

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022517Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**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**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: January 28, 2015

Reviewer(s): Amariyls Vega, M.D., M.P.H, Medical Officer
Division of Risk Management (DRISK)

Team Leader: Naomi Redd, Pharm.D. Acting Team Leader
DRISK

Division Director: Cynthia LaCivita, Pharm.D. Acting Division Director
DRISK

Drug Name(s): Desmopressin (Nocdurna™)

Therapeutic Class: 8-arginine vasopressin analogue

Dosage and Route: 25 µg (females) and 50 µg (males) once daily, oral
disintegrating sublingual tablets

Application Type/Number: NDA 22517

Submission Number: 0027

Applicant/sponsor: Ferring Pharmaceuticals

OSE RCM #: 2014-1542 and 2014-1543

TSI #:

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

CONTENTS

Executive Summary	1
1 Introduction	2
1.1 Background	2
1.2 Regulatory History	3
2 Materials Reviewed	5
2.1 Data and Information Sources	5
3 Review Results	5
3.1 Benefit: Risk Assessment	5
3.1.1 Clinical Development Program	5
3.1.2 Risk Management Approach Proposed by the Applicant	8
3.1.3 Internal FDA Consults	9
3.1.4 Endocrinologic and Metabolic Drugs Advisory Committee Recommendations	10
3.1.5 FDA Overall Benefit:Risk Assessment	10
3.2 Risk Management Approach	10
3.2.1 DRISK Assessment of Need for a REMS	10
4 Conclusions and Recommendations	11

EXECUTIVE SUMMARY

This review documents the Division of Risk Management's (DRISK) evaluation of whether a Risk Evaluation and Mitigation Strategy (REMS) is necessary for desmopressin (NDA 22517, Nocdurna).

Ferring Pharmaceuticals is seeking approval for desmopressin for the following indication: "Nocdurna is indicated for treatment of nocturia due to nocturnal polyuria in adults who awaken two or more times each night to void. Prior to treatment with Nocdurna, lifestyle changes and other treatable medical causes of nocturia should be addressed." Nocdurna comes in 25 mcg and 50 mcg orally disintegrating sublingual tablets. The proprietary name Nocdurna was conditionally approved by FDA on October 16, 2014.

Ferring Pharmaceuticals did not submit a REMS with this application but proposed a voluntary risk management program to address the serious risk of hyponatremia associated to the use of Nocdurna including: a serum sodium monitoring plan, initiation pack for at-risk patients, a 1-month prescription limit for at-risk patients, a medication guide, program website, educational program for healthcare professionals, enhanced pharmacovigilance, and a postmarketing epidemiologic study.

This application received a complete response (CR) letter on April 22, 2010 and on January 30, 2013 because of insufficient evidence of clinical benefits in light of the associated serious risks, including the risk of hyponatremia. On November 21, 2013 the Applicant submitted a dispute resolution request which was denied by the Agency on January 15, 2014. A class 2 resubmission was received on August 19, 2014.

On January 12, 2015 the application was presented to the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC). Panel members voted 10:5 (2 abstentions) against approval of Nocdurna because, while there were statistically significant differences between placebo and Nocdurna in the co-primary endpoints in Phase III trials, the clinical benefit of these findings was unclear. The committee provided advice to the Applicant on how to demonstrate a clinical benefit of Nocdurna to patients with nocturia due to nocturnal polyuria.

The Division of Metabolism and Endocrinology Products (DMEP) conclude that the benefit:risk balance of Nocdurna for the treatment of nocturia due to nocturnal polyuria does not favor approval of this product. DMEP plans to issue a third CR letter. Therefore, DRISK defers recommendations on the management of the risks associated with Nocdurna and labeling at this time.

1 INTRODUCTION

This review documents the Division of Risk Management's (DRISK) evaluation of whether a Risk Evaluation and Mitigation Strategy (REMS) is necessary for desmopressin (NDA 22517, Nocdurna).

Ferring Pharmaceuticals is seeking approval for desmopressin for the following indication: "Nocdurna is indicated for treatment of nocturia due to nocturnal polyuria in adults who awaken two or more times each night to void. Prior to treatment with Nocdurna, lifestyle changes and other treatable medical causes of nocturia should be addressed." Nocdurna comes in 25 mcg and 50 mcg orally disintegrating sublingual tablets. The proprietary name Nocdurna was conditionally approved by FDA on October 16, 2014.

Ferring Pharmaceuticals did not submit a REMS with this application but proposed a voluntary risk management program to address the serious risk of hyponatremia associated to the use of Nocdurna including: a serum sodium monitoring plan, initiation pack for at-risk patients, a 1-month prescription limit for at-risk patients, a medication guide, program website, educational program for healthcare professionals, enhanced pharmacovigilance, and a postmarketing epidemiologic study.

1.1 BACKGROUND

*Desmopressin.*¹ Desmopressin is a synthetic analogue of anti-diuretic hormone arginine vasopressin. Its action in the kidneys results in reabsorption of water and reduction in urine production. Desmopressin has marketing authorization in more than 120 countries worldwide. Desmopressin was originally approved by FDA in 1978 and is currently approved in the US for diabetes insipidus of central origin, primary nocturnal enuresis, hemophilia A, type 1 von Willebrand's disease, and as a diagnostic test to assess renal concentrating capacity. It is available in intranasal (10 mcg/spray), parenteral (4 mcg/mL) and oral formulations (tablets 0.1 and 0.2 mg). The FDA approved desmopressin label includes a warning for the risk of hyponatremia, particularly for patients in both ends of the age spectrum (i.e., pediatric and geriatric patients). There has been rare post-marketing case reports of hyponatremic convulsions associated with concomitant use with the following medications: oxybutinin and imipramine.

Orally disintegrating sublingual tablets come in two forms: Nocdurna (25 µg and 50 µg of desmopressin) and desmopressin Melt (60 µg, 120 µg and 240 µg of desmopressin). Desmopressin tablets and Desmopressin Melt are approved in other jurisdictions to treat nocturia due to nocturnal polyuria for patients <65 years at doses higher than those proposed for use in the US. Consistent with its mechanism of action, the use of desmopressin is associated to water intoxication and hyponatremia. Elderly patients are at increased risk of developing hyponatremia. Due to the increased risk of hyponatremia, the Applicant formulated Nocdurna at lower doses because they intend this drug to be used by patients >65 years. Nocdurna (25 µg and 50 µg) is approved in Canada for the treatment of nocturia.

¹ Ferring Pharmaceuticals, Nocdurna, Desmopressin Orally Disintegrating Tablet for the Treatment of Nocturia Due to Nocturnal Polyuria in Adults, Briefing Document, Endocrinologic and Metabolic Drugs Advisory Committee, January 12, 2015.

Hyponatremia.^{2, 3} Hyponatremia is defined as serum sodium concentration < 135 mEq/L and is more clinically significant when the concentration is < 130 mEq/L. Signs and symptoms of hyponatremia correlate to the severity of derangement of serum sodium. Patients with serum sodium levels > 130 mEq/L are asymptomatic. Patients with levels from 120 mEq/L to 130 mEq/L may have nausea, vomiting, abdominal symptoms, mild cognitive and gait disturbances and those with < 125 mEq/L may experience headache, agitation, and confusion. Levels below 120 mEq/L have been associated with seizures and coma. In the US, the risk of hyponatremia associated to treatment with desmopressin is managed through labeling only.

Nocturia. Nocturia is defined as voiding at least once during the normal hours of sleep; however, experts suggest that nocturia is clinically meaningful if a patient voids 2 or more times per night.^{1,4} Nocturia affects approximately half of men and women over the age of 50.¹ The three main causes of nocturia are lower urinary tract dysfunction, nocturnal polyuria, and sleep disturbances.⁴ Nocturia may result in sleep disturbance and related morbidity including excessive daytime sleepiness and increased risk of falls.¹

Nocturnal Polyuria. Nocturnal polyuria occurs when one-third or greater of the daily urine output is excreted during normal sleeping hours.⁴ Nocturnal polyuria is common in older persons (both genders) – some may excrete 50% or more of their 24-hour urine output during the night.^{1,4} Therefore, one episode of nocturia is considered normal in older persons.⁴ Causes of nocturnal polyuria include: (1) age-related delay in urine excretion, (2) late afternoon and evening liquid intake, (3) peripheral edema, and (4) medical conditions (e.g., obstructive sleep apnea and uncontrolled diabetes mellitus).⁴ Nocturnal polyuria has also been linked to abnormalities of circadian rhythmic secretion of the endogenous antidiuretic hormone.¹ Therefore, the treatment of nocturia due to nocturnal polyuria should specifically address the primary underlying cause.

There is an unmet medical need for the treatment of nocturia due to nocturnal polyuria given there are no drug approved in the US for the treatment of this condition.

1.2 REGULATORY HISTORY

The regulatory history of Nocdurna, in pertinent part, is as follows:

- **August 21, 2009:** Ferring submitted NDA for Nocdurna for treating nocturia in adults (all ages and etiology). The application included the Phase 3 trial CS29 as the pivotal clinical trial for approval, the proposed doses were 25 µg once daily at bedtime for

² Stern S.C., Cifu A.S., Altkorn D (2015). Hyponatremia and Hypernatremia. In Stern S.C., Cifu A.S., Altkorn D (Eds), *Symptom to Diagnosis: An Evidence-Based Guide*, 3e. Retrieved December 18, 2014 from <http://accessmedicine.mhmedical.com/content.aspx?bookid=1088&Sectionid=61699500>.

³ Desmopressin acetate label, accessed December /2014 at: <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0727da38-afe7-4e45-821b-2ab5ac5a8e5f#boxedwarning>.

⁴ DuBeau C.E. (2009). Chapter 50. Benign Prostate Disorders. In Halter J.B., Ouslander J.G., Tinetti M.E., Studenski S, High K.P., Asthana S (Eds), *Hazzard's Geriatric Medicine and Gerontology*, 6e. Retrieved December 17, 2014 from <http://accessmedicine.mhmedical.com/content.aspx?bookid=371&Sectionid=41587661>.

females and 100µg once daily at bedtime for men. The trial CS29 investigated 10 µg, 25 µg, 50 µg, 100 µg Nocdurna or placebo in both males and females.

- **April 22, 2010:** FDA issued a Complete Response (CR) letter because the benefits of the product were outweighed by its risks. FDA requested testing of lower dosages (than 100 µg) in males due to the higher incidence of hyponatremia with the 100 µg dose in males. In addition, FDA specified that the primary endpoint must include the co-primary endpoint of 33% responder rate. Ferring conducted confirmatory trials CS40 (females) and CS41 (males) to evaluate the efficacy of 25 µg Nocdurna in females and 50 µg and 75 µg Nocdurna in males. Both trials used the following co-primary endpoints: (1) change from baseline in the mean number of nocturnal voids during 3 months of treatment and (2) 33% responder status during 3 months of treatment. A 33% responder is defined as a subject with a decrease of at least 33% in the mean number of nocturnal voids.
- **November 19, 2010:** Special Protocol Assessment (SPA) Agreement letter for trial (CS41) in men sent from the FDA. FDA noted that: “The safety monitoring scheme for the 50 µg and 75 µg doses should be sufficient to demonstrate the utility of measuring serum sodium on Day 4 and 28 in order to predict the risk of hyponatremia during the next two months”. The Applicant agreed and implemented prospective safety monitoring scheme in the CS41 protocol.
- **August 2, 2012:** Resubmission of the NDA. NDA amendment including complete response submission.
- **January 30, 2013:** FDA issued a second CR letter requesting Ferring provides additional evidence of clinical benefit.
- **July 17, 2013:** Ferring submitted a complete response to the second CR letter issued by FDA on January 30, 2013.
- **August 14, 2013:** FDA issued a letter to acknowledge receipt of an incomplete response to the January 30, 2013 CR letter. The deficiency that was not addressed by Ferring’s July 17, 2013 submission was listed by FDA as follows: “You need to conduct a trial demonstrating a clinically meaningful impact of Nocdurna on reducing the frequency of nocturnal voids.”
- **November 21, 2013:** Ferring submits a dispute resolution request.
- **January 15, 2014:** Dispute appeal was denied by FDA.
- **August 19, 2014:** FDA receives a class 2 resubmission from Ferring. FDA will take the application to the advisory committee. The proposed indication was modified to: “for the treatment of nocturia due to nocturnal polyuria in all adult patients who awaken at least twice per night to void.”
- **October 16, 2014:** Proprietary name, Nocdurna, conditionally granted.
- **January 12, 2015:** Advisory committee meeting. The panel voted against product approval (Yes-5; No-10; Abstain-2).
- **January 31, 2015:** PDUFA goal date.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Complete Response Letter issued by FDA on April 22, 2010.
- Complete Response Letter issued by FDA on January 30, 2013.
- Review by Curtis Rosebraugh MD. MPH, Director, Office of Drug Evaluation II, Office of New Drugs, Dispute Appeal Denied, dated January 15, 2014.
- Ferring Pharmaceuticals, Nocdurna, Clinical Overview, dated July 29, 2014.
- Ferring Pharmaceuticals, Nocdurna, Summary of Clinical Safety, dated July 29, 2014.
- Ferring Pharmaceuticals, Nocdurna, Desmopressin Orally Disintegrating Tablet for the Treatment of Nocturia Due to Nocturnal Polyuria in Adults, Briefing Document, Endocrinologic and Metabolic Drugs Advisory Committee, January 12, 2015.
- Review by Roger Wiederhorn MD, Division of Bone, Reproductive and Urologic Products, dated December 4, 2014.
- Review by Tiffany R Farchione, M.D., Division of Psychiatry Products, dated December 4, 2014.
- Review by Patricia L. Bright, MSPH, PhD, Division of Epidemiology 1 (DEPI-1), dated December 12, 2014.
- Nocdurna Advisory Committee Meeting slide presentations: FDA and Ferring Pharmaceuticals, dated December 3, 2014.

3 REVIEW RESULTS

3.1 BENEFIT: RISK ASSESSMENT

3.1.1 Clinical Development Program

The clinical development program for Nocdurna included 4 phase 3 trials:

- CS29, CS31 – CS29 is a 4-week randomized, double-blind, placebo-controlled, parallel group. Part I, which was followed by a non-controlled Part II (1-6-month) group, leading to CS31 which is an open-label extension to CS29 (up to 96 weeks in total). These trials included males and females ≥ 18 years old and tested 10 mcg (CS29 only), 25 mcg, 50 mcg, and 100 mcg doses versus placebo. The 2 co-primary endpoints of CS29 were: (1) change in the mean number of nocturnal voids from baseline to final visit (Day 28) and (2) the proportion of subjects with $\geq 33\%$ decrease in the mean number of nocturnal voids from baseline to Day 28. Secondary efficacy endpoints included: (1) change in First Undisturbed Sleep

Period (FUSP)⁵, (2) change in duration of total sleep time, (3) change in nocturia-specific Quality of Life (N-QoL)⁶, (4) change in quality of sleep⁷, and (5) change in overall QoL⁸.

- CS40 – 3-month randomized, double-blind, placebo-controlled trial including females only and testing 25 mcg dose versus placebo.
- CS41 – 3-month randomized, double-blind, placebo-controlled trial including males only and testing 50 mcg and 75 mcg doses versus placebo.

Efficacy. The following is a summary of the demonstrated efficacy in the trials listed above.

- **CS29 (females and males)**
 - Co-primary endpoint ‘decrease in mean number of nocturnal voids from baseline to Day 28’ – the adjusted differences compared to placebo were -0.61 (p<0.0001) voids for the 100 mcg dose group and -0.28 (p=0.0207) voids for the 50 mcg dose group.
 - Co-primary endpoint ‘proportions of subjects with >33% decrease in the mean number of nocturnal voids from baseline to Day 28’ – there was a statistically significant (p <0.0001) increase in the proportion of patients achieving this endpoint in the 100 µg (71%) compared to placebo (47%).
 - CS29 confirmed a gender difference in dose response, with a lower minimum effective dose of 25 µg in females compared to 50-100 µg Nocturna in males. CS40 and CS41 were conducted to confirm efficacy and safety of Nocturna at a dose of 25 mcg for females and 50 mcg and 75 mcg for males, respectively.
- **CS 40 (females)**
 - Co-primary endpoint ‘decrease in mean number of nocturnal voids from baseline to Day 28’ – there was a statistically significant adjusted difference (-0.22 voids/night) compared to placebo.
 - Co-primary endpoint ‘proportions of subjects with >33% decrease in the mean number of nocturnal voids from baseline to Day 28’ – there was a statistically significant (p=0.006) increased on desmopressin 25 µg (76%) compared to placebo (64%).
 - There was an increase from baseline to 3 months in the FUSP/time to first void of 155 minutes for desmopressin compared to 106 minutes for placebo (difference +49 minutes).
 - The Applicant also reported benefits related to quality of life (e.g., improvements in quality of sleep and activity levels).
- **CS 41 (males)**

⁵ First Undisturbed Sleep Period (FUSP) was defined as the elapsed time in minutes from going to bed with the intention of sleeping to the time of awakening for the first nocturnal void (duration of time to first void).

⁶ Assessed by the International Consultation on Incontinence Modular Questionnaire-Nocturia (ICIQ-N) and Nocturia Quality of Life (N-QoL).

⁷ Assessed by the Pittsburgh Sleep Quality Index.

⁸ Assessed by the Short-form 12 Questionnaire Health Survey.

- Primary and secondary efficacy was similar with the 50 and 75 µg doses and adverse effects were more frequent with the 75 µg dose.
 - Efficacy results for 50 µg desmopressin and placebo are summarized below.
 - Co-primary endpoint ‘decrease in mean number of nocturnal voids from baseline to Day 28’ – there was a statistically significant adjusted difference (-0.37 voids/night) compared to placebo.
 - Co-primary endpoint ‘proportions of subjects with >33% decrease in the mean number of nocturnal voids from baseline to Day 28’ – there was a statistically significant (p=0.0009) increased on desmopressin 50 µg (67%) compared to placebo (50%).
 - There was an increase from baseline to 3 months in the FUSP/time to first void of 112 minutes for desmopressin compared to 73 minutes for placebo (difference +39 minutes).
 - The Applicant also reported benefits related to quality of life (e.g., improvements in quality of sleep and activity levels).
- **CS29 (Part II) and CS 31**
 - After 92 weeks of treatment,
 - Mean decrease in the number of nocturnal voids for males and females combined was -1.39 voids in the 25 µg group, -1.91 voids in the 50 µg group and -2.09 voids in the 100 µg group.
 - Proportion of subjects with >33% decrease in the number of nocturnal voids was 63% in the 25 µg group, 77% in the 50 µg group and 89% in the 100 µg group.
 - For the females (proposed label dose of 25 µg), the mean decreases in the number of nocturnal voids were -1.22 and -1.82 at 4 and 92 weeks, respectively.
 - For the males (proposed label dose of 50 µg), the mean decreases in the number of nocturnal voids were -1.13 and -1.91 at 4 and 92 weeks, respectively.

Safety Concerns. The safety assessment was based on data from Phase 3 trials (CS29/CS30, CS40, and CS41). The main safety concern with Nocdurna is hyponatremia. The percent of subjects reporting 1 or more treatment-emergent adverse events was 46% in the placebo group and from 40-69% in the desmopressin groups. There were no deaths during the 3-month placebo-controlled treatment period in any of the Phase 3 trials. Six deaths identified in the long-term extension to CS29 (CS31) (4 during trial and 2 after end of trial) were reported by the investigator as unrelated to trial drug.

- **CS40 (females)**
 - Urinary tract infection, headache and upper respiratory tract infection were most commonly reported AEs (≥5%).
 - Reported adverse event (AE) hyponatremia was 1% (2 subjects) in the 25 µg Nocdurna group and <1% (1 subject) in the placebo group. There were no reports of AE blood sodium decrease in either treatment group.
 - Two (2%) placebo subjects and 11 (8%) desmopressin 25 µg subjects had a post-baseline serum sodium level between 130-134 mmol/L (mild

hyponatremia). Three (2%) desmopressin subjects had a serum sodium level 126-129 mmol/L (moderate hyponatremia). No subject had a serum sodium level \leq 125 mmol/L. There were no severe cases of hyponatremia reported.

- **CS41 (males)**
 - Dry mouth and headache were most commonly reported adverse events.
 - Reported AE hyponatremia was 3% in the 50 μ g Nocdurna group and 4% in the 75 μ g Nocdurna treatment group. The frequency of the AE blood sodium decreased was $<$ 1% (1 subject) in the 50 μ g Nocdurna treatment group and 2% (2 subjects) in the 75 μ g Nocdurna treatment group. There were no AE of hyponatremia or blood sodium decreased reported in the placebo treatment group.
 - Two subjects on desmopressin 50 μ g and 4 subjects on desmopressin 75 μ g had a post-baseline serum sodium level \leq 125 mmol/L (severe hyponatremia). Nine subjects on desmopressin 50 μ g had a serum sodium level between 130 and 134 mmol/L (mild hyponatremia). The 50 μ g Nocdurna dose was selected as the optimal dose for males based on the hyponatremia-related data obtained in this trial.

Risk Management Approach Employed in Clinical Trials. The Applicant implemented a sodium monitoring plan in trials CS40 and CS41. The plan consisted on measuring serum sodium at baseline, during the first week and at Month 1 in order to predict the risk of hyponatremia. Implementation of the sodium monitoring plan resulted in the identification of all cases of severe hyponatremia and a reduction of hyponatremia to 2-4%, which is similar that that in the placebo group. It is important to note that the protocols required subjects to be withdrawn if serum sodium was 125 mmol/L or below during monitoring; this occurred in 0-3% of subjects across all trial groups. Application of the monitoring plan to the long-term trial resulted in the identification of many of the chronic mild hyponatremia; chronic cases that were not captured were mild and the sodium level returned to normal.

3.1.2 Risk Management Approach Proposed by the Applicant¹

The Applicant proposed inclusion of the risk of hyponatremia in the Warnings and Precaution section of the label, risk management activities, and enhanced pharmacovigilance including the following elements:

- **Serum sodium monitoring plan:** All patients, irrespective of age, should have a serum sodium level \geq 135 mmol/L or mEq/L prior to initiating Nocdurna. In addition, all patients of 65 years or older and patients with increased risk of hyponatremia due to concomitant medication should have their serum sodium checked during the first week 1 (4 -8 days) of Nocdurna treatment and again at one month.

- **Initiation pack for at-risk patients:** Initiation packs will be available (as patient coupon program or physician sample) to distribute to patients who are monitored (i.e., at risk for hyponatremia). The initiation pack has a limited amount of medication (8 tablets for 8 days of treatment) to support compliance with labeled sodium monitoring during the first week (4-8 days).
- **1-month prescription limit for at-risk patients:** Recommendation for a 1 month prescription to enforce compliance with labeled sodium monitoring plan for patients at risk of hyponatremia.
- **Medication guide and website:** Will provide key product information including the importance of the sodium monitoring plan.
- **Enhanced pharmacovigilance:** The Applicant will monitor all reported cases of hyponatremia cases and will treat these as SAEs to be reported in an expedited manner to the FDA. Case reports will be enriched by collection of additional information via a questionnaire.
- **Educational program for healthcare professionals:** This program will highlight the importance of sodium monitoring and patient diagnosis.
- **Postmarketing pharmacoepidemiologic study:** The Applicant proposed conducting a postmarketing epidemiologic study employing a medical claim database to evaluate the incidence of severe hyponatremia in patients prescribed Nocurna compared to those treated with drugs for other lower urinary tract symptoms, and to gather the demographic and medical characteristics of hospitalized cases of hyponatremia.

DRISK Reviewer's Comments: See section 3.2.1 below.

3.1.3 Internal FDA Consults

The Division of Metabolism and Endocrinology Products (DMEP) requested input from the Division of Bone, Reproductive and Urologic Products (DBRUP), Division of Psychiatry Products (DPP), and the Division of Epidemiology (DEPI).

Division of Bone, Reproductive and Urologic Products (DBRUP)

DBRUP reviewers concluded that the clinical meaningfulness of the small effect of Nocurna is not interpretable in the absence of a validated measure of the clinical benefit of reduction of episodes of nocturia. DBRUP recommends the conduct of a new study including a homogenous population that has simple overproduction of urine at night, a normal capacity bladder, and no bothersome lower urinary tract symptoms due to overactive bladder or benign prostatic hyperplasia. In addition, DBRUP emphasized the need for additional information regarding the risk of hyponatremia, particularly, in regard to the potential of hyponatremia at times distant from initiating therapy, the increased risk of hyponatremia in geriatric patients, and the justification for proposed monitoring.

Division of Psychiatry Products (DPP)

DPP considers that the clinical development program provides insufficient objective evidence to support the Applicant's claim that improvements in FUSP associated with use of Nocdurna are related to increases in slow wave sleep (SWS). If the Agency takes a CR action for Nocdurna, DPP recommends requesting the Applicant conduct a trial including polysomnography at baseline and endpoint as a secondary outcome measure. Such a study will allow investigators to directly measure the time spent in SWS during the FUSP, as well as total SWS during the entire sleep episode.

Division of Epidemiology (DEPI)

The Applicant submitted a proposal for a post-marketing study using an administrative claims database (Wolters Kluwer Source® Lx database) to assess the risk of severe hyponatremia (serum sodium level < 125 mmol/L) while on treatment with Nocdurna. DEPI reviewers concluded that the proposed administrative claims study design is inadequate to assess the incidence of severe hyponatremia with desmopressin use for nocturnal polyuria. The proposed study relies on admission International Classification of Diseases (ICD) codes to identify hyponatremia. However, published literature shows that patients with laboratory values that confirm hyponatremia frequently have ICD hospital discharge codes that do not include hyponatremia (sensitivity of the ICD codes was less than 30%).

3.1.4 Endocrinologic and Metabolic Drugs Advisory Committee Recommendations

Members of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) voted 10:5 (2 abstentions) against approval of Nocdurna because of insufficient evidence of the clinical benefit of the efficacy findings demonstrated in clinical trials. The committee provided advice to the Applicant on how to demonstrate a clinical benefit of Nocdurna to patients with nocturia due to nocturnal polyuria.

3.1.5 FDA Overall Benefit:Risk Assessment

DMEP determined that the demonstrated clinical benefits of Nocdurna do not outweigh the associated risks, including the risk of hyponatremia.

3.2 RISK MANAGEMENT APPROACH

3.2.1 DRISK Assessment of Need for a REMS

DRISK defers recommendations for the management of the risks associated with Nocdurna given the demonstrated clinical benefit of Nocdurna does not outweigh the associated risks, including the risk of hyponatremia. However, DRISK has the following comments on several factors that must be considered in the assessment of the need for REMS for Nocdurna.

Benefit:Risk Profile. The demonstrated clinical benefits of Nocdurna do not outweigh the associated risks, including the serious risk of hyponatremia. Consistent with its mechanism of action and confirmed by data from clinical trials and post-marketing experience, hyponatremia is the most concerning serious risk associated to the use of desmopressin. This concern is augmented in patients in the extremes of the age spectrum.

Hyponatremia is a difficult risk to manage given that sodium homeostasis depends on multiple factors which are subject to frequent changes (i.e., sodium intake, extra-renal sodium loss, and renal sodium excretion). In clinical trials, a sodium monitoring plan implemented by the Applicant helped with identifying cases of hyponatremia.

The voluntary risk management program proposed by the Applicant is complex. The proposed sodium monitoring plan is limited to patients ≥ 65 years; however, patients ≤ 65 years are also at risk of hyponatremia. Compliance with the voluntary plan proposed by the Applicant is a concern. If it is determined that a REMS is necessary to ensure the benefits outweigh the risks of desmopressin, a program that includes elements to assure safe use (ETASU) linking prescriber and patient education and sodium monitoring to drug distribution is a consideration. Programs that include prescribing requirements which are linked to distribution ensure a programmatic approach to stakeholder education and sodium monitoring but will add burden to the healthcare delivery system. The risk of hyponatremia associated to treatment with desmopressin is managed through labeling only for all FDA approved indications.

Anticipated Patient Population: The use of Nocdurna requires that lifestyle changes and other treatable medical causes of nocturia be addressed prior to initiation of therapy. If Nocdurna is approved for the indication sought by the Applicant, the target patient population will most likely include elderly patients, who are at a higher risk for hyponatremia. The size of the anticipated patient population who will receive Nocdurna in practice is uncertain at this time.

Anticipated Prescriber Population: The anticipated prescriber population will probably include primary care providers (e.g., family practice, internal medicine) and specialists (e.g., urologists, endocrinologists, nephrologists).

Anticipated Duration of Use: Nocdurna is administered orally and treatment is likely to continue for prolonged periods of time because nocturia due to nocturnal polyuria is unlikely to resolved spontaneously. The impact of chronic use of Nocdurna on sodium homeostasis has not been studied.

4 CONCLUSIONS AND RECOMMENDATIONS

The benefit:risk balance of Nocdurna for the treatment of nocturia due to nocturnal polyuria is unfavorable. DMEP plans to issue a Complete Response (CR) letter. Therefore, DRISK defers recommendations on the management of the risks associated with Nocdurna and labeling at this time. A discussion on the appropriate risk management strategy will be undertaken if the sponsor submits a satisfactory response to the CR letter. Please include DRISK in all future discussions of the management of the risks associated to this product.

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

/s/

AMARILYS VEGA
01/28/2015

CYNTHIA L LACIVITA
01/28/2015
Concur



**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 27, 2010

To: Mary Parks, M.D., Director
Division of Metabolism and Endocrinology Products (DMEP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management (DRISK)

From: Barbara Fuller, RN, MSN, CWOCN
Patient Labeling Reviewer
Division of Risk Management (DRISK)

Subject: Memo to file re: Review of Patient Labeling (Medication Guide), and Risk Evaluation Mitigation Strategy (REMS)

Drug Name(s): NOCDURNA (desmopressin) Orally Disintegrating Tablets

Application Type/Number: NDA 22-517/S-003

Applicant/sponsor: Ferring Pharmaceuticals Inc.

OSE RCM #: 2009-1722

The Division of Metabolism and Endocrinology (DMEP) requested that the Division of Risk Management (DRISK) review the proposed Medication Guide and Risk Evaluation Mitigation Strategy (REMS) for New Drug Application (NDA) 22-517/S-003 submitted by Ferring Pharmaceuticals Inc. for NOCDURNA (desmopressin) Orally Disintegrating Tablets.

DMEP does not plan to approve the 100 mcg dosage form of NOCDURNA (desmopressin) Orally Disintegrating Tablets. Therefore the DMEP consult request for DRISK to review the proposed Medication Guide and Risk Evaluation Mitigation Strategy (REMS) was withdrawn since these provided for safety monitoring of the drug at the 100 mcg dose. This memo serves to close out the DRISK consult request for NOCDURNA (desmopressin) Orally Disintegrating Tablets.

Please let us know if you have any questions.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22517	ORIG-1	FERRING PHARMACEUTICA LS INC	NOCDURNA

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

/s/

BARBARA A FULLER
04/27/2010

LASHAWN M GRIFFITHS
04/27/2010
I concur