CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022517Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022517

COMPLETE RESPONSE

Ferring Pharmaceuticals Inc.
Attention: Brenda Marczi, Pharm.D.
Vice President, U.S. Regulatory Affairs
100 Interpace Parkway
Parsippany, NJ 07054

Dear Dr. Marczi:

Please refer to your New Drug Application (NDA) dated June 19, 2009, received June 22, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nocdurna (desmopressin) Orally Disintegrating Tablets, 25 mcg and 50 mcg.

We acknowledge receipt of your amendments dated August 17 (2) and 25, September 18 and 30, October 20, November 3, December 22, 2009, January 14, March 11, April 15 and 19, 2010, May 24 and October 14, 2011, July 30 and 31, October 12 and 16, 2012, January 9, July 17, 2013, July 31, September 9 and 23, and November 18, 2014.

The July 31, 2014, submission constituted a complete response to our January 30, 2013, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL/STATISTICAL

We have reviewed the information submitted in your July 31, 2014, Complete Response to our January 30, 2013, action letter. On January 12, 2015, the efficacy and safety findings from the Nocdurna clinical development program were discussed publicly at a meeting of the Endocrinologic and Metabolic Drugs Advisory Committee. After considering the information in your submission and discussions at the advisory committee meeting we have determined that you have provided insufficient evidence to conclude that the effect of Nocdurna relative to placebo on the number of nocturnal voids in adults with nocturia due to nocturnal polyuria is clinically meaningful and outweighs the risks of hyponatremia associated with use of the drug.

To address this deficiency you will need to conduct a trial to demonstrate that Nocdurna provides a meaningful clinical benefit that is associated with the reduction in number of nocturnal voids in adults with nocturia due to nocturnal polyuria. To meet this objective, the trial should employ efficacy endpoint(s) that measure patient benefit in the treatment of nocturia due to nocturnal

polyuria; for example, a validated patient-reported outcome instrument that captures the clinical impact of the changes in nocturnal voids. In this new trial, you should also prospectively evaluate hyponatremia monitoring strategies that you intend to recommend for mitigating the risk of hyponatremia in the postmarketing setting.

In your Complete Response, include strategies for mitigating the risk of hyponatremia that would ensure safe postmarketing use of Nocdurna in the intended population.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

PROPRIETARY NAME

Please refer to correspondence dated July 31, 2014, which addresses the proposed proprietary name, Nocdurna. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please call Jennifer Johnson, Regulatory Health Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

JEAN-MARC P GUETTIER
01/30/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022517

COMPLETE RESPONSE

Ferring Pharmaceuticals Inc.
Attention: Laura Cooper
Director, Regulatory Affairs
4 Gatehall Drive, 3rd Floor
Parsippany, NJ 07054

Dear Ms. Cooper:

Please refer to your New Drug Application (NDA) dated June 19, 2009, received June 22, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Nocdurna (desmopressin) Orally Disintegrating Sublingual Tablets, 25 mcg and 50 mcg..

We acknowledge receipt of your amendments dated August 17 and 25, September 18 and 30, October 20, November 3, and December 22, 2009, and May 7 and August 17, 2010, and May 24 and October 14, 2011, and July 30 and 31, October 12 and 16, 2012, and January 9, 2013.

The July 30, 2012, submission constituted a complete response to our action letter dated April 22, 2010.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL/STATISTICAL

The treatment effect size of Nocdurna relative to placebo in the currently studied patient population with nocturia is modest and of unclear benefit.

In Study CS40, Nocdurna 25 mcg in women was nominally significant versus placebo ($p<0.05$) for the co-primary endpoints of change from baseline in the average number of nocturnal voids over 3 months and 33% responder status over 3 months. The results for the continuous endpoint of change from baseline in average number of nocturnal voids was non-robust, as evidenced by non-significant results from sensitivity analyses based on per protocol population and "as treated" population. In Study CS41, Nocdurna 50 mcg and 75 mcg in men were each statistically significant versus placebo for the same co-primary endpoints and supported by sensitivity analyses. However, in both studies the placebo-subtracted difference yielded modest treatment effects of -0.22 voids/night in CS40 and -0.37 and -0.40 voids/night in CS41. The treatment effect was modest relative to within-group changes from baseline. The substantial change from baseline was likely due to the contribution of behavior and lifestyle modification that consisted of instructing patients to limit their fluid intake at bedtime and avoid drinks that may have a

diuretic effect (caffeine, tea, etc). Because both treatment groups received similar instructions on behavior and lifestyle modification, the efficacy of Nocdurna is properly measured by the treatment difference with placebo. It is inappropriate to ignore the placebo response and assign clinical benefit based solely on a change from baseline in the Nocdurna treatment groups.

Although the newly proposed dosing regimen for men and women was associated with a lower incidence of hyponatremia than your originally proposed dose of 100 mcg, Nocdurna-treated patients still experienced a higher rate of low serum sodium levels than patients treated with placebo. In CS40, three women receiving Nocdurna 25 mcg versus none on placebo had serum sodium levels between 126 and 129 mmol/L. In CS41, severe hyponatremia (serum sodium ≤ 125 mmol/L) was seen in two men receiving Nocdurna 50 mcg and four men receiving Nocdurna 75 mcg versus none on placebo. No serious adverse events were reported as a result of these laboratory abnormalities but this is not unexpected given the closer monitoring in a clinical trial prompting treatment discontinuation.

Given the modest treatment effect and a persistent risk for hyponatremia, we remind you that in our April 22, 2010, Complete Response letter, we referenced the importance of an acceptable health-related quality of life tool to provide supportive evidence for the clinical benefit of treating nocturia. A positive patient-reported outcome is particularly important to offset a safety concern such as dilutional hyponatremia.

Your resubmission included patient-reported outcome measures based on the Nocturia Quality of Life (NQoL) questionnaire, the Work Productivity and Activity Index (WPAI), and a recently developed Nocturnal Impact Diary. We have previously communicated with you that the NQoL and WPAI were not acceptable measures in support of labeling. Regardless, the results on these two measures were not consistent. Although the Nocturnal Impact Diary appears to be an acceptable measure, its evaluation in Study 000034 did not yield evidence of efficacy due to the insufficient study sample size.

In order to address this deficiency you will need to conduct a trial demonstrating a clinically meaningful impact of Nocdurna on reducing the frequency of nocturnal voids. The patient population and evidence for clinical benefit can be discussed at an End-of-Review meeting.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have

such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Jennifer Johnson, Regulatory Health Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

MARY H PARKS
01/30/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-517 **COMPLETE RESPONSE**

Ferring Pharmaceuticals Inc.
Attention: John C. Kim, R.Ph., J.D.
Senior Director, Regulatory Affairs
4 Gatehall Drive, Third Floor
Parsippany, NJ 07054

Dear Mr. Kim:

Please refer to your June 19, 2009, New Drug Application (NDA), received June 22, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Nocdurna (desmopressin) Orally Disintegrating Tablets, 25 mcg and 100 mcg.

We acknowledge receipt of your amendments dated August 17, 25, September 18, 30, October 20, November 3, and December 22, 2009, and January 14, March 11, April 15, and 19, 2010.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

CLINICAL/STATISTICAL

1. The placebo-controlled portion of your pivotal trial, FE992026 CS029, demonstrated efficacy on two co-primary endpoints with only Nocdurna 100 mcg daily doses for 28 days, as determined by the pre-specified sequential testing procedure for controlling type 1 error across the 4 doses. However, this dose was also associated with a high incidence of hyponatremia, a known side-effect of desmopressin that may have a serious clinical consequence outweighing any perceived benefit of reducing frequency of nocturnal voids. Post-hoc analyses of different subgroups at different time points in this trial suggest differential efficacy by gender at lower doses which may have a more acceptable safety profile. However, these additional analyses were not controlled at the overall 5% level of significance and cannot serve as sufficient evidence of efficacy for a different proposed dosing regimen.

   In order to address this deficiency, you must conduct a clinical trial to confirm that a lower dosing regimen is a safe and effective treatment of adult nocturia. This trial should be a placebo-controlled trial with a minimum duration of 3 months to evaluate a longer period of durability and safety relative to placebo.

CLINICAL PHARMACOLOGY

2. The pharmacokinetic information of the to-be-marketed formulation including the bioequivalence study (CS019) was derived using an analytical method that was not properly validated. In order to address this deficiency, you should:
   - Reanalyze the bioequivalence study (CS019) pharmacokinetic samples with a validated analytical method and submit the data to the Agency for review, or
   - Collect the pharmacokinetic samples in future clinical trials and make every effort to improve and properly validate the bioanalytical method to analyze study samples at the proposed dose strength(s).

NONCLINICAL

3. The nonclinical data you have provided qualify impurities new to this formulation and assess local toxicity. There are no nonclinical data provided to bridge to any listed desmopressin product. This bridge was supposed to be provided by the clinical bioequivalence study which utilized an analytic method that was not properly validated. In the absence of adequate clinical bridging information a comparative toxicology study of one month duration comparing your product to the listed drug product is needed.

LABELING

4. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

5. Describe in detail any significant changes or findings in the safety profile.

6. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

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- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

7. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

8. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

9. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

10. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

11. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

12. Provide English translations of current approved foreign labeling not previously submitted.

CLINICAL COMMENTS NOT RELATED TO APPROVABILITY

1. Your clinical development program did not provide any direct evidence that reduced frequency of nocturnal voids is associated with a clinical benefit. References to increased risk of fractures in patients with nocturia are examples of an association and no conclusion can be made that treating nocturia will reduce the incidence of fractures. Similarly, you were not able to determine if reduced frequency in nocturnal voids would provide a meaningful benefit in the individual's health-related quality of life. Although improved health-related quality of life does not form the basis for approval of this product, demonstration of such an improvement utilizing a tool that is acceptable to the Agency's Study Endpoints and Labeling Development (SEALD) team will provide supportive evidence for treating nocturia.

2. You proposed a monitoring scheme to mitigate the risk of hyponatremia with the use of Nocdurna through the measurement of serum sodium on Days 4 and 28 of treatment based on an argument that decreased sodium occurs shortly after the initiation of therapy. This monitoring scheme was not tested in your clinical development program. However, it was noted that several patients in your program presented with hyponatremia, some severe, beyond Day 28. Any risk mitigation strategy for hyponatremia will need to be evaluated in your clinical development program for consideration in labeling.

3. You should collect the pharmacokinetic samples in future clinical trials for obtaining exposure-response relationship. You should make every effort to improve and properly validate the bioanalytical method to analyze study samples at the proposed dose strength(s).

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

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If you have any questions, call Jennifer Johnson, Regulatory Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

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/s/

MARY H PARKS
04/22/2010