO THE DIVISION

A. Insert Labeling

1. We note a discrepancy between the dosage form (orally disintegrating tablet) and the route of administration (sublingual) that the Applicant recommends in the Dosage and Administration section of the insert labeling. According to the definition of an Orally Disintegrating Tablet provided in the Guidance for Industry: Orally Disintegrating Tablets (ODT), an ODT is defined as a solid dosage form containing medicinal substances which disintegrate rapidly, usually within a matter of seconds, when placed upon the tongue. Although this definition does not specify between the top or bottom of the tongue, DMEPA recommends maintaining consistency with other approved ODT products and revising the route of administration to recommend placing the tablets on the tongue.
2. After internal discussions with the review team, the Division is not recommending approval of the 100 mcg dose in men, therefore DMEPA recommends the revision of the insert label to reflect this recommendation in all applicable sections of the insert labeling (i.e. Dosage and Administration, Dosage Forms and Strengths, How Supplied, etc).

3.2 COMMENTS TO THE APPLICANT

A. General Comments

We note the proprietary name is presented in all-caps. Consider revising the proprietary name to appear in title case (i.e. Nocdurna). Words set in upper and lower case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all-caps.

B. Carton Labeling

1. Relocate the strength (i.e. 25 mcg) to follow the dosage form.
For example: Nocdurna
 (desmopressin) Orally Disintegrating Tablets
 25 mcg
2. Revise the statement, “30 Oral Tablets” to read “30 Orally Disintegrating Tablets”
3. Revise the dosage statement to read, “See package insert for dosage information”.
4. On the side panel, under the Contents section, revise the statement to read, “30 foil blisters, each containing 1 individually sealed 25 mcg **orally disintegrating tablet**...”

C. Blister Label

See comment B.1. above

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Appendix C: Summary of AERS cases identified in search of the AERS database

ISR #	Receipt Date	Type of Error	Narrative	Outcome
5900858-0	September 24, 2008	Improper Dose	At an unknown date desmopressin dose was increased by the patient from 0.1 mg daily to 0.375 mg.	Hospitalization
4823916-0	November 9, 2005	Improper Dose	Patient was administered 22 tablets (6 mg) in three days.	Hospitalization
5875045-5	September 5, 2008	Improper Dose	Patient administered overdose which was due to incorrect dosing by the pharmacy.	Hospitalization

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22517	ORIG-1	FERRING PHARMACEUTICA LS INC	NOCDURNA

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/s/

Latoya S TOOMBS
04/15/2010

CARLOS M MENA-GRILLASCA
04/15/2010

DENISE P TOYER
04/15/2010

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: March 5, 2010

TO: Jennifer Johnson, Regulatory Project Manager
William Lubas, M.D., Medical Officer
Division of Metabolic and Endocrine Drugs Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22-517

APPLICANT: Ferring Pharmaceuticals Inc.

DRUG: Nocdurma (desmopressin) Orally Disintegrating Tablets

NME: No

THERAPEUTIC
CLASSIFICATION: Standard Review

INDICATION: Treatment of nocturia in adults

CONSULTATION
REQUEST DATE: August 25, 2009

DIVISION ACTION
GOAL DATE: April 22, 2010

PDUFA DATE: April 22, 2010

I. BACKGROUND:

This application was submitted in support of the use of desmopressin for the treatment of nocturia. Two pivotal studies were submitted in support of the indication. The conduct of Protocol #FE992026 (CS29) entitled “A Randomized, Double Blind, Placebo Controlled, Parallel Group, Multi-Center Study with a Double Blind Extension Investigating the Efficacy and Safety of a Fast-Dissolving (“Melt”) Formulation of Desmopressin for the Treatment of Nocturia in Adults” and Protocol #FE992031 (CS31) entitled “A Multi-Center Extension Study Investigating the Long Term Efficacy and Safety of a Fast Dissolving (“Melt”) Formulation of Desmopressin for the Treatment of Nocturia in Adults” was inspected.

Protocol #FE992026 (CS29)

For this study, the co- primary endpoints were the change in the mean number of nocturnal voids from baseline to final visit (day 28) and change in the proportion of subjects with > 33% reduction in the mean number of nocturnal voids from baseline to day 28.

The study was conducted in two parts: during Part I, patients were on treatment for 4 weeks, and during Part II, patients remained on treatment following the final visit of Part I for approximately 1-6 months depending on the availability of results of Part I. The primary objective of Part I of this study was to compare the effect of several doses of desmopressin melt to placebo on the change in the number of nocturnal voids and the proportion of subjects with > 33% reduction from baseline in mean number of voids per night and to determine treatment safety. The primary objective of Part II of this study was to demonstrate the durability of effect of several doses of desmopressin melt and to determine treatment safety.

Protocol # FE992031 (CS31)

This was an extension study open to those subjects enrolled in Protocol CS29 and who had completed at least Visit 3E in Part II. Subjects were initially assigned in a blinded manner to the same treatment group they were assigned to upon entering Part II of Protocol CS29.

The following multiple endpoints were assessed in this extension study and changes were measured relative to the baseline values established in protocol CS29.

- Change in mean number of nocturnal voids
- Proportion of subjects with > 33% reduction in the mean number of nocturnal voids
- Change in the duration of the first sleep period
- Change in duration of total sleep time
- Change in nocturia-specific quality of life as assessed by scores on the International Consultation on Incontinence Modular Questionnaire – Nocturia (ICIQ-N) and The Nocturia Quality of Life Questionnaire (NQoL)
- Change in quality of sleep as assessed by the global score of the Pittsburgh Sleep Quality Index (PSQI)
- Change in overall Quality of Life as assessed by the SF-12
- Treatment safety

The primary objective of this study was to investigate the long-term efficacy and safety of the melt formulation of desmopressin in a broad population of subjects with nocturia.

The clinical sites of Drs. Efros and Fehnel were selected for inspection because Dr. Efros's site enrolled the largest number of patients (99 patients screened and 68 in the ITT population), had the largest number of protocol deviations (104), and had the second highest number of cases of hyponatremia (three patients with nine events). Dr. Fehnel's site was chosen because it had the largest number of cases of hyponatremia (six patients with 18 events).

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ # of Subjects/	Inspection Dates	Final Classification
Site 020 Mitchell Efros, M.D. AccuMed Research Associates 1305 Franklin Avenue, Suites 100 & 150 Garden City, NY 11530	FE992026 and FE992031/	8-19 Feb, 2010	Pending: Interim classification: NAI
Stephen Fehnel, M.D. Advance Clinical Concepts 301 S. Seventh Ave., Suite 155 West Reading, PA 19611	FE992026 and FE992031/	26 Jan-1 Feb, 2010	NAI

Key to 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.

1. Mitchell Efros, M.D.

AccuMed Research Associates
1305 Franklin Avenue, Suites 100 & 150
Garden City, NY 11530

- a. **What was inspected:** For Study CS29, 35 subject records of the 99 subjects screened, were audited, and for Study CS31, 18 subject records of the 46 subjects enrolled were audited. The records were reviewed for, but not limited to, protocol adherence, adverse event reporting (in particular, hyponatremia), concomitant medications, and number of voids.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Inspection revealed minor deviations regarding out-of-window visits, and scattered discrepancies between CRFs and line listings for adverse events, number of voids, and concomitant medications.

c. Assessment of data integrity: The observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR). The deviations/discrepancies noted above would not appear to have a significant impact on data integrity, and the data appear acceptable in support of the respective application.

2. Stephen Fehnel, M.D.
Advanced Clinical Concepts
301 S. Seventh Ave., Suite 155
West Reading, PA 196116

a. What was inspected: At this site, 23 subjects were screened, 16 were enrolled, and nine completed the study. Informed consent forms were reviewed for all enrolled subjects. The audit compared source data (progress notes, laboratory reports, case report forms (CRFs), and subject diaries) with the line listings. CRFs were also compared with source documents maintained on site. Primary efficacy data regarding the number of daily voids for the 52 week duration of both studies was reviewed and compared with subject diary data. Other records reviewed included, but were not limited to, IRB correspondence, laboratory certifications, test article accountability, and adverse events.

b. General observations/commentary: A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies/regulatory violations.

c. Assessment of data integrity: Data appear acceptable in support of the respective application.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigator sites of Dr. Efros and Fehnel were inspected in support of this NDA. The study appears to have been conducted adequately, and the data generated by the clinical sites of Drs. Efros and Fehnel appear acceptable in support of the respective indication.

Please note that the final classification of the inspection of Dr Efros's site is pending receipt and review of the EIR. An addendum to this clinical inspection summary will be forwarded to the review division should there be a change in the final classification or additional observations of clinical and regulatory significance are discovered after reviewing the EIR.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22517	ORIG-1	FERRING PHARMACEUTICA LS INC	NOCDURNA

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/s/

ROY A BLAY
03/05/2010

TEJASHRI S PUROHIT-SHETH
03/05/2010

STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	2009.002.A.00049
APPLICATION NUMBER	2009.002.A.00084
LETTER DATE/SUBMISSION NUMBER	IND 65,890 SDN 56 NDA 22-517
	IND submission: May 6, 2009 NDA submission: June 19, 2009
REVIEW DIVISION	Division of Metabolism and Endocrinology Products (DMEP)
MEDICAL REVIEWER	William Lubas
REVIEW DIVISION PM	Jennifer Johnson
SEALD REVIEWER(S)	Ann Marie Trentacosti
REVIEW COMPLETION DATE	October 1, 2009
ESTABLISHED NAME	Desmopressin Orally Disintegrating Tablets (Melt)
TRADE NAME	Nocurna (proposed)
APPLICANT	Ferring Pharmaceuticals, Inc.
ENDPOINT(S) CONCEPT(S)	Health Related Quality of Life and Impact of Nocturia
INSTRUMENT(S)	Nocturia Quality of Life (N-QOL) questionnaire; Pittsburgh Sleep Quality Index (PSQI); International Consultation on Incontinence Questionnaire for Nocturia (ICIQ- N)
INDICATION	Treatment of Nocturia in Adults

1 EXECUTIVE SUMMARY

This Study Endpoints and Label Development (SEALD) review is provided as a response to a request for consultation by the Division of Metabolism and Endocrinology Products (DMEP) regarding IND 65,890 and NDA 22-517. IND 65,890 SDN56 included information concerning the development and validation of three patient-reported outcome (PRO) instruments [Nocturia Quality of Life (N-QOL) questionnaire; Pittsburgh Sleep Quality Index (PSQI); and International Consultation on Incontinence Questionnaire for Nocturia (ICIQ-N)] to support their use as measures of the impact of nocturia. NDA 22-517 included information to support the safety and efficacy of Desmopressin Melt for the proposed indication: treatment of nocturia. The Desmopressin Melt pivotal study, Study FE 92026 CS29 (CS29), utilized the three PRO instruments as secondary endpoints in support of the primary indication, but not to support specific stand-alone labeling claims.

The review concludes that the ICIQ-N and PSQI are not measures of the impact of nocturia and cannot support clinical efficacy or labeling claims. Since the instruments were developed as measures of other concepts (the ICIQ-N was developed as a screening tool to assess pelvic floor symptoms and the PSQI was developed to evaluate a variety of sleep disturbances), they include domains and items that are not pertinent to nocturia patients.

The N-QOL was developed to measure the impact of nocturia and its treatment on a patient's quality of life. Insufficient information has been submitted to adequately assess whether the instrument represents a comprehensive, interpretable, and appropriate measure of its intended concept (content validity). However, the summary of the qualitative studies submitted suggests that the instrument omits a key domain that is important to the health-related quality of life (HRQL) of patients with nocturia, psychological/emotional impacts of nocturia. In addition, the instrument includes items that are not measures of treatment effect (e.g., "worried that there is no effective treatment for this condition"). Therefore, the N-QOL does not appear to represent an adequate measure of the impact of nocturia or HRQL in nocturia patients in order to effectively support clinical efficacy or labeling claims.

Finally, the pivotal study CS29 report submitted in NDA 22-517, noted that no statistically significant differences were observed in any of the Desmopressin Melt treatment groups compared to placebo in any of the quality of life (QoL) instrument scores. These findings would also support against the use of the data from instruments in the support of clinical efficacy.

2 ENDPOINT REVIEW

Desmopressin, an analogue of antidiuretic hormone (vasopressin), is currently available in several formulations, including intranasal, intravenous, and oral forms. A new formulation of desmopressin has been developed, which is an orally disintegrating tablet that instantly dissolves when placed under the tongue, without the need for water. Ferring Pharmaceuticals is using this formulation in their clinical development program to evaluate Desmopressin Melt for the indication of treatment of nocturia in adults.

STUDY ENDPOINT REVIEW

In October 2008, a Pre-NDA meeting was held with Ferring and FDA. During the meeting, FDA recommended that the sponsor submit additional evidence to support their clinical development program, including the use of the three patient reported outcome measures, the Nocturia Quality of Life (N-QOL) questionnaire, the International Consultation on Incontinence Questionnaire for Nocturia (ICIQ-N), and the Pittsburgh Sleep Quality Index (PSQI) that were included as secondary endpoints in the Desmopressin Melt pivotal trial, Study FE992026 CS29 (CS 29).

In May 2009, the sponsor submitted the information requested from FDA during the Pre-NDA meeting in IND 65,890 SDN 56. Subsequently, on June 19, 2009, the sponsor submitted NDA 22-517 to FDA, which provided the safety and efficacy data in support of the proposed indication, Desmopressin Orally Disintegrating Tablets (Melt) for the treatment of nocturia.

The following is a review of the information submitted in IND 65,890 SDN 56 and NDA 22-517. IND 65,890 SDN 56 includes information which describes the development and validation of the N-QOL, ICIQ-N, and PSQI as measures of impact of nocturia and its treatment. NDA 22-517 includes the data obtained from the use of these PRO measures as secondary endpoints in pivotal Study CS29. None of the PRO instruments have been used to support specific labeling claims. A copy of each instrument is located in the Appendix of this review.

2.1 Instruments

Information concerning the measurement properties, including the content validity of the N-QOL, ICIQ-N, and PSQI, were provided by study reports from both Oxford Outcomes and Mapi Values.

N-QOL

The N-QOL was developed to measure the impact of nocturia and its treatment on a patient's quality of life. The instrument includes 13 items, with 12 items directly related to nocturia plus a global quality of life item. An overall score of the 12 nocturia items as well as a measure of the 2 N-QOL domain scores (sleep/energy and bother/concern) can be obtained. Each domain includes 6 items. The global item of life quality is scored separately. All 13 items are scored from 0 to 4, with higher scores indicating better quality of life. The recall period is the past 2 weeks.

The instrument development was based upon a review of the literature, four focus groups with 7 to 8 men with nocturia, pilot testing with 5 men in the United States, and psychometric evaluation in the United Kingdom. Three additional evaluations were performed with women with nocturia.

Since the initial N-QOL development was based only on men with nocturia, Oxford Outcomes performed a focus group assessment with 15 females with nocturia, in order to assess the content validity of the instrument. A copy of the focus group protocol, questions posed, summary of responses and evidence of saturation (point when no new relevant or important information emerges and collecting additional data will not add to the understanding of how patients perceive the concept of interest) was not provided, only study conclusions. As noted in the conclusions:

STUDY ENDPOINT REVIEW

- All N-QOL items were appropriate for US females, except item 8 which was not relevant to those living alone.
- The N-QOL does not capture the psychosocial impact of nocturia on females and would therefore not be able to measure all concepts of HRQL in females with nocturia. Notably, the instrument excludes items related to mood disturbances and concerns of falling, which were noted by women during focus group interviews.
- Although coping strategies are an important part of living with nocturia, there is no place for coping/management items in a PRO which is used in clinical trials. These items are not sensitive to change with treatment and their inclusion in the measure will make it less sensitive to change overall.

In addition to the focus group testing, cognitive debriefings were obtained with 5 females with nocturia in order to assess the interpretability of the N-QOL. The study summary notes that although the majority of participants may not have found every item to be highly relevant, each item was applicable to at least one study participant. It was noted that it would be useful to include items that capture the emotional impact of the limitations associated with nocturia.

Comments: The N-QOL does not appear to represent a comprehensive, appropriate, and interpretable measure of HRQL or the impact of nocturia in order to effectively support labeling claims.

Since only the study conclusions and not the summary of patient responses from the focus group interviews, including evidence of saturation was submitted, an adequate review of content validity was not possible. However, as noted in conclusion of both the focus group and cognitive debriefing studies, the N-QOL omits a significant measurement concept (psychological/emotional impacts of nocturia) which was noted to be an important concern of patients interviewed.

In addition, several items included in the N-QOL do not describe a direct impact of treatment on nocturia and would not be appropriate measures of treatment impact.

For example:

- *One item queries patients about their overall quality of life (QoL). QoL is a general concept that implies an evaluation of the effect of all aspects of life on general well-being. Because this term implies the evaluation of nonhealth-related aspects of life, such as economic and marital status, and because the term is too general and undefined, it is not considered appropriate for a medical product claim.*
- *Items such as “worried that there is no effective treatment for this condition.”, and “worried that this condition will get worse in the future” are not measures of how a treatment impacts nocturia and cannot effectively support labeling claims.*
- *Items such as, “has required me to nap during the day”, and “has caused me to be careful when or how much I drink”, are remote impacts of nocturia; can be influenced by other factors other than nocturia; and are not measures that isolate the impact of treatment from the impact of other variables in patients’ lives. Including these items in the “impact of nocturia on sleep and daytime functioning” domain may influence the*

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total domain score and dilute the contribution of more important direct impacts, such as “has made it difficult for me to concentrate the next day” in the score.

- *It is unclear if patients can effectively recall and average their symptoms over a two week period of time.*

An assessment of the other measurement properties was submitted by the sponsor. However, since the content validity of the instrument has not been effectively established, then the measurement properties cannot be adequately interpreted.

ICIQ-N

The ICIQ-N is the nocturia module of the International Consultation on Incontinence Modular Questionnaire that was developed to assess pelvic symptoms (lower urinary tract dysfunction, vaginal symptoms, and lower bowel dysfunction).

The ICIQ-N consists of 4 items: 1 frequency item (daytime voiding frequency), 1 nocturia item (nighttime voiding frequency), and 2 bother items related to daytime and nighttime voiding frequency and includes a 4 week recall period.

As noted in the MAPI Values report, the ICIQ-N was not developed to provide a comprehensive measurement of quality of life in patients with nocturia. It was intended as a simple self-administered symptom screener for nocturia suitable for use in general practice.

Comments: The ICIQ-N was developed as a screening tool and is not an adequate measure of the impact of treatment on nocturia and cannot effectively support labeling claims. The instrument measures concepts (e.g., daytime urination) that are unrelated to the target indication. The instrument only includes a single global item which assesses the actual impact of nocturia [how much does this (nighttime urination) bother you?] A single item cannot adequately capture all of the important individual subconcepts that are associated with the condition.

An assessment of the other measurement properties was submitted by the sponsor. However, since the instrument is not an appropriate, comprehensive, and interpretable measure of the concept of interest, the measurement properties cannot be adequately interpreted.

PSQI

The PSQI is a self-administered instrument, that was developed to provide a clinical assessment of a variety of sleep disturbances that might affect sleep quality; discriminate between “good and “bad” sleepers; and provide an index that is easy for subjects to use and for clinicians and researchers to interpret.

The instrument items were derived from a clinical intuition and experience with sleep disorder patients; a review of previous sleep quality questionnaires reported in the literature; and a clinical experience with the instrument during 18 months of field testing.

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As noted in the MAPI Values report, nocturia patients were not involved in the development of the PSQI, which leaves questions about the content validity of the instrument, capturing the sleep related concerns for the target population.

MAPI also notes that face validity of the PSQI suggest that only a few items may be relevant for patients with nocturia:

- The Subjective sleep quality item: “During the past month, how would you rate your sleep quality overall?”
- The Sleep duration item: “During the past month, how many hours of actual sleep did you get at night?”
- The Daytime dysfunction item: “During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?” and “During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?”
- One of the Sleep disturbances items: “How often have you had trouble sleeping because you have to get up to use the bathroom?”

Comments: The PSQI was developed to assess a variety of several sleep disturbances and is not a specific or adequate measure of the impact of a treatment on nocturia and cannot support labeling claims. The instrument includes many items (e.g., sleep disturbance due to difficulty initiating sleep, snoring, breathing difficulty, pain, and bad dreams), that are unrelated to the target indication. Therefore, the PSQI does not represent a comprehensive measure of impacts of the nocturia.

An assessment of the other measurement properties was submitted. However, since the instrument is not an appropriate, comprehensive, and interpretable measure of the concept of interest, the measurement properties cannot be adequately interpreted.

2.2 Target Labeling Claims

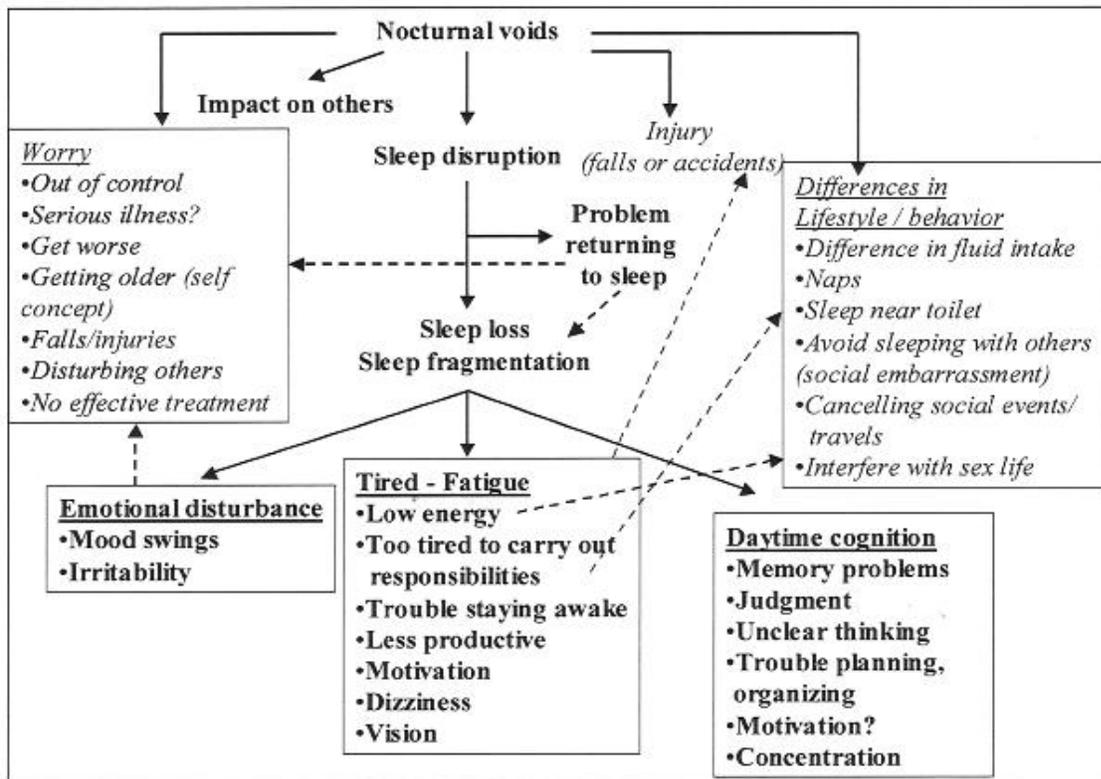
The proposed Desmopressin Orally Disintegrating Tablets (Melt) label submitted in NDA 22-517 does not include any information concerning the PRO instruments or data obtained from the use of these instruments in the Clinical Trials section of the label.

Based upon a literature review, input from experts, and patient interviews, a “conceptual model” (Figure 1) was developed.

At the center of the diagram is the primary impact of nocturia on sleep and the problems impaired sleep causes for patients. Sleep is disrupted when patients must awaken to get up to void; some patients also experience difficulties falling back to sleep. Impacts of sleep loss are noted.

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Figure 1. Conceptual Model of Impacts of Nocturia



Comments: As noted in the conceptual model, the primary impact of nocturia is related to sleep loss. Based on the proposed conceptual model, it appears that domains of emotional disturbances, tiredness, and daytime cognition (solid lines) represent the direct impacts; while the domains of worry and differences in lifestyle and behavior (dashed lines) represent indirect impacts of sleep loss due to nocturia.

2.3 Conceptual Framework

The conceptual framework for the N-QOL, ICIQ-N, and PSQI is noted in Table 1.

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Table 1. Conceptual Framework for the N-QOL, ICIQ-N, and PSQI

PRO Instrument	Concept measured / score used		Items used to measure the concept		
N-QOL	Nocturia-specific quality of life	Bother due to nocturia	Over the past 2 weeks, having to get up at night to urinate....	6. Has caused me to be careful about when or how much I drink	
			Over the past 2 weeks, I have been...	8. Concerned that I am disturbing others in the house because of having to get up at night to urinate	
	Overall score	Bother/concern domain score		9. Preoccupied about having to get up at night to urinate	
				10. Worried that this condition will get worse in the future	
			11. Worried that there is no effective treatment for this condition (having to get up at night to urinate)		
			12. Overall how bothersome has having to get up at night to urinate been during the past 2 weeks?		
	Impact of Nocturia on Sleep and daytime functioning	Sleep/energy domain score	Over the past 2 weeks, having to get up at night to urinate....	7. Has made it difficult for me to get enough sleep at night	
				1. Has made it difficult for me to concentrate the next day	
				2. Has made me feel generally low in energy the next day	
				3. Has required me to nap during the day	
				4. Has made me less productive the next day	
				5. Has caused me to participate less in activities I enjoy	
	Global quality of life	Global quality of life score	13. Overall I would rate my quality of life to be...		
ICIQ-N	Daytime voiding severity		How often do you urinate during the day?		
	Nighttime voiding severity		During the night, how many times do you have to get up to urinate, on average?		
	Impact of daytime voiding frequency		How much does this bother you?		
	Impact of nighttime voiding frequency		How much does this bother you?		
PRO Instrument	Concept measured		Items used to measure the concept		
PSQI	Sleep quality	Overall score	Subjective sleep quality	6. During the past month, how would you rate your sleep quality overall?	
			Sleep latency	2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?	
			Sleep duration	5a. During the past month, how often have you had trouble sleeping because you cannot get to sleep within 30 minutes?	
			Habitual sleep efficiency	4. During the past month, how many hours of actual sleep did you get at night?	
				3. During the past month, what time have you usually gotten up in the morning?	
			Sleep disturbances	1. During the past month, what time have you usually gone to bed at night?	
				During the past month, how often have you had trouble sleeping because you...	5b. Wake up in the middle of the night or early morning
					5c. Have to get up to use the bathroom
					5d. Cannot breathe comfortably
					5e. Cough or snore loudly
		5f. Feel too cold			
		5g. Feel too hot			
		5h. Had bad dreams			
		5i. Have pain			
		5j. Other reason(s)			
Daytime dysfunction	8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
	9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?				
Use of sleeping medication	7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?				

Comments: None of the three PRO instruments include all three of domains that were identified in the conceptual model as being the most important measures of the impact of nocturia (emotional disturbances, tiredness, and daytime cognition).

2.4 Protocol and Analysis Plan

Study FE992026 CS29 (CS29) is the primary study submitted to support the indication of Desmopressin Melt for the treatment of nocturia. The study enrolled men and women aged 18 and older with an average of ≥ 2 nocturia voids per night and was conducted in 2 parts. Part I was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study investigating the efficacy and safety of 4 doses (10 μg , 25 μg , 50 μg , or 100 μg) of Desmopressin Melt administered for 28 days for the treatment of nocturia in adults. Randomization was stratified by age (<65 , ≥ 65 years), and by the absence/presence of nocturnal polyuria, defined as a ratio of nighttime urine volume/24-hour urine volume $\geq 33\%$.

Upon completion of Part I of the study, all subjects on active treatment were allowed to continue into Part II on the same treatment for approximately 1 to 6 months. Subjects assigned to placebo in Part I were randomly assigned to 1 of the 4 active treatments in Part II. To ensure that the study remained fully blinded during the full extent of both Parts I and II, re-randomization of subjects assigned to placebo after 4 weeks of treatment was predetermined at the time of initial randomization.

In addition, a long-term, open-label efficacy and safety extension study (FE 992026 CS31) is currently ongoing until approximately February 2010.

The 2 co-primary efficacy endpoints, measured from baseline to the final visit in CS29 Part I (Day 28), were the change in the mean number of nocturnal voids and the proportion of subjects with $>33\%$ reduction in the mean number of nocturnal voids (as referred to as 33% responders). Onset of effect was assessed by examining efficacy results at Day 8, Day 15, and Day 22 of treatment. Secondary efficacy endpoints, measured from baseline to Day 28, included change in initial period of undisturbed sleep, nocturnal urine volume, the Nocturnal Polyuria Index, and nocturnal polyuria status. Persistence of effect was assessed by pooling efficacy results across CS29 and CS31; formal statistical analyses were not performed.

Four self-administered questionnaires were utilized to assess the impact of treatment for nocturia on quality of life (QoL): Nocturia Quality of Life Questionnaire (N-QOL), the International Consultation on Incontinence Modular Questionnaire - Nocturia (ICIQ-N), Pittsburgh Sleep Quality Index (PSQI), and Short Form-12 version 2 (SF-12v2). Questionnaires were completed by patients at randomization, final visit in Part I, and visit 7E in Part II.

Superiority to placebo was evaluated in a step-down approach simultaneously on the two co-primary endpoints. The first co-primary was analyzed by an analysis of covariance (ANCOVA) with the change from baseline in the average number of nocturnal voids as the outcome (dependent) variable, main effects for each of two factors used to stratify the randomization (age < 65 , ≥ 65), and presence/absence of nocturnal polyuria), the five study treatments, and a covariate for the baseline average number of nocturnal voids as independent variables. Resulting two-sided 95% confidence limits of adjusted treatment contrasts and associated P values of each of the dose groups versus placebo was provided.

The second co-primary was analyzed by a logistic regression analysis on 33% responder status as dependent variable, and main effects for each of two factors used to stratify the

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randomization (age < 65, > 65), and presence/absence of nocturnal polyuria), the five study treatments, and a covariate for the baseline number of nocturnal voids as independent variables. Resulting two-sided 95% confidence limits of adjusted odds ratios and associated P values of each of the dose-groups versus placebo was provided.

All secondary endpoints, including the data from the PRO instruments, were tested in a manner identical to the first co-primary endpoint.

Four doses of desmopressin were compared to placebo for the 2 co-primary endpoints. As noted in the study report, the reduction in mean number of nocturnal voids, compared to placebo, was statistically significant for the 100 µg and 50 µg groups. The trend of greater decreases in mean number of nocturnal voids with increasing dose of desmopressin was evident in subjects stratified by age (<65 years, ≥65 years) and in subjects with nocturnal polyuria. Too few subjects did not have nocturnal polyuria to make meaningful comparisons. The reduction in mean number of nocturnal voids, compared to placebo, was statistically significant for the 100 µg group for all 4 stratification factors and for the 50 µg group for subjects with nocturnal polyuria.

Similarly, the proportions of subjects with >33% reduction in the mean number of nocturnal voids from baseline to Day 28 increased with increasing dose, with the greatest increase between the 50 µg and 100 µg doses (53% to 71%). The proportion of subjects with >33% reduction in mean number of nocturnal voids, compared to placebo, was statistically significant for the 100 µg group.

As noted in the study report, improvements in QoL occurred in all treatment groups. Although differences from placebo were not statistically significant, individual responses to the QoL questionnaires indicated some clinically significant effects for desmopressin Melt compared to placebo (a clinically significant effect was defined in a validation study as a 9-point difference in N-QOL score between patients with 2 vs. 3 nocturia episodes per night). The N-QOL showed improvements in all treatment groups in both the sleep/energy and bother/concern domains. For the sleep/energy domain, placebo changed 15.2 points from baseline while 100 µg changed 16.3 points. The bother/concern domain changed 12.7 and 18.2 points for placebo and 100 µg, respectively. The global quality of life item and the summary item: “overall, how bothersome was having to get up at night to urinate been during the past 2 weeks?” showed similar results. The change from baseline for placebo and 100 µg was 0.70 and 1.18, respectively, for the global quality-of-life item and was 0.25 and 0.35, respectively, for the summary item. The essential nocturia question in the ICIQ-N questionnaire: “Nighttime urination: How much does this bother you?” showed mean decreases of 1.4 for placebo and 2.5 for 100 µg. Mean global PSQI decreased from baseline to Day 28 in all treatment groups, indicating improvement, with the largest mean decreases in the 50 µg (-2.0) and 100 µg (-1.9) groups. The SF-12v2 demonstrated only small changes in all treatment groups.

Comments: As noted in the study report, none of the PRO instruments showed a statistically significant improvement compared with placebo.

3 APPENDICES

3.1 N-QOL

QOL QUESTIONNAIRE (NQOL)

OVER THE PAST 2 WEEKS , HAVING TO GET UP AT NIGHT TO URINATE...

1. Has made it difficult for me to concentrate the next day

- 0 Every day
- 1 Most days
- 2 Some days
- 3 Rarely
- 4 Never

2. Has made me feel generally low in energy the next day

- 0 Every day
- 1 Most days
- 2 Some days
- 3 Rarely
- 4 Never

3. Has required me to nap during the day

- 0 Every day
- 1 Most days
- 2 Some days
- 3 Rarely
- 4 Never

4. Has made me less productive the next day

- 0 Every day
- 1 Most days
- 2 Some days
- 3 Rarely
- 4 Never

5. Has caused me to participate less in activities I enjoy

- 0 Extremely
- 1 Quite a bit
- 2 Moderately
- 3 A little bit
- 4 Not at all

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6. Has caused me to be careful when or how much I drink

- 0 All the time
- 1 Most of the time
- 2 Some of the time
- 3 Rarely
- 4 Never

7. Has made it difficult for me to get enough sleep at night

- 0 Every night
- 1 Most nights
- 2 Some nights
- 3 Rarely
- 4 Never

OVER THE PAST 2 WEEKS , I HAVE BEEN...

8. Concerned that I am disturbing others in the house because of having to get up at night to urinate

- 0 Extremely
- 1 Quite a bit
- 2 Moderately
- 3 A little bit
- 4 Not at all

9. Preoccupied about having to get up at night to urinate

- 0 All the time
- 1 Most of the time
- 2 Some of the time
- 3 Rarely
- 4 Never

10. Worried that this condition will get worse in the future

- 0 Extremely
- 1 Quite a bit
- 2 Moderately
- 3 A little bit
- 4 Not at all

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11. Worried that there is no effective treatment for this condition (having to get up at night to urinate)
- 0 Extremely
 - 1 Quite a bit
 - 2 Moderately
 - 3 A little bit
 - 4 Not at all
12. Overall, how bothersome has having to get up at night to urinate been during the past 2 weeks?
- 4 Not at all
 - 3 A little bit
 - 2 Moderately
 - 1 Quite a bit
 - 0 Extremely
13. Overall I would rate my quality of life to be...
- 0 Very Good
 - 1 Good
 - 2 Fair
 - 3 Poor
 - 4 Very Poor

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3.2 ICIQ-N

Nocturia

Many people experience urinary symptoms some of the time. We are trying to find out how many people experience urinary symptoms, and how much they bother them. Please answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS

1a. How often do you urinate during the day?

- 0 1 to 6 times
- 1 7 to 8 times
- 2 9 to 10 times
- 3 11 to 12 times
- 4 13 times or more

1b. How much does this bother you?

Please circle a number between 0 (not at all) and 10 (a great deal)

- 0 1 2 3 4 5 6 7 8 9 10
- not at all a great deal

2a. During the night, how many times do you have to get up to urinate, on average?

- 0 none
- 1 one
- 2 two
- 3 three
- 4 four or more

2b. How much does this bother you?

Please circle a number between 0 (not at all) and 10 (a great deal)

- 0 1 2 3 4 5 6 7 8 9 10
- not at all a great deal

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3.3 Pittsburgh Sleep Quality Index

PITTSBURGH SLEEP QUALITY INDEX

INSTRUCTIONS:

The following questions relate to your usual sleep habits during the past month only . Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, what time have you usually gone to bed at night?

BED TIME 24 -hour clock (00:01 -- 23:59)

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

NUMBER OF MINUTES

3. During the past month, what time have you usually gotten up in the morning?

GETTING UP TIME 24 -hour clock (00:01 -- 23:59)

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)

HOURS OF SLEEP PER NIGHT

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you...

a) Cannot get to sleep within 30 minutes

- 0 Not during the past month
1 Less than once a week
2 Once or twice a week
3 Three or more times a week

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b) Wake up in the middle of the night or early morning

- 0 Not during the past month
- 1 Less than once a week
- 2 Once or twice a week
- 3 Three or more times a week

c) Have to get up to use the bathroom

- 0 Not during the past month
- 1 Less than once a week
- 2 Once or twice a week
- 3 Three or more times a week

d) Cannot breathe comfortably

- 0 Not during the past month
- 1 Less than once a week
- 2 Once or twice a week
- 3 Three or more times a week

e) Cough or snore loudly

- 0 Not during the past month
- 1 Less than once a week
- 2 Once or twice a week
- 3 Three or more times a week

f) Feel too cold

- 0 Not during the past month
- 1 Less than once a week
- 2 Once or twice a week
- 3 Three or more times a week

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g) Feel too hot

- 0 Not during the past month
- 1 Less than once a week
- 2 Once or twice a week
- 3 Three or more times a week

h) Had bad dreams

- 0 Not during the past month
- 1 Less than once a week
- 2 Once or twice a week
- 3 Three or more times a week

i) Have pain

- 0 Not during the past month
- 1 Less than once a week
- 2 Once or twice a week
- 3 Three or more times a week

j) Other reason(s), please describe

--

k) How often during the past month have you had trouble sleeping because of this?

- 0 Not during the past month
- 1 Less than once a week
- 2 Once or twice a week
- 3 Three or more times a week

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6. During the past month, how would you rate your sleep quality overall?
- 0 Very good
 - 1 Fairly good
 - 2 Fairly bad
 - 3 Very bad
7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?
- 0 Not during the past month
 - 1 Less than once a week
 - 2 Once or twice a week
 - 3 Three or more times a week
8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?
- 0 Not during the past month
 - 1 Less than once a week
 - 2 Once or twice a week
 - 3 Three or more times a week
9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?
- 0 No problem at all
 - 1 Only a very slight problem
 - 2 Somewhat of a problem
 - 3 A very big problem
10. Do you have a bed partner or room mate?
- 0 No bed partner or room mate
 - 1 Partner/room mate in other room
 - 2 Partner in same room, but not same bed
 - 3 Partner in same bed

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/s/

ANN M TRENTACOSTI
10/01/2009

LAURIE B BURKE
10/01/2009