**OFFICE OF CLINICAL PHARMACOLOGY REVIEW**

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| NDA: 21-795 | Submission Date: September 27, 2007 |
| Brand Name | MINIRIN |
| Generic Name | Desmopressin acetate |
| Reviewer | Manoj Khurana, Ph.D. |
| Team Leader | Sally Y. Choe, Ph.D. |
| OCP Division | Clinical Pharmacology 2 |
| OND Division | Metabolism and Endocrinology Products |
| Sponsor | Ferring Pharmaceuticals, Inc. |
| Submission Type | Complete Response to Approvable Letter |
| Formulation; Strength(s) | Tablets; 0.1 mg and 0.2 mg |
| Indication | Central diabetes insipidus, primary nocturnal enuresis |

## 1. Executive Summary

### 1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed the information provided in the Complete Response to Approvable Letter for MINIRIN (NDA 21-795) and found it acceptable. However, the bioequivalence study demonstrated that MINIRIN 0.2 mg tablet is not bioequivalent to DDAVP 0.2 mg tablet. This recommendation and the following comments should be sent to the sponsor as appropriate.

**Comments to the Sponsor:**

Although not approvability issues, we have the following comments and recommendations:

- The exclusion of certain subjects from pharmacokinetic analysis was not in agreement with the definitions of per-protocol population and pharmacokinetic analysis population specified in the protocol and statistical analysis plan. Such deviations from the planned analysis should be appropriately justified.
- The actual collection-times and concentration data from the subjects excluded from pharmacokinetic analysis population were excluded from the individual subject data listings. In future, the sponsor is advised to disclose and submit all available data for Agency's review.

### 1.2 PHASE IV COMMITMENTS

None

### 1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

In NDA Approvable Letter of December 21, 2005, Agency recommended that before the application may be approved, it would be necessary to conduct another bioequivalence (BE) study or to rerun the stored samples from Study FE992026 CS025 with acceptable quality control performance. In response, the sponsor has conducted a new BE study, FE992026 CS28, entitled "An Open-labeled, Randomized, Two-Sequence, Two-treatments Cross-over Study Determining the Relative Bioavailability of a single 0.6 mg dose of MINRIN Tablets (3 x 0.2 mg) compared to a single 0.6 mg Dose of DDAVP® Tablets (3 x 0.2 mg) in Healthy Male and Female Subjects". The following are the key findings of the review of the study:

- The exclusion of certain subjects from pharmacokinetic analysis was not in agreement with the definitions of per-protocol population and pharmacokinetic analysis population specified in the protocol and statistical analysis plan. Such deviations from the planned analysis should be appropriately justified.
- The sponsor's BE analysis from 69 subject data shows that while $AUC_{0-\infty}$ and $AUC_t$ met the BE criteria, $C_{max}$ did not meet the BE criteria (See Table Below).
- This reviewer's BE analysis using all available concentration data from all of the subjects (N=73 after excluding # 071; insufficient data and # 076; protocol violation) showed that MINIRIN tablet is not bioequivalent to DDAVP tablet. Further,

excluding Period 1 data for subject # 078 and 079 (uncertainty indicated by Division of Scientific Investigation review due to a possible sample switch) and re-run of the BE analysis showed the same outcome.

**Summary of BE Analysis**

| | LSM Ratio% (90% CIs) for Parameter | | |
|---|---|---|---|
| **Analysis** | **$C_{max}$** | **$AUC_t$** | **$AUC_{0-\infty}$** |
| **Sponsor's (Excluding 013, 040, 071, 076)** | 88.0 (79.8-97.0%) | 80.4 (80.1-97.5%) | 90.9 (93.0-99.5%) |
| **Reviewer's (Excluding 071 and 076)** | 87.96 (79.79-97.37%) | 87.99 (79.51-96.96%) | 92.57 (83.97-102.06%) |
| **Reviewer's (Excluding 071, 076, and Period 1 for 078 and 079)** | 86.23 (78.44-94.79%) | 87.39 (78.78-96.93%) | 92.16 (83.35-101.91%) |

- In the PK analysis, the % extrapolation of AUC was around 20% in the $AUC_{0-\infty}$ computations for both MINIRIN and DDAVP tablets; therefore, use of $AUC_t$ is more reliable for assessment of desmopressin exposure resulting from a single dose.
- The actual collection-times and available concentration data from the subjects excluded from PK analysis population were excluded from the individual subject data listings.
- DSI audit of the analytical portion of the study did not find any serious deficiencies that may affect the outcome of the study (see DSI Review under section 4.3).

Overall, the Complete Response to the Approvable Letter, which involved BE assessment of MINIRIN tablets in comparison to DDAVP tablets from study FE992026 CS28, is acceptable.

## 2. QBR

## 2.1 GENERAL ATTRIBUTES

### *2.1.1 What relevant regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?*

In 2005, Ferring Pharmaceuticals, Inc. submitted NDA21-795 (dated March 2, 2005 and received on March 4, 2005) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for MINIRIN (desmopressin acetate) Tablets, 0.1 and 0.2 mg. With this application, the sponsor submitted a clinical summary report of their pivotal bioequivalence study entitled "An Open-Label, Randomized, Cross-over Study with Two Treatment Periods Investigating the Bioequivalence of a Single Dose of Minirin Tablets (0.2 mg) and a Single Dose of DDAVP Tablets (0.2 mg) in Healthy Male and Female Participants" (FE992026 CS025).

The Agency's review (Original NDA reviews by Dr. William Lubas dated 08 Dec, 2005 and by Dr. Sang Chung dated 30 Nov, 2005) regarded the application approvable and informed the sponsor regarding the deficiencies found during the audit of the analytical

portion of the bioequivalence study (DSI Review December 7, 2005). The accuracy of a large number of analytical runs was not demonstrated due to unacceptable quality control performance. Agency recommended that before the application may be approved, it will be necessary to conduct another bioequivalence study or to rerun the stored samples from Study FE992026 CS025 with acceptable quality control performance (NDA Letter dated December 21, 2005).

During the End of Review meeting (See meeting minutes March 21, 2006), the sponsor asked for Agency's feedback on their questions around this issue and was provided the responses as quoted below:

> *"a. Would the old data be acceptable provided we re-analyze samples from CS025 with an updated, cross-validated analytical method with acceptable quality control performance? We have 1246 of 1855 samples left (67%).*
>
> *OR*
>
> *b. Would demonstration of bioequivalence be accepted following re-analysis with an updated, robust method of the samples left from the study? Full profiles in both treatment periods are expected to be available for 36 of the 56 completing subjects.*
>
> **FDA Response:** The Sponsor needs to improve the assay and submit the assay validation data for review. If the assay validation is found acceptable, re-run the stored samples from Study FE992026 CS025. Number of subjects should be large enough to maintain statistical power for BE analysis. Otherwise, it will be necessary for the Sponsor to conduct another bioequivalence study. The key point is to improve the assay.
>
> *c. If the new bioanalytical method (LLOQ 0.8 pg/mL) does not show the expected improvements, a new BE study will be performed with 80 subjects and using a bioanalytical method with a LLOQ of 5 pg/mL. Using a bioanalytical method with such a relatively high LLOQ results in not being able to measure 'complete' profiles. To minimize this effect, the highest approved dose of 0.6 mg (3 x 0.2 mg) will be administered. Based on PK modeling the observed area under the curve (AUCt) of exposure is estimated to be above 80% of the total AUC for approximately 72% of individuals. Does the Division have any comments?*
>
> **FDA Response:** Response deferred until Sponsor makes the decision to conduct a new bioequivalence study instead of re-running stored samples."

The sponsor later submitted a method operating procedure entitled *Quantitative Determination of Desmopressin in Human Plasma* and a validation report entitled *Quantitative Determination of Desmopressin in Human Plasma by Immunoassay* on August 9, 2006. The Agency review noted the following comments (Clinical Pharmacology Review dated November 27, 2006), which were provided to the sponsor (NDA Letter dated December 8, 2006):

- The major issues in the DSI review of the bioequivalence trial were (a) high rate of run failure during the study sample analysis (70%) and (b) low criterion for a run acceptance (i.e., 33% of QCs at each concentration to be accurate). The validation of method may not guarantee the acceptable results on the study sample analysis.

- The observed plasma desmopressin levels in the bioequivalence study of the original application were between 0.8 and 55 pg/mL, and most levels were less than 20 pg/mL. In this regard, the new QC concentrations (15, 75, 250, and 1000 pg/mL) did not reflect properly the range of potential plasma desmopressin levels.
- The lower limit of quantitation was 5.0 pg/mL in the August 9, 2006 submission, which is significantly higher than that of the value (i.e., 0.8 pg/mL) reported for the assay method in the original submission. The assay may not be sensitive enough to characterize the absorption and elimination phases of the drug.

On September 27, 2007, the sponsor submitted the Complete Response to the Agency's Approvable Letter. With this submission, the sponsor provided a final report for a new bioequivalence study (FE992026 CS28), entitled "An Open-labeled, Randomized, Two-Sequence, Two-treatments Cross-over Study Determining the Relative Bioavailability of a single 0.6 mg dose of MINRIN Tablets (3 x 0.2 mg) compared to a single 0.6 mg Dose of DDAVP® Tablets (3 x 0.2 mg) in Healthy Male and Female Subjects".

### *2.1.2 Does the information submitted addresses the deficiencies identified in the original NDA review?*

The sponsor conducted and submitted a final study report with a bioanalytical report for a new bioequivalence (BE) study entitled, "An Open-labeled, Randomized, Two-Sequence, Two-treatments Cross-over Study Determining the Relative Bioavailability of a single 0.6 mg dose of MINRIN Tablets (3 x 0.2 mg) compared to a single 0.6 mg Dose of DDAVP® Tablets (3 x 0.2 mg) in Healthy Male and Female Subjects" (FE992026 CS28). The sponsor conducted this new BE study in support of their original NDA application. In order to ensure that the systemic exposure was sufficiently high for reliable measurements of plasma concentrations of desmopressin, the highest approved single dose of 0.6 mg desmopressin was used in the study. Also the bioanalysis was conducted using the improved assay method and the sponsor provided the report for the bioanalytical method with this submission. Overall, the submission sufficiently addressed the concerns raised in the Approvable Letter by the Agency by:

(a) improving the bioanalytical method (see section 2.6 below for details), and
(b) conducting another BE study using the maximum approved dose of 0.6 mg of desmopressin with an expectation that resulting concentration data will be covered by the analytical range of the new assay method.

## 2.2 GENERAL CLINICAL PHARMACOLOGY

*Please refer to Office of Clinical Pharmacology review of the Original NDA by Dr. Sang Chung dated 30 Nov, 2005 in DFS for other details. The information related to the current application is reviewed below:*

### *2.2.1 Was the new bioequivalence study acceptable?*

Comparability of MINIRIN to DDAVP® was evaluated via a BE study (Study FE992026 CS28). Study FE992026CS28 was an open-label, randomized, two-sequence, two-

treatment cross-over study evaluating the bioequivalence between of MINIRIN and DDAVP® in healthy fasted subjects.

***Study Design:***

Formulations used in the study are summarized in Table 1 below.

**Table 1.** Description of Study Products(s)

| Dosage Form | Study Product | Appearance | Dose Unit | Lot Number | Source of Supply | Expiry Date |
|---|---|---|---|---|---|---|
| Tablet | DDAVP® | White, round | 0.2 mg | GF9047 | Ferring AB, Limhamn, Sweden | June 2008 |
| Tablet | MINIRIN® | White, round | 0.2 mg | AA0395 | Ferring AB, Limhamn, Sweden | Oct 2008 |

DDAVP tablets 0.2 mg is listed in the Orange Book. In order to ensure that the systemic exposure was sufficiently high for reliable measurements of plasma concentrations for desmopressin, the highest approved single dose of 0.6 mg desmopressin was used in the study. Overnight fasted subjects were randomized to different dosing sequences and received a single oral dose of 0.6 mg MINIRIN tablets (3 x 0.2 mg) in one dosing period and a single oral dose of 0.6 mg DDAVP® tablets (3 x 0.2 mg) in the other dosing period.

**Table 2.** Study treatments

| Sequence | Period 1 | Period 2 |
|---|---|---|
| Sequence 1 | 0.6 mg (3 × 0.2 mg) MINIRIN | 0.6 mg (3 × 0.2 mg) DDAVP |
| Sequence 2 | 0.6 mg (3 × 0.2 mg) DDAVP | 0.6 mg (3 × 0.2 mg) MINIRIN |

Blood samples were drawn at pre-dose, and 15 min, 30 min, 45 min, and at 1 h, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 14 h post-dose. A washout period of three to seven days separated the two dosing periods.

***PK Analysis Data Sets:***

Sponsor stated in their clinical report that a total of 73 subjects completed the study (36 subjects completed Dosing Sequence 1 and 37 subjects completed Dosing Sequence 2). The pharmacokinetic analysis dataset (N=69) was defined as all subjects from the per-protocol (PP) analysis set with measurements of plasma desmopressin concentrations. Thirty-three (92%) subjects in Sequence 1 and 36 (92%) subjects in Sequence 2 were included in the PK dataset. In Sequence 1, Subject Nos. 013, 040, and 071 were excluded from the PK dataset because the limited data available were insufficient for a pharmacokinetic analysis. In Sequence 2, Subject Nos. 008, 017 (both did not receive MINIRIN in Period 2) and 076 (source data untraceable) were excluded from the PP dataset and, therefore, were also excluded from the PK dataset.

Ten of the subjects originally randomized were replaced by five alternates (found ineligible on Day -1 prior to dosing) and given the same randomization number as the withdrawn original subjects. Sponsor acknowledged that it is possible that a true randomization to treatment sequence was not achieved but claimed that the overall

outcome of the study was not affected since this relates to only five out of 75 subjects, and it was a cross-over study,.

***Study Results:***

Results from the bioequivalence ANOVA model for the primary pharmacokinetic parameters including sequence, treatment, and period as the fixed effects and subject (sequence) as the random effect, are shown in Table 3. Based on the 69 subjects in the PK population, sponsor claimed that the bioequivalence is established for both $AUC_{0-\infty}$ (referred as AUC in sponsor's analysis) and AUCt since the 90% CI were within the predefined limits (80.00-125.00%). For Cmax, the borderline bioequivalence has been demonstrated with a lower bound of 90% CI, 79.8%, just outside of the 80.00% lower limit.

**Table 3.** Summary of Bioequivalence Analysis

| | MINIRIN | | DDAVP | | Geometric | |
|---|---|---|---|---|---|---|
| PK parameter | N | Geometric Mean | N | Geometric Mean | Mean Ratio, % | 90% CI |
| AUC (pg·hr/mL) | 69 | 104 | 69 | 114 | 90.9 | 93.0 - 99.5 |
| $AUC_t$ (pg·hr/mL) | 69 | 85.0 | 69 | 86.2 | 80.4 | 80.1 - 97.5 |
| $C_{max}$ | 69 | 32.7 | 69 | 37.2 | 88.0 | 79.8 - 97.0 |

The mean desmopressin concentration-time profiles from two tablets are shown in Figure 1 below. The mean desmopressin primary and secondary PK parameters are summarized below in Tables 4 and 5, respectively.

**Figure 1.** MINIRIN and DDAVP Mean Concentration vs. Time Profiles. Bars represent SD.

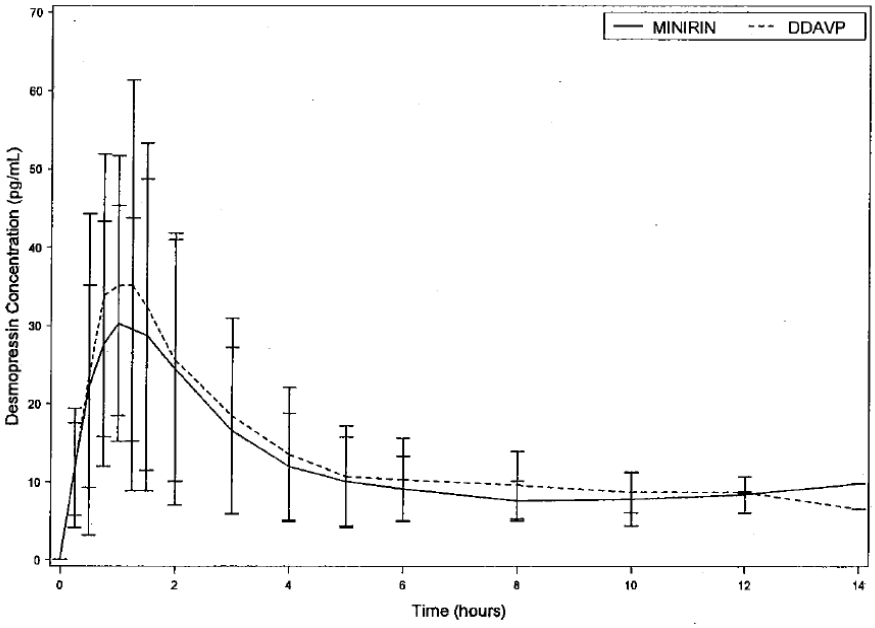

**Table 4.** Primary pharmacokinetic parameters:

| Pharmacokinetic Parameter | MINIRIN (N=69) | DDAVP (N=69) |
|---|---|---|
| AUC (hr·pg/mL) | | |
| Mean (SD) | 116 (63.2) | 132 (83.1) |
| Median | 99.6 | 104 |
| Range | 37.3-454 | 41.6-529 |
| Geometric mean | 104 | 114 |
| CV% | 54.6% | 63.1% |
| $AUC_t$ (hr·pg/mL) | | |
| Mean (SD) | 98.7 (63.6) | 114 (77.1) |
| Median | 76.4 | 88.7 |
| Range | 24.6-439 | 38.2-486 |
| Geometric mean | 85.2 | 95.9 |
| CV% | 64.5% | 67.9% |
| $C_{max}$ (pg/mL) | | |
| Mean (SD) | 36.7 (21.4) | 42.7 (29.8) |
| Median | 31.7 | 34.4 |
| Range | 14.0-156 | 14.8-211 |
| Geometric mean | 32.7 | 37.2 |
| CV% | 58.4% | 69.7% |

**Table 5.** Secondary pharmacokinetic parameters

| | MINIRIN (N=69) | DDAVP (N=69) |
|---|---|---|
| $t_{max}$ (hr) | | |
| Mean (SD) | 1.12 (0.442) | 1.04 (0.478) |
| Median | 1.00 | 1.00 |
| Range | 0.500-3.00 | 0.500-4.00 |
| Geometric mean | 1.05 | 0.966 |
| CV% | 39.4% | 46.1% |
| $\lambda_z$ (1/hr) | | |
| Mean (SD) | 0.356 (0.099) | 0.369 (0.117) |
| Median | 0.340 | 0.357 |
| Range | 0.154-0.733 | 0.083-0.870 |
| Geometric mean | 0.343 | 0.348 |
| CV% | 27.9% | 31.6% |
| %Extrap AUC (%) | | |
| Mean (SD) | 22.0 (10.1) | 19.8 (9.22) |
| Median | 20.5 | 19.9 |
| Range | 4.76-57.4 | 6.29-57.5 |
| Geometric mean | 19.8 | 17.9 |
| CV% | 45.8% | 46.7% |
| $t_{½}$ (hr) | | |
| Harmonic mean (SD) | 1.95 (0.584) | 1.88 (1.19) |
| Median | 2.04 | 1.94 |
| Range | 0.946-4.51 | 0.796-8.40 |
| Inter-quartile range | 0.537 | 0.537 |
| Geometric mean | 2.02 | 1.99 |
| CV% | 27.9% | 54.8% |

***Reviewer's comment:***
The reason for excluding subjects # 008, # 017, # 013, and # 040 from the PK analysis population was not clear from the information submitted by the sponsor. The individual data listing provided by the sponsor did not list concentration data for subjects excluded from the PK analysis population. However, review of the concentration data available in the analytical report revealed that these subjects had sufficient concentration in at least one period to derive meaningful PK parameters. Therefore, the exclusion based on either the availability of data in one period only or BLQ concentrations in one of the two periods is not in agreement with the definition of PP population and PK population stated in the Statistical Analysis Plan (SAP) and the study protocol. According to these documents, any subject that receives the treatment and has measurable concentrations should be included in the PK population.

This reviewer, however, agrees with the sponsor on the exclusion of subjects # 071 and # 076, which was appropriate based on the SAP and the study protocol.

PK analysis (using WinNonlin) and bioequivalence analysis (using SAS) utilizing data from 73 subjects showed the following results:

**Table 5.1** Summary of reviewer's BE analysis (excluding subjects # 071 and # 076)

| PK Parameter | MINIRIN Geometric Mean | DDAVP Geometric Mean | Geometric Mean Ratio (%) | 90% CI Lower | 90% CI Upper |
|---|---|---|---|---|---|
| **AUC (pg.hr/mL)** | 105.90 | 114.40 | 92.57 | 83.97 | 102.06 |
| **AUCt (pg.hr/mL)** | 79.55 | 90.40 | 87.99 | 79.51 | 97.37 |
| **Cmax (pg/mL)** | 32.35 | 36.70 | 87.96 | 79.79 | 96.96 |

[**Note:** In absence of the information on actual collection times (not included in the dataset by the sponsor) for the 4 subjects included in the analysis, the nominal collection time was used in PK parameter calculation for these subjects.]

**Table 5.2** Summary of reviewer's BE analysis (excluding subjects # 071, 076, and Period 1 data for 078 and 079)

| PK Parameter | MINIRIN Geometric Mean | DDAVP Geometric Mean | Geometric Mean Ratio (%) | 90% CI Lower | 90% CI Upper |
|---|---|---|---|---|---|
| **AUC (pg.hr/mL)** | 105.34 | 114.31 | 92.16 | 83.35 | 101.91 |
| **AUCt (pg.hr/mL)** | 78.96 | 90.36 | 87.39 | 78.78 | 96.93 |
| **Cmax (pg/mL)** | 31.72 | 36.78 | 86.23 | 78.44 | 94.79 |

Based on these results, this reviewer concludes that MINIRIN tablets 0.2 mg did not demonstrate bioequivalence to DDAVP tablets 0.2 mg.

## 2.3 ANALYTICAL SECTION

### *2.3.1 What bioanalytical method is used to assess desmopressin acetate concentrations in this NDA and are they acceptable?*

***Quantitative determination of desmopressin in human plasma by RIA:***
The quantitative determination of desmopressin in human plasma was done by a validated radioimmunoassay (RIA). The bioanalysis was conducted by ----- ---------- ---- ---------- ---------- -- ---- - --------- - - - ------ ---------- - . The human plasma samples are extracted by liquid/liquid extraction (LLE). In the radioimmunoassay, a known amount of antibody and tracer (Desmopressin labeled with $^{125}I$) are added to the reconstituted extract and incubated. Desmopressin present in the sample and the tracer added will compete in forming a complex with the antibody. After separation, using charcoal suspension followed by centrifugation, only the complexes remain in the supernatant. The radioactivity is measured in a gamma counter. The higher the concentration of desmopressin in the sample extracted from plasma, the lower the radioactivity will be. The concentration of desmopressin in extracted plasma samples is read against a standard curve.

The calibration curves were analyzed at desmopressin concentrations of 2.5, 5.0, 10.0, 20, 40, 80, 160, 320, 640, and 1280 pg/mL. The desmopressin lower limit of quantitation (LLOQ) was 5.0 pg/mL using 1.0 mL human plasma. Upper limit of quantitation (ULOQ) was 320 pg/mL. The inter-assay inaccuracy, as assessed from %bias at LLOQ or above up to ULOQ of the calibration standards, was within the range of -1.36% to 2.05%. Intra-assay precision was within the range of 3.34% to 7.41%. The inter-assay inaccuracy, as assessed from %bias for low quality control (LQC) to upper quality control (UQC) was within the range of 0.93% to 3.22%. Inter-assay precision was within the range of 7.68% to 11.5% for LQC to UQC.

***Reviewer's comment:*** DSI audit of the analytical portion of the study did not find any serious deficiencies that may affect the outcome of the study (see DSI Review under section 4.3). The identified deficiencies were mostly related to the inadequate documentation that could verify some of the analytical procedures followed by the laboratory, ---- ----------. Under the light of these findings and based on the clinical pharmacology review, the analytical report submitted by the sponsor as well as the concentration data generated using this analytical method, are acceptable.

## 4.2 INDIVIDUAL STUDY DETAILS

### *4.2.1 Clinical Study FE992026 CS28*

**TITLE:** An Open-labelled, Randomized, Two-sequence, Two-treatments Cross-over Study Determining the Relative Bioavailability of a Single 0.6 mg Dose of MINIRIN Tablets (3 x 0.2 mg) Compared to a Single 0.6 mg Dose of DDAVP Tablets (3 x 0.2 mg) in Healthy Male and Female Subjects (# FE 992026 CS28)

**INVESTIGATOR(S) AND STUDY CENTER(S):**

**Investigator and Study Center(s)**

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**STUDY SPONSOR:**

Ferring Pharmaceuticals A/S
Kay Fiskers Plads 11
2300 Copenhagen S, Denmark
Tel: +45 8833 8834

**BIOANALYTICAL ANALYSIS:**

**STUDY PERIOD:** 02 DEC 2006 (First Subject First Visit) – 23 DEC 2006 (Last Subject Last Visit)

**OBJECTIVE:**
The primary objective of this study was to determine if a single 0.6 mg dose of MINIRIN tablets is bioequivalent with a single 0.6 mg dose of DDAVP tablets.

**STUDY DESIGN:**
This study was an open-labelled, randomized, crossover two-sequence study with two dosing periods investigating the relative bioavailability of two types of desmopressin tablets administered orally in healthy male and female subjects. Subjects were randomized to one of two sequences to receive in Periods 1 and 2 either MINIRI/DDAVP or DDAVP/MINIRIN. The study was conducted in three study visits. An outpatient screening visit took place 2-21 days before dosing. Subjects participated in two residential dosing periods separated by a washout period of three to seven days. Each dosing period consisted of confinement to the clinical investigation unit for three days/two nights (admission the day before dosing and discharge approximately 30 to 36 hours after dosing). During the residential dosing periods, subjects received study medication and underwent safety and pharmacokinetic procedures. End-of-study assessment was performed before discharge from the clinical investigation unit in the second dosing period.

**BLOOD SAMPLE COLLECTION:**

Blood samples were drawn at pre-dose, and 15 min, 30 min, 45 min, and at 1 h, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 and 14 h post-dose.

**SAFETY ASSESSMENT:** Safety was evaluated by adverse event (AE) reporting, clinical laboratory testing including clinical chemistry with serum sodium, hematology and urinalysis, vital signs measurement, 12-lead electrocardiogram (ECG), and physical examination.

**SUBJECTS:**
A total of 80 subjects were planed for inclusion.

**ANALYTICAL METHOD:**
Desmopressin was measured in human plasma samples using radioimmunoassay technique after extraction.

**PHARMACOKINETICS**

Pharmacokinetic parameters were evaluated in any subjects who provided sufficient samples for PK assessment. For the purpose of pharmacokinetic analysis and computation of descriptive statistics (observed and Baseline-adjusted data), serum concentrations that fell below the limit of quantification for the assay (BLQ) were assigned a value of zero. For observed data, if a concentration was not reported for a sample time point, then it was assigned a value of missing.

Pharmacokinetic parameters included the following:
Desmopressin pharmacokinetic parameters used for demonstration of bioequivalence, i.e., AUC, AUCt, and Cmax, were determined by non-compartmental analysis (NCA).

The average bioequivalence of the two treatments was addressed by analyzing the primary pharmacokinetic endpoints separately by an analysis of variance (ANOVA) in the natural logarithmic scale. Bioequivalence between the two treatments was claimed if the two-sided 90% confidence interval for the ratio of treatment means of AUC, AUCt, and Cmax were within 80.00-125.00%. Descriptive statistics were provided for secondary pharmacokinetic endpoints.

**SAFETY:**
Descriptive statistics were provided for safety parameters.

**RESULTS:**
Based on the 69 subjects in the PK population, the results of the primary analysis demonstrated that the 90% confidence intervals for the ratio of the means of AUC (CI=93.0-99.5%) and AUCt (CI=80.1-97.5%) were completely within the generally accepted bioequivalence limits of 80.00% and 125.00%, as pre-specified in the study protocol. However, the Cmax presented with a borderline bioequivalence since the 90% confidence limit lower bound for Cmax was just outside 80.00% (CI=79.8-97.0%). Therefore, bioequivalence of the test product, MINIRIN, to the reference product, DDAVP, could be claimed for AUC and AUCt, and borderline bioequivalence for Cmax.

**Summary of Observed Pharmacokinetic Parameters in 69 Subjects**

**Primary Pharmacokinetic Parameters in 69 Subjects**

| Pharmacokinetic Parameter | MINIRIN (N=69) | DDAVP (N=69) |
|---|---|---|
| AUC (hr·pg/mL) | | |
| Mean (SD) | 116 (63.2) | 132 (83.1) |
| Median | 99.6 | 104 |
| Range | 37.3-454 | 41.6-529 |
| Geometric mean | 104 | 114 |
| CV% | 54.6% | 63.1% |
| $AUC_t$ (hr·pg/mL) | | |
| Mean (SD) | 98.7 (63.6) | 114 (77.1) |
| Median | 76.4 | 88.7 |
| Range | 24.6-439 | 38.2-486 |
| Geometric mean | 85.2 | 95.9 |
| CV% | 64.5% | 67.9% |
| $C_{max}$ (pg/mL) | | |
| Mean (SD) | 36.7 (21.4) | 42.7 (29.8) |
| Median | 31.7 | 34.4 |
| Range | 14.0-156 | 14.8-211 |
| Geometric mean | 32.7 | 37.2 |
| CV% | 58.4% | 69.7% |

**Secondary Pharmacokinetic Parameters in 69 Subjects**

| | MINIRIN (N=69) | DDAVP (N=69) |
|---|---|---|
| $t_{max}$ (hr) | | |
| Mean (SD) | 1.12 (0.442) | 1.04 (0.478) |
| Median | 1.00 | 1.00 |
| Range | 0.500-3.00 | 0.500-4.00 |
| Geometric mean | 1.05 | 0.966 |
| CV% | 39.4% | 46.1% |
| $\lambda_z$ (1/hr) | | |
| Mean (SD) | 0.356 (0.099) | 0.369 (0.117) |
| Median | 0.340 | 0.357 |
| Range | 0.154-0.733 | 0.083-0.870 |
| Geometric mean | 0.343 | 0.348 |
| CV% | 27.9% | 31.6% |
| %Extrap AUC (%) | | |
| Mean (SD) | 22.0 (10.1) | 19.8 (9.22) |
| Median | 20.5 | 19.9 |
| Range | 4.76-57.4 | 6.29-57.5 |
| Geometric mean | 19.8 | 17.9 |
| CV% | 45.8% | 46.7% |
| $t_{½}$ (hr) | | |
| Harmonic mean (SD) | 1.95 (0.584) | 1.88 (1.19) |
| Median | 2.04 | 1.94 |
| Range | 0.946-4.51 | 0.796-8.40 |
| Inter-quartile range | 0.537 | 0.537 |
| Geometric mean | 2.02 | 1.99 |
| CV% | 27.9% | 54.8% |

**Summary of Bioequivalence Analysis**

| | MINIRIN | | DDAVP | | Geometric | |
|---|---|---|---|---|---|---|
| PK parameter | N | Geometric Mean | N | Geometric Mean | Mean Ratio, % | 90% CI |
| AUC (pg·hr/mL) | 69 | 104 | 69 | 114 | 90.9 | 93.0 - 99.5 |
| $AUC_t$ (pg·hr/mL) | 69 | 85.0 | 69 | 86.2 | 80.4 | 80.1 - 97.5 |
| $C_{max}$ | 69 | 32.7 | 69 | 37.2 | 88.0 | 79.8 - 97.0 |

## Summary of Safety Results

A total of 15 treatment emergent adverse events (TEAEs) were reported by 11 (15%) of75 subjects in this study, the incidence of AEs reported being similar after dosing with MINIRI OR DDAVP. There were no serious or severe AEs and no subjects were withdrawn from the study due to a TEAE. There were no reports of hyponatremia. Six subjects experienced seven TEAEs, all gastrointestinal disorders that were considered to be related to desmopressin.

## Pharmacokinetic Conclusions

Based on the 69 subjects in the PK population, bioequivalence could be claimed for AUC and AUCt. Cmax presented with a borderline bioequivalence, displaying a 90% confidence lower bound of 79.8%, just outside of the 80.00% lower limit.

## 4.3 DIVISION OF SCIENTIFIC INVESTIGATION REVIEW

**MEMORANDUM** **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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DATE: March 17, 2008

FROM: John A. Kadavil, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 21-795
MINIRIN® (desmopressin acetate) Tablets, 0.1 mg and 0.2 mg, Sponsored by Ferring Pharmaceuticals

TO: Mary Parks, M.D.
Director
Division of Metabolism and Endocrinology Products (OND/ODEII/DMEP)

At the request of DMEP, the Division of Scientific Investigations conducted an audit of the analytical portion of the following bioequivalence study:

**Study Number:** FE992026 CS28

**Study Title:** "An Open-labeled, Randomized, Two-sequence, Two-treatments Cross-over Study Determining the Relative Bioavailability of a Single 0.6 mg Dose of MINIRIN® Tablets (3 x 0.2 mg) Compared to a Single 0.6 mg Dose of DDAVP® Tablets (3 x 0.2 mg) in Healthy Male and Female Subjects"

The analytical portion (radioimmunoassay) of Study FE992026 CS28 was conducted at . Audit of the clinical portion of Study FE992026 CS28 was not requested.

Following the inspection at (3/3-6/08), Form FDA-483 was issued (attachment 1). Our evaluation of the significant findings is as follows:

**Findings at [redacted]**

**1. The firm failed to maintain clear and adequate documentation for the following:**

**a. Verification that assay buffer, antibody, and the monoiodinated tracer ($^{125}$I-DDAVP) were added to dried extracts per the firm's method operating procedure**
**b. The actual incubation time of the reconstituted extracts with the antibody and tracer**
**c. The biological matrix used for subject sample dilutions**
**d. Storage conditions for the charcoal plasma suspension and assay buffer solution used during the study.**

Although the firm stated during the inspection that the method operating procedure (QA199, Final E02, "Quantitative Determination of Desmopressin in Human Plasma") was followed, their was no documentation verifying critical steps performed for the radioimmunoassay (see 1(a) and 1(b)).

$K_3$EDTA human plasma was used during pre-study validation of dilution integrity. However, the firm did not document the actual matrix used during the study when diluting subject samples.

Per the method operating procedure, the charcoal plasma suspension and assay buffer solution were to be stored at 5°C ± 3°C. However, the firm did not document the storage location of either reagent.

Although the firm needs to improve their documentation practices, the above findings should not impact study outcome. Calibrators and QCs processed with the subject samples suggest adequate sample processing, and less than 0.5% of study samples required dilution.

During the inspection, the firm's management promised to implement corrective actions.

**2. The firm failed to verify that samples were loaded on the gamma counter according to the sample analysis sequence file for all runs.**

For subjects 78 and 79, P1, 30 min samples (see attachment 2), the firm could not explain the aberrant values. Since the firm did not conduct sample sequence verification, a switching of samples could not be ruled out.

The firm needs to improve their documentation practices. During the inspection, the firm's management promised to implement corrective actions.

**Conclusion:**

Following our evaluation of the inspectional findings, DSI finds the accuracy of data from subjects 78 and 79 to be questionable, in light of the anomalous results for subjects 78 and 79 and the lack of investigation and sample sequence verification. The review division should consider this issue in their review.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

John A. Kadavil, Ph.D.

**Final Classification:**

**- VAI**

cc:
OC DSI/RF
OC/Vaccari
OC DSI GLPBB/Kadavil/Himaya/CF
OND ODEII DMEP/Johnson (via DFS)
OTS OCP DCP2/Khurana (via DFS)
HFR-PA1530/Shrifter
Draft: JAK 3/14/08
Edits: JAO 3/14/08; MKY 3/17/08
DSI: 5824; O:\BE\eircover\21795b_fer.des.doc
FACTS: 914724

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**FOOD AND DRUG ADMINISTRATION**

| DISTRICT OFFICE ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| **1431 Harbor Bay Parkway**<br>**Alameda, CA 94502**<br>**(510) 337-6700** | **03 - 06 Mar 2008**<br>FEI NUMBER |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

**TO:**

| FIRM NAME | STREET ADDRESS |
|---|---|
| CITY, STATE AND ZIP CODE | TYPE OF ESTABLISHMENT INSPECTED<br>**Bioanalytical Laboratory** |

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVES DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT, CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVES DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

In regards to the QA 504 study entitled: "An Open-Labeled, Randomized, Two-sequence, Two-treatments Cross-over Study Determining the Relative Bioavailability of a Single 0.6 mg Dose of MINIRIN® Tablets (3 x 0.2 mg) Compared to a Single 0.6 mg Dose of DDAVP® Tablets (3 x 0.2 mg) in Healthy Male and Female Subjects", Study number: FE992026 CS28, NDA 21-795, Sponsor: Ferring Pharmaceuticals:

1) Failure to maintain clear and adequate documentation for the following:
   a) Verification that assay buffer, antibody, and the monoiodinated tracer ($^{125}$I-DDAVP) were added to dried extracts in accordance with the method operating procedure QA199, Final E02, "Quantitative Determination of Desmopressin in Human Plasma",
   b) The actual incubation time of the reconstituted extract with the antibody and tracer,
   c) The biological matrix used for the subject sample dilutions. For validation of dilutional integrity, $K_3$EDTA human plasma (from pooled plasma) was used,
   d) Storage conditions for the charcoal plasma suspension and the assay buffer solution which were used during the study.

2) Failure to verify that samples were loaded on the gamma counter according to the sample analysis sequence file for all runs.

| SEE REVERSE OF THIS PAGE | EMPLOYEE(S) SIGNATURE | EMPLOYEE(S) NAME AND TITLE *(Print or Type)* | DATE ISSUED |
|---|---|---|---|
| | | **Jeffrey W. Shrifter, C.S.O.**<br>**John A. Kadavil, Pharmacologist** | **06 Mar 2008** |

FORM FDA 483 (4/97) PREVIOUS EDITION OBSOLETE INSPECTIONAL OBSERVATIONS PAGE 1 OF 1 PAGE

Results Desmopressin [pg/mL]

| | Subject 78 | | Subject 79 | |
|---|---|---|---|---|
| Time point | Period 1 | Period 2 | Period 1 | Period 2 |
| Predose | | | | |
| 15 min | | | | |
| 30 min | | | | |
| 45 min | | | | |
| 1h | | | | |
| 1h15min | | | | |
| 1h30min | | | | |
| 2h | | | | |
| 3h | | | | |
| 4h | | | | |
| 5h | | | | |
| 6h | | | | |
| 8h | | | | |
| 10h | | | | |
| 12h | | | | |
| 14h | | | | |

bold: LFU; samples not interchanged at AAI, Neu-Ulm

| | Subject 80 | |
|---|---|---|
| Time point | Period 1 | Period 2 |
| Predose | | |
| 15 min | | |
| 30 min | | |
| 45 min | | |
| 1h | | |
| 1h15min | | |
| 1h30min | | |
| 2h | | |
| 3h | | |
| 4h | | |
| 5h | | |
| 6h | | |
| 8h | | |
| 10h | | |
| 12h | | |
| 14h | | |

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

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/s/
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Manoj Khurana
3/26/2008 11:09:28 AM
BIOPHARMACEUTICS

Sally Choe
3/26/2008 02:50:11 PM
BIOPHARMACEUTICS