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APPLICATION NUMBER:

022517Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 65,890

Ferring Pharmaceuticals Inc.
Attention: Ronald T. Hargreaves, Ph.D.
Vice President, Regulatory Affairs
4 Gatehall Drive, 3rd Floor
Parsippany, NJ 07054

Dear Dr. Hargreaves:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for FE992026, Minirin (desmopressin acetate) Sublingual Melt.

We also refer to the meeting between representatives of your firm and the FDA on October 20, 2008. The purpose of the meeting was to discuss the submission of desmopressin acetate sublingual melt under the 505(b)(2) NDA regulatory pathway for the treatment of nocturia.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of Pre-NDA Meeting Minutes for FE992026, Minirin (desmopressin acetate) Sublingual Melt

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 20, 2008
TIME: 10:30 am – 12:00 pm
LOCATION: CDER, White Oak Campus
APPLICATION: IND 65,890
DRUG NAME: FE992026, Minirin (desmopressin acetate) Sublingual Melt
TYPE OF MEETING: Type B; Pre-NDA

MEETING CHAIR: Mary H. Parks, M.D.

MEETING RECORDER: Jennifer Johnson

FDA ATTENDEES: (Title and Office/Division)

Division of Metabolism and Endocrinology Products

Mary Parks, M.D.	Director and Clinical Team Leader
William Lubas, M.D., Ph.D.	Clinical Reviewer
Lina AlJuburi, Pharm.D., M.S.	Chief, Project Management Staff
Jennifer Johnson	Regulatory Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology II

Sally Choe, Ph.D.	Clinical Pharmacology Team Leader
Sang Chung, Ph.D.	Clinical Pharmacology Reviewer

Office of Biostatistics, Division of Biometrics II

J. Todd Sahlroot, Ph.D.	Deputy Director and Team Leader
Lee Ping Pian, Ph.D.	Biometrics Reviewer

Office of New Drug Quality Assessment, Division of Premarketing

Houda Mahanyni, R.Ph., Ph.D.	Biopharmaceutics Reviewer
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Office of Surveillance and Epidemiology, Division of Pharmacovigilance

Joslyn Swann, Pharm.D., M.G.A.	Safety Evaluator
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Division of Reproductive and Urologic Products

George Benson, M.D.	Division Deputy Director
Suresh Kaul, M.D.	Clinical Team Leader
Olivia Easley, M.D.	Clinical Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Representing Ferring Pharmaceuticals, Inc.

Marianne Kock, M.Sc. Pharm., MBA	Senior Vice President, Global Regulatory Affairs, Pharmacovigilance
----------------------------------	--

Ronald Hargreaves, Ph.D.
John Kim, R.Ph., J.D.
Kenneth Kashkin, M.D.

Vladimir Yankov, M.D.
Jens Peter Nørgaard, M.D.

Per Cantor, M.D.

Pascal Danglas, M.D.

Bjarke Mirner Klein

Lene Holdrup, M.Sc. Pharm.

(b) (4) M.D.
(b) (4) M.D.

Vice President, Regulatory Affairs
Executive Director, Regulatory Affairs
Senior Vice President, Global Clinical Research and
Development, Chief Medical Officer
Executive Medical Director, Clinical Research
Executive Director of Clinical Research and
Development, Urology, Medical Science
Senior Vice President, Clinical Research and
Development
Executive Vice President, Clinical & Product
Development
Global Biometrics, Clinical Research &
Development
Deputy QPPV, Director, Urology, Global
Pharmacovigilance
Consultant
Consultant

BACKGROUND:

Minirin (desmopressin acetate) Sublingual Melt is an analogue of antidiuretic hormone (vasopressin). It is a rapid melting oral lyophilisate to be taken sublingually. The proposed doses are: 10, 25, 50 and 100 mcg desmopressin as a free base.

The proposed indication for Minirin Melt is for the treatment of nocturia. It has also been studied for the treatment of central diabetes insipidus (CDI) and of primary nocturnal enuresis (PNE). The latter two indications were discussed at a Pre-NDA meeting held on June 27, 2005.

NDA 21-333 Minirin Nasal Spray (desmopressin acetate) is currently approved for the management of CDI and PNE.

NDA 21-795 Minirin Tablets (desmopressin acetate) received an approvable action on December 22, 2005, for the following proposed indications: the management of central diabetes insipidus and primary nocturnal enuresis, and for the Renal Concentration Capacity Test (RCCT) used to determine the capacity of the kidney to concentrate urine.

A complete response to the approvable action was submitted on September 24, 2007. NDA 21-795 was approved without a trade name (i.e., approved with the established name desmopressin acetate) on May 8, 2008, for the following indications: as antidiuretic replacement therapy in the management of CDI and for the management of the temporary polyuria and polydipsia following head trauma or surgery in the pituitary region, the management of PNE, and to determine the capacity of the kidney to concentrate urine in pediatric patients (RCCT). (b) (4)

An End-of-Phase 2 meeting for Minirin Melt was held on March 26, 2007.

The Sponsor requested a Pre-NDA meeting on July 30, 2008. A meeting background package was submitted on September 19, 2008. Preliminary comments were sent to the Sponsor via email on October 17, 2008.

MEETING OBJECTIVES:

To obtain comments on the existing clinical and CMC data and their suitability to support the treatment of nocturia indication in a 505(b)(2) NDA for Minirin Melt. This application will refer to FDA's previous finding of safety and effectiveness for DDAVP Tablets, marketed in the U.S. by sanofi aventis under NDA 19-955.

DISCUSSION POINTS:

The Sponsor's questions are listed below, followed by the Division pre-meeting response (italics), followed by the meeting discussion and final Division responses (bolded).

Questions for the Agency

Question #1

Ferring has submitted a request for a waiver of PK studies with the doses of Minirin Melt used in our clinical studies. **Does the Agency agree to our request for a waiver?**

***Preliminary FDA Response:** Independently, the dose strengths (10, 25, 50 and 100 mcg) are proportionally similar; however, how these lower strengths (10, 25, 50 and 100 mcg) are proportionally similar to the higher strengths (60, 120, 240 mcg) used in the PK study cannot be determined because the component and composition information on the higher strengths was not submitted.*

Decision about the biowaiver is pending the review of the components and composition of the Minirin Melt formulation (60, 120, 240 mcg).

Please submit the components and composition of the Minirin Melt formulations (60, 120, and 240 mg).

Discussion during FDA meeting: The Sponsor plans to submit this information in an upcoming amendment to the IND.

FDA Final Response: This is acceptable.

Question #2

The proposed indication for MINIRIN Melt is treatment of nocturia.

Does the Agency agree with the proposed indication?

Preliminary FDA Response: *The preliminary review of your proposed pivotal trial reveals efficacy only at the 100 mcg dose. The increased risk of hyponatremia, particularly in the elderly, is very concerning. As we view acute hyponatremia to be a potentially serious adverse event, you will need to establish that the reduction in nocturnal voids represents a clinical benefit that would outweigh the risk of hyponatremia.*

- *Submit evidence to support increased duration in the initial period of sleep is a validated measure of quality of life.*
- *Submit any evidence you may have correlating the number of night time awakenings to void with the risk for hip fracture in the elderly population.*
- *Submit evidence to support the use of the Pittsburgh Sleep Quality Index and Nocturia Quality of Life and International Consultation on Incontinence questionnaires as validated outcome measures.*
- *Submit any data available on the incidence and distribution of nocturnal polyuria in the elderly population.*

Discussion during FDA meeting: **Initially, the Sponsor agreed to provide this information in the New Drug Application (NDA) submission. After discussion of Question #5, the Sponsor agreed to submit its methodology as an amendment to the IND prior to its NDA submission.**

FDA Final Response: **This is acceptable.**

Question #3

In study CS29 (see Attachments), the 100 mcg dose achieved statistical significance for both co-primary endpoints at 28 days. The 50 mcg dose was statistically significant for the change in nocturnal voids at 28 days. A clear dose response for the primary efficacy parameters at 28 days was demonstrated, with the 10 mcg dose an apparent “no effect” dose. Compared to placebo, statistically significant differences were observed for the 25 mcg, 50 mcg, and 100 mcg doses in decreasing nocturnal urine volume and in increasing the initial duration of undisturbed sleep. The efficacy was maintained and, in some cases, improved beyond Day 28 and for up to seven months in subjects maintained on all treatment doses. **Based on the data presented, does the Agency agree that the efficacy results for study CS29 will support a filing of an NDA for MINIRIN Melt?**

Preliminary FDA Response: *The results to this question will depend on your response to Question 2.*

Discussion during FDA meeting and final FDA response: **See response to Question #2.**

Final FDA Response: **See response to Question #2.**

Question #4

Labeling for MINIRIN Melt dosage and administration will be structured to provide physicians and patients with a favorable risk:benefit profile. The incidence of hyponatremia (serum sodium

<130 mmol/L) with a 25 mcg dose was not different than the incidence with placebo, and the incidence of hyponatremia with the 50 mcg dose was substantially less than the incidence with a 100 mcg dose. During the period of highest risk for hyponatremia (the first 2 weeks of treatment), the 25, 50 and 100 mcg doses provide statistically significantly better outcome than placebo on the primary efficacy parameters. The 25, 50 and 100 mcg doses demonstrated clinically significant response in a substantial proportion of patients. Compared to placebo, statistically significant differences were observed for the 25 mcg, 50 mcg, and 100 mcg doses in decreasing nocturnal urine volume and in increasing the initial duration of undisturbed sleep.

Pending a complete review, would the Agency consider providing physicians with labeling for dosage and administration suggesting an initial dose of 25 mcg, and higher doses of 50 and 100 mcg, if greater response is desired, as this appears to provide efficacy to a substantial portion of the patient population with reduced risks for hyponatremia?

Preliminary FDA Response: *Suggesting a safer lower initial dose with dose titration as needed is an acceptable option. However, a preliminary review of the data suggests that the 25µg dose has insufficient efficacy to be considered as a start dose.*

Discussion during FDA meeting: It is apparent that the 25 mcg dose did not show efficacy with either of the co-primary endpoints. Efficacy is shown at 50 mcg using the change from the baseline co-primary endpoint and for the 33% responder co-primary endpoint when measured at times other than the pre-specified time point of 28 days (see Fig. 6 and Table 15); whether this will be an acceptable starting dose will be a review issue. More data mining will be needed to demonstrate other benefits for the 25 mcg dose. A full data package will be submitted for review. It is possible that for some patients (e.g., an elderly sub-population) a lower dose may be beneficial. The 25 mcg dose is not approved elsewhere for this indication.

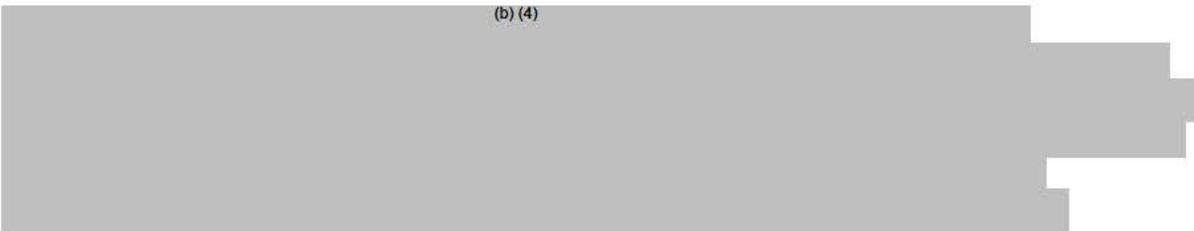
Final FDA Response: See discussion during FDA meeting.

Question #5

Desmopressin-associated hyponatremia is the major potential safety issue. When hyponatremia occurs, it does so rapidly, almost always by the fourth day of treatment. Study CS29 demonstrated that serum sodium monitoring is effective in preventing serious hyponatremia. An analysis of sodium monitoring paradigms applied to the study CS29 data demonstrates that monitoring will markedly improve the risk:benefit ratio of MINIRIN Melt.

Based on the data provided in this Briefing Book, does the Agency consider the following labeling for sodium monitoring to be reasonable?

(b) (4)



(b) (4)

Preliminary FDA Response: *A discussion of labeling must be deferred until we have had the opportunity to review the raw clinical data. The Division considers hyponatremia a serious adverse event. Monitoring to prevent such an event should be demonstrated to be effective and reliable.*

Discussion during FDA meeting and final FDA response: The Sponsor sought clarification of the FDA response, and discussed its hyponatremia monitoring plan using a slide presentation. Concern was raised regarding the ease of implementation for practicing physicians, as there were some patients who did not undergo this monitoring plan (and in real-world practice, it would be expected that more patients would not undergo the necessary safety monitoring).

FDA asked if there is evidence that hyponatremia occurs before the initial serum sodium measurement on Day 4 post-dose. The Sponsor responded with a discussion of 72 elderly patients studied, in which 7/72 experienced hyponatremia at Day 1. They advised patients to drink only to satisfy thirst, and all decreased fluid intake by 200-300 mL per day in patients who developed hyponatremia (although it was pointed out that retention of 200-300 mL is not sufficient to overcome hyponatremia). Diaries were kept, and no seizures occurred.

The function of duration of drug action was discussed. The risk of seizure was said to be low over the initial 4 day period, but concern was expressed that some patients who may have hyponatremia may not have symptoms severe enough to prompt seeing a physician. In addition, it was not clear whether serum sodium levels were obtained in the morning or later in the day. Lab work obtained after the drug's half-life might not detect hyponatremia.

The Sponsor used the slide presentation to demonstrate how lower doses were effective in the elderly. It was pointed out that AUC was higher in males than in females but females showed a higher incidence of hyponatremia, as they tended to have a higher fluid intake.

One proposal was to market (b) (4) to decrease the risk of hyponatremia since patients would be reminded to get serum sodium tested prior to renewal of the prescription.

The Sponsor was reminded that the NDA would likely require a Risk Evaluation Mitigation Strategy (REMS) at the time of the NDA submission, but that FDA cannot commit on efficacy at this point. Proper education will be an important part of the REMS (patients will need to be counseled on water intake). FDA is dubious of the outpatient serum sodium monitoring program; the Sponsor needs to show evidence that safety monitoring has been set up. As stated in the response to question #2 above, the Sponsor needs to provide additional information to demonstrate evidence of the clinical benefit (the

benefit could possibly overcome the hyponatremia risk). There is no doubt that the drug can decrease night time urine production, but can it be efficacious without causing harm?

The Sponsor did not include Quality of Life questionnaire results because it was not known that they would be important, but will submit them. FDA pointed out that this should come in before the NDA submission, which the Sponsor agreed to submit under the IND (FDA advised the Sponsor to submit the methodology prior to data submission, and that FDA would consult this to the review division responsible for treatment of sleep disorders.) The Sponsor inquired about submitting to the SEALD group for a consult on the methodology, labeling claims, or risk-benefit analysis. Since labeling is premature at this point, the risk-benefit analysis would be reviewed first. The Sponsor should prove both co-primary endpoints to demonstrate efficacy and they will be used to establish benefit versus risk.

It was mentioned during the End-of-Phase 2 meeting that nocturia has been viewed as a convenience indication despite an improvement in Quality of Life. It will be important to identify the potential causes of nocturia prior to assessing and initiating treatment.

In Europe, Minirin is not is not approved for the treatment of nocturia in patients over 65 years of age. The Sponsor decided to study the risk of hyponatremia more closely in this elderly population prior to seeking approval in this age group.

Final FDA Response: See discussion during FDA meeting.

Question #6

A total of 1758 nocturia patients were exposed to MINIRIN tablet and MINIRIN Melt in clinical studies. Of those, 701 patients were exposed for at least six months, and 524 patients were exposed for at least 1 year. A total of 1113 nocturia patients were exposed to at least the highest proposed commercial dose (100 mcg MINIRIN Melt) or higher (0.2 and 0.4 mg MINIRIN tablet). A total of 298 patients on the proposed commercial dose or higher were exposed for at least six months, and 198 patients were exposed for at least 1 year. A total of 658 patients were exposed to MINIRIN Melt in study CS29. Of these patients, 496 were exposed to 25, 50 and 100 mcg doses, and it is expected that 285 of these patients will remain on treatment for up to 18 months. Approximately 100 patients will be exposed to the 100 mcg (the highest dose) for at least one year.

Does the Agency agree that there are sufficient safety data to support the submission of an NDA for MINIRIN Melt?

Preliminary FDA Response: *The Agency requests the following additional information before it can make this assessment.*

- *A list of all countries which currently have approved the adult nocturia indication, date of approval, approximate number of patients treated as of this year, dosages approved, and labeling to describe the indication, treatment population and specific monitoring recommendations for each of these countries.*

- *Number of cases in each country of hyponatremia, hyponatremia associated with hospitalization, seizure or death. Provide cases reports if available.*
- *A justification for why the initial measurement of serum sodium is not performed until Day 4. Do you have evidence that it doesn't occur earlier?*
- *Has any country withdrawn this indication because of concern over adverse events? If so, which one and why?*
- *A bibliography including all published articles describing the use of desmopressin in the adult nocturia population and a summary of the literature with respect to hyponatremia in patients treated with desmopressin for nocturia.*

Discussion during FDA meeting: The Sponsor will provide this information in the NDA submission. The Sponsor stated that it may not be possible to provide all of the information requested in bullet point #1 above, since the primary nocturnal enuresis (PNE) indication cannot be split from the nocturia indication in all countries; however, the Sponsor will provide all information available for patients over 50 years of age in the Integrated Summary of Safety. The Sponsor also sought clarification for bullet point #1; FDA requests information regarding all cases of hyponatremia, hyponatremia associated with hospitalization, seizure or death for the oral formulations (age adjusted for patients less than 50 years of age and for patients over 50 years of age).

Final FDA Response: This is acceptable.

Question #7

Ferring intends to provide both MINIRIN tablet and MINIRIN Melt data for the nocturia indication in the ISE and the ISS. **Does the Agency agree with this approach?**

FDA Response: Yes.

ACTION ITEMS:

1. The Sponsor will submit the data requested by FDA in response to Question 1.
2. The Sponsor will submit its methodology and additional information requested by FDA in response to Question 2 as an amendment to the IND prior to the NDA submission.
3. The Sponsor will explore 50 mcg as a starting dose and submit additional data requested by FDA in response to Question 4.

ATTACHMENTS/HANDOUTS:

- Slides presented at Pre-NDA meeting
- A. Rembratt, et al, "Desmopressin in elderly patients with nocturia: short-term safety and effects on urine output, sleep and voiding patterns," *BJU*, 91, 2003, 642-646

Linked Applications

Sponsor Name

Drug Name

IND 65890

FERRING
PHARMACEUTICALS
INC

MINIRIN SL MELT

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

/s/

JENNIFER L JOHNSON
11/20/2008



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 65,890

Ferring Pharmaceuticals Inc.
Attention: Ronald T. Hargreaves, Ph.D.
Vice President, Regulatory Affairs
4 Gatehall Drive, Third Floor
Parsippany, NJ 07054

Dear Dr. Hargreaves:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Minirin (desmopressin) Sublingual Melt (FE992026).

We also refer to the meeting between representatives of your firm and the FDA on March 26, 2007. The purpose of the meeting was to discuss whether the available data together with data from your proposed Phase 3 program will be adequate to support submission of a New Drug Application (NDA) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Minirin Melt.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Jennifer Johnson
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: FDA version of End-of-Phase 2 meeting minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 26, 2007
TIME: 2:00-3:30 P.M.
LOCATION: CDER, White Oak, Building 22, C/R 1313
APPLICATION: IND 65,890
DRUG NAME: Minirin (desmopressin) Sublingual Melt (FE992026)
TYPE OF MEETING: Type B, End-of-Phase 2

MEETING CHAIR: Mary H. Parks, M.D.

MEETING RECORDER: Jennifer Johnson

FDA ATTENDEES: (Title and Office/Division)

Mary H. Parks, M.D.	Director, Division of Metabolism and Endocrinology Products (DMEP)
Theresa Kehoe, M.D.	Clinical Team Leader
William Lubas, M.D.	Clinical Reviewer
Karen Davis Bruno, Ph.D.	Pharmacology Team Leader
J. Todd Sahlroot, Ph.D.	Biometrics Team Leader
Lee Ping Pian, Ph.D.	Biometrics Reviewer
S.W. Johnny Lau, Ph.D.	Acting Clinical Pharmacology Team Leader
Sang Chung, Ph.D.	Clinical Pharmacology Reviewer
Joslyn Swann, Pharm.D., M.G.A.	Safety Evaluator, Division of Drug Risk Evaluation
Janice Weiner, J.D., M.P.H.	Regulatory Counsel, Office of Regulatory Policy
Lina AlJuburi, Pharm.D., M.S.	Regulatory Project Manager
Jennifer Johnson	Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Ferring Pharmaceuticals, Inc.

Jens Peter Nørgaard, M.D.	Chief Scientific Officer, Medical Science, Clinical Research and Development, Urology
Kenneth Kashkin, M.D.	Senior Vice President, Global Clinical Research and Development, Chief Medical Officer
Brad Shumel, M.D.	Medical Director, Global Clinical Research and Development
Per Cantor, M.D., Ph.D.	Senior Vice President, Clinical and Non-Clinical Research and Development
Marianne Kock, M.Sc., MBA	Senior Vice President, Global Regulatory Affairs, Pharmacovigilance
Ronald Hargreaves, Ph.D.	Vice President, Regulatory Affairs
Ingbritt Madsen, M.Sc.	Regulatory Manager, Global Regulatory Affairs
Jørgen Wittendorff, M.Sc.	Senior Director, Global Project Management

IND 65,890

Ole Østerberg, Ph.D.

Pharmacokineticist, Clinical Research and Development,
Experimental Medicine

Egbert van der Meulen, Ph.D.

Director, Statistical Services, Global Biometrics

Ted Sullivan, Esq.

Attorney, Buchanan Ingersoll & Rooney

BACKGROUND:

Minirin (desmopressin) Sublingual Melt is an analogue of antidiuretic hormone (vasopressin). It is a fast melting oral lyophilisate to be taken sublingually. The proposed doses are: 10, 25, 50 and 100 mcg desmopressin as a free base.

The proposed indication for Minirin Melt is for the treatment of nocturia. It is also being studied for the treatment of central diabetes insipidus (CDI) and of primary nocturnal enuresis (PNE). The latter two indications were discussed at a PreNDA meeting held on June 27, 2005.

NDA 21-333 Minirin Nasal Spray (desmopressin acetate) is currently approved for the management of CDI and PNE.

NDA 21-795 Minirin Tablets (desmopressin acetate) received an approvable action on December 22, 2005, for the following proposed indications: the management of central diabetes insipidus and primary nocturnal enuresis, and for the Renal Concentration Capacity Test (RCCT) used to determine the capacity of the kidney to concentrate urine.

The sponsor requested this End-of-Phase 2 meeting on January 12, 2007, and the background package was submitted on February 28, 2007.

MEETING OBJECTIVES:

To discuss the adequacy of available data as well as data from the proposed Phase 3 program to support submission of an NDA under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.

DISCUSSION POINTS:

The Sponsor's questions are listed below, followed by the Division pre-meeting response (bolded), followed by the meeting discussion (in italics).

Non-Clinical

1. The 505(b)(2) NDA would refer to the approved NDA19-955 DDAVP tablets for non-clinical pharmacology and toxicology data. Is this acceptable to the Division?

A summary of your nonclinical development plan has not been provided in the meeting package. Submissions to date indicate completion of a local tolerance study in Syrian Hamster, a 13-week SC rat toxicity study with spiked impurities as well as *in vitro* genotoxicity studies to qualify any impurities in the formulation. It is unclear if the local tolerance study report has been submitted to the IND for review. The 505(b)2 approval pathway may be used, however scientific justification of

similarity remains a review issue and is based on the supporting information provided.

The Sponsor stated that the Syrian hamster and pig pharmacokinetic (PK) studies would be submitted soon.

Additional Pre-Meeting Regulatory Comments:

If the Sponsor intends to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for a listed drug, the Sponsor must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug. If the Sponsor intends to rely on literature or other studies in which there is no right of reference to but that are necessary for approval, reliance on the studies described in the literature is scientifically appropriate must be established.

The Division recommends that Sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 C.F.R. 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/cder/guidance/index.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408), and in its May 30, 2006, response to citizen petitions challenging the use of section 505(b)(2) for approval of follow-on protein products (see Dockets 2003P-0176, 2004P-0171, and 2004P-0231).

Bioassay/Pharmacokinetics

2. The quantitative determination of desmopressin in human plasma is performed using a validated radioimmunoassay of liquid-liquid extracted plasma samples. The lower limit of quantification of this assay is 5 pg/ml.

The relative bioavailability between the tablet and melt formulations has been investigated in a phase I, single center open-label, randomized two-period crossover study in 28 healthy subjects. Subjects were administered 400 µg tablet (as 2x200µg desmopressin acetate, equivalent to 356 µg desmopressin free base) and 240 µg Melt. The subjects were divided into two groups, balanced according to gender, in a randomized order and administered the two treatments separated by a seven day washout period.

A summary of the pharmacokinetic parameters for both treatments is provided in the table below. (The LLOQ of the assay used in this study was 0.8 pg/ml; however this assay was subsequently rejected by FDA.)

Parameter	Unit	Tablet (2x200 µg)		Melt (240 µg)	
		Geometric Mean	95% CI	Geometric Mean	95% CI
AUC	hr*pg/ml	77.2	[63-94]	79.0	[64-98]
AUC _t	hr*pg/ml	71.8	[58-88]	73.2	[59-91]
C _{max}	pg/ml	20.8	[17-26]	18.0	[15-22]
t _{max}	hr	1.0 ¹	0.5-3.0 ²	1.5 ¹	0.5-4.0 ²

¹ median

² range

Desmopressin is produced as the acetate salt and doses of the tablet are defined accordingly. To relate this dose to the active substance (desmopressin free base) the strength should be multiplied by 0.89. Thus a 400 µg dose of desmopressin tablet equals 356 µg free base. The desmopressin content of the melt is specified using the free base.

The mean values of AUC were 77.2 pg/ml and 79.0 pg/ml for the tablet and melt, respectively. Accounting for the difference in specification (free base vs. acetate salt), the relative bioavailability is calculated to be 1.5. Thus, a 100 µg tablet would result in an exposure similar to that of 60 µg melt.

For the proposed study, Ferring plans to utilize doses of 10, 25, 50, and 100 µg (please refer to Question 5 below). Given the limits of the currently approved assay (LLOQ 5 pg/ml), it will not be possible to provide full PK curves for the proposed doses. Ferring therefore does not intend to conduct any pharmacokinetic analyses for this new indication. Does the Division agree?

The Division agrees that a new pharmacokinetic study does not need to be conducted because the pharmacokinetic studies for new lower strengths of Minirin Sublingual Melt can be waived provided the different formulation strengths are proportionally similar and their dissolution profiles are comparable to those of the higher strength(s) used in previous pharmacokinetic studies

Additional Comment: The dosage form and route of administration is described as “a fast melting oral lyophilisate to be taken sublingually.” Please clarify whether the absorption of Minirin Sublingual Melt is via the sublingual absorption route or via the combination of oral and gastrointestinal absorption route.

The Division agrees that a new pharmacokinetic study does not need to be conducted because the pharmacokinetic studies for new lower strengths of Minirin Sublingual Melt can be waived, provided: 1) desmopressin pharmacokinetics is linear over the proposed dose range, 2) the different formulation strengths are proportionally similar in their active and inactive ingredients and 3) their dissolution profiles are comparable to those

of the higher strength(s) used in previous pharmacokinetic studies (Reference: Guidance for Industry, BA and BE studies for orally administered drug products – general consideration, link on <http://www.fda.gov/cder/guidance/5356fml.pdf>)

SUPAC IR Guidance for Industry (<http://www.fda.gov/cder/guidance/cmc5.pdf>) can be referenced, if there is any excipient(s) difference across strengths and need for the assessment of composition similarity.

The Sponsor requested using Minirin tablets (under NDA 21-795 which received an AE action) as the reference product for the PK study since they are similar to the approved DDAVP tablets. However, the Division stated that if the Minirin tablets are not approved prior to marketing the Minirin Melt product, they cannot be used as the reference product through which to bridge to the Agency’s finding of safety and/or effectiveness for DDAVP.

Clarification was made by the Sponsor regarding the “Additional Comment” above. It was stated that all studies have been done with sublingual administration, but that absorption by oral mucosa does take place, as was observed in the pig PK study. Absorption occurs via a combination of both the GI and oral mucosa; even though, the Minirin Melt formulation disintegrates immediately due to the humid environment of the mouth. Regarding the point that dry mouth conditions could affect absorption and PK, the Sponsor stated that no studies had been conducted.

Indication

3. A protocol for a phase III pivotal study, FE992026 CS29, is attached (Attachment A). Based on the patient population described in the protocol, Ferring proposes the following indication:

Treatment of nocturia

Does the Division agree with the proposed indication?

The Division views treatment of nocturia as a convenience indication. Nocturia is a symptom associated with many confounding treatments and disease states. Approval of such an indication will require demonstration of efficacy with minimal safety risks.

The Sponsor does not view this as a convenience indication (see slide “Q3 Indication”).

Study Design

4. Does the Division concur with the overall design of the protocol and/or have any comments? Specifically, we would appreciate review and comments with respect to the following:

- Inclusion/Exclusion criteria

The Division believes that the Phase 3 program should provide a realistic assessment of the risk of hyponatremia in patients concomitantly treated with selective serotonin reuptake inhibitors (SSRIs), chronic non-steroidal anti-inflammatory drugs (NSAIDs), chlorpropamide, amiodarone, carbamazepine and tricyclic antidepressants (TCAs). Product labeling does not necessarily protect against inappropriate use of concomitant medications. Specifically, SSRIs and chronic NSAIDs are commonly prescribed in the elderly population and patients may receive prescriptions for such medications from different physicians who are unaware of their chronic treatment for nocturia. The safety program should be designed to determine whether the risk for hyponatremia may be adequately assessed with serum sodium measurements at the initiation of therapy and during dose adjustments, or whether there is a significant risk with chronic use that concomitant use of these agents should be contraindicated or a risk management plan developed to deal with this issue.

The Sponsor accepts this recommendation. The Division prefers that patients entering at four weeks be on stable doses.

- Duration of treatment

The trial is of sufficient length to determine short term efficacy. A longer duration will be required to document the durability of the effect and the long-term safety profile, including the risk of hyponatremia. An open-label extension of the proposed study may be adequate to address these requirements.

The Sponsor accepts this recommendation.

- Randomization Scheme
- Statistical Methods

The analysis model for the primary efficacy variables should include the following factors used to stratify the randomization: age (< 65, >= 65) and the absence/presence of nocturnal polyuria. Please also provide additional details on the residual and alternate analyses. These details are not difficult to work out and can be provided at the protocol stage, prior to the start of the study.

The Sponsor accepts this recommendation. The issue of drop-outs should be addressed in the protocol submission.

- Safety Monitoring

4a. Primary Endpoint

Ferring proposes the following primary endpoint: "Change from baseline in the number of nocturnal voids." Does the Division concur?

The Division recommends an endpoint which measures a clinically significant response in a substantial proportion of patients and not just a decrease in the mean

number of voids per night. The efficacy of the drug should be assessed using co-primary endpoints including change from baseline to final visit in mean number of nocturnal voids, in addition to a measure of treatment success defined as greater than 33% reduction from baseline in the mean number of voids per night. A statistically significant difference between groups would be required for both endpoints with each test conducted at the 5% alpha level.

Both endpoints need to be met because of the risk of hyponatremia. The Sponsor agrees with the co-primary endpoints.

4b. Secondary Endpoint – Sleep

The most pernicious effect of nocturia is not excessive voiding *per se*, but its impact on sleep quality and subsequent daytime function as a consequence of nighttime sleep disturbance. There is a well established relationship between nocturia and sleep quality. A community-based Dutch survey of 1485 people age 50 and older reported that 25.3% reported disturbed sleep maintenance, for which nocturia was the most frequent cause (67.5%). (1)

Asplund and Aberg investigated the relationship between sleep and nocturia in a sample of 3000 women and found that sleep deteriorated in association with increased nighttime voiding. Women with 3 or more voids per night reported four times more often that they lacked sleep and suffered from daytime sleepiness compared to women with no nocturnal voids. (2)

Insufficient sleep and daytime fatigue have been linked with depression, mood alteration and diminished quality of life. (3-5) A community-based Swedish survey of 203 working individuals with nocturia and 80 randomly selected controls showed that the group with nocturia had significantly lower levels of vitality and utility and greater impairment of work and activity as a consequence of sleep deprivation. (6)

To assess the effect on the initial period of undisturbed sleep, Ferring proposes to

(b) (4)

[REDACTED], does the Division agree it would be appropriate for inclusion in the label?

No.

(b) (4)

[REDACTED]

[REDACTED]

4c. Quality of Life

Older adults often cite nocturia as one of the most bothersome lower urinary tract symptoms. In a UK community-based survey of 423 men over age 40, 14% reported nocturia at least twice per night. Of these, 67% reported that it was “at least a bit of a problem” – the second most bothersome symptom after frequency at least 9 times per day (92%), and more bothersome even than nocturnal incontinence (60%). (8) A community-based survey conducted in the USA including 720 subjects with nocturia showed that as little as one void per night was not only bothersome, but negatively affected health-related quality of life and sleep. Additional increases in voids per night had further significant effects on symptom bother, sleep and QOL. For respondents with nocturia ≥ 2 times per night, the impact on health related quality of life was similar to that of type 2 diabetes and greater than that of hypertension. (9)

The International Consultation on Incontinence has developed a series of validated, international standardized questionnaire modules to assess lower urinary tract dysfunction, vaginal symptoms and lower bowel dysfunction. Two of these questionnaires are nocturia-specific. The ICIQ-Nocturia Module (ICIQ-N) is a four item questionnaire designed to assess the frequency and bother of daytime and night-time urination. The Nocturia Quality of Life Questionnaire (NQoL) is a 13 item questionnaire designed to assess the impact of nocturia on quality of life and contains a sleep/energy domain, a bother/concern domain and one global QoL question. The psychometric properties of both instruments have been established using standard procedures and review criteria for validity and reliability, including content and construct validity, internal consistency and test-retest reliability. The NQoL is currently validated only for men. (10)

As noted above, sleep disturbance may pose the greatest burden on patients with nocturia. To assess sleep disturbance and its impact on sleep quality and burden in patients with nocturia, the Pittsburgh Sleep Quality Index (PSQI) will be administered. The PSQI is a psychometrically sound, 19-item questionnaire which has been used extensively in clinical trials.

Short Form-12 (SF-12 v2) will be used in this trial to measure the impact of nocturia and lack of sleep on general quality of life and to obtain utility measures for a pharmacoeconomic evaluation. SF-12 has been studied extensively and meets standard criteria for reliability and validity. It is composed of 12 items and eight domains: general health, vitality, physical functioning, social functioning, role function-physical, role function-emotional, bodily pain, and mental health. These scales are combined yielding two summary measures – Physical Health Summary and Mental Health Summary.

The proposed clinical program will incorporate the ICIQ-N, NQoL, PSQI, and SF-12 as quality of life measures. Copies of the questionnaires are provided as Appendix I to the clinical protocol, CS 29. Does the Division agree with the selection of these

instruments? If Ferring obtains appropriate treatment response data correlated with these instruments, would the results be acceptable for labeling?

The use of quality of life measures is helpful to the Division in assessing the clinical significance of the proposed indication and the adequacy of the therapeutic intervention. However, inclusion of such data into the label is unlikely. Before such information could be considered for inclusion into the label, the Division would require adequate evidence that these instruments provide data that are reproducible and consistent across several clinical trials.

The Sponsor agrees with this recommendation.

Quantitative Assay/Dose Selection

5. Studies previously conducted for the nocturia indication investigated tablet doses of 100, 200 and 400 µg. Data from these studies are summarized in Attachment B. All three doses demonstrated a clear effect on pharmacodynamic and clinical endpoints. The 200 and 400 µg doses provided only a marginal benefit in efficacy compared to the 100 µg dose.

Ferring wishes to investigate lower doses in the proposed study. The current validated Liquid Chromatography-Ultraviolet assay method cannot reliably analyze for desmopressin content in the drug product below 7.5 µg. Ferring therefore proposes 10 µg as the lowest dose to be investigated in the proposed study, with additional doses of 25, 50, and 100 µg. Does the Division concur with this dose selection?

Yes.

The Division inquired about the possibility of a 125 mcg and 150 mcg dose. The Sponsor stated that drug dosages were chosen to limit safety concerns which increase at higher doses. The half-life of the drug is approximately 3 hours, but the Sponsor expects the drug at the proposed doses should still be effective for the entire sleep cycle because of a delay in time for urine production and bladder filling .

Efficacy

6. Provided positive results are obtained from the proposed phase III study FE992026 CS29, Ferring intends to submit this study along with additional supportive efficacy data from the previously completed European clinical studies. These studies are summarized in Attachment B. In addition, data from PK/PD and clinical studies using the melt formulation are provided in Attachment C. Does the Division agree that the data from the proposed Phase III study together with the supportive data from the European studies would be sufficient to establish the efficacy of Minirin melt for the treatment of nocturia?

Assuming the results of the proposed Phase 3 trial are robust enough to show a clinically relevant response in a substantial proportion of the study population, these data would support the short term efficacy of this product. As this product is

likely to be used as a chronic medication in the proposed treatment population, longer term efficacy data will be necessary to demonstrate the durability of the effect and to support approval.

The Sponsor agrees with this recommendation.

Safety

7. Ferring intends to create a safety database to address labeling for hyponatremia related to treatment with desmopressin. Ferring plans to utilize data from the proposed study to establish appropriate safety monitoring guidelines for serum sodium. The safety database would comprise patients from the proposed study, the previously completed European studies, as well as safety data from studies in pediatric nocturnal enuresis and post marketing surveillance that Ferring has amassed since 1972 when desmopressin was first approved.

In the tablet studies summarized in Attachment B, 377 patients participated in Phase I and II studies, 632 patients participated in the Phase III studies, and 249 of these went on to participate in the one-year extension studies. Total exposure in the extension studies was 194 patient-years, almost half at the highest dose of 0.4 mg. The highest dose in the proposed study is 100 µg melt, which corresponds to approximately 170 µg in the tablet formulation.

The data clearly indicate that the only serious adverse event related to desmopressin treatment is hyponatremia. The subset of elderly subjects predisposed to develop hyponatremia almost invariably do so within one to three weeks of treatment initiation or dose escalation and the risk does not increase with treatment duration. This condition is amenable to early detection via sodium monitoring. In controlled Phase III trials, there were no cases of neurological injury.

Assuming that the proposed study demonstrates an acceptable safety profile, does the Division agree that this combined data package would be adequate to support the safety of MINIRIN Melt?

No. We would like a robust Minirin Melt database with a substantial number of patients exposed to the highest proposed dose for six months to one year to clarify the risk of hyponatremia in the elderly nocturia population.

The Sponsor plans on exposing approximately 500 patients to all study doses for 6 months (approximately 125 at each dose, with about 50% of the patients being from the elderly population). The Sponsor proposed submitting 6 months of data at the time of NDA filing, and then would continue collecting data for another 6 months. The Division stated that whether or not the Sponsor meets the criteria for the safety database would depend upon how many patients are assigned to the final proposed dosages and that this would be a review issue.

The Division typically requires a safety database including 300-600 patients dosed for 6 months, and 100-200 dosed for 1 year for medications which are to be dosed chronically,

with most of the exposure typically at the highest proposed dose. According to ICH guidelines for new chemical entities, 100 patients need to be dosed for 1 year, and 1500 patients total, as the minimum requirement.

Including the one year safety data in the 4-month safety update report is not acceptable.

The Sponsor agreed to include patients on multiple medications after the first 4 week efficacy phase of the trial to get long term concomitant use safety data. The Division inquired as to how many patients over the age of 75 year they expected to enroll in the trial; the Sponsor stated that number would be about 10% of the 500 patients, and that the study would include patients up to 90 years of age.

ATTACHMENTS:

Slides presented by Sponsor during meeting.

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/s/

Jennifer Johnson
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