Medical Officer Review
of Minirin complete response to AE letter

NDA#: 21-795/S-000
Sponsor: Ferring Pharmaceuticals Inc.
Drug Product: Minirin® (desmopressin acetate)
Dosage Strength: 0.1 and 0.2mg tablets

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Background

Minirin tablets (NDA 21-795) contain desmopressin acetate, the same vasopressin analogue, currently marketed in DDAVP tablets (NDA 19-955). The original Minirin submission included a bioequivalence study comparing Minirin tablets to DDAVP tablets seeking the indications currently approved for DDAVP e.g. use in the treatment of central diabetes insipidus (DI) and the treatment of children 6 years of age and older with primary nocturnal enuresis (PNE). In addition, new clinical studies were included seeking the following new indications:

- Use of Minirin tablets (0.6mg) for renal concentration capacity testing (RCCT) in children ----------, and
- Management of PNE in adults ---------- ----------.

In a letter from the Agency finalized 21 Apr-2006, the sponsor was given an approvable (AE) indication because of unacceptable quality control performance associated with the

bioequivalence PK study (FE992026 CS025). The sponsor has now submitted a new bioequivalence study FE992026 CS028, "An Open-labeled, Randomized, Two-Sequence, Two-treatments Cross-over Study Determining the Relative Bioavailability of a Single 0.6mg Dose of DDAVP Tablets (3 X 0.2mg) compared to a single 0.6mg Dose of DDAVP Tablets in Healthy Male and Female Subjects." and Periodic Safety Updates covering the periods from June 2006 through June 2007, as a complete response to the Agency's AE letter.

Sources of Clinical Data

The complete response to the AE letter was included in 11 volumes in the Sept. 24, 2007 paper submission.

- Volume 1 contained the index and Clinical Study Report for FE992026 CS028, "An Open-labeled, Randomized, Two-sequence, Two-treatments, Cross-over Study Determining the Relative Bioavailability of a single 0.6mg Dose of DDAVP Tablets (3 X 0.2mg) compared to a Single 0.6mg Dose of DDAVP Tablets (3 X 0.2mg) in Healthy Male and Female Subjects."
- Volume 9 contained the Periodic Safety Report covering the period between June 7, 2006 and Dec. 6, 2006.
- Volume 10 contained the Periodic Safety Report covering the period between Dec. 7, 2006 and June 6, 2007.
- Volume 11 had foreign labeling for Minirin Tablets.

The Feb. 26, 2008 paper submission contained Financial Disclosure information for study FE992026 CS028.

There were two electronic submissions

- the 2007-9-24 submission contained raw PK data from study FE992026 CS028 in Excel spread sheets
- the 2007-11-01 submission contained revised label information

Clinical Review of FE992026 CS028

"An Open-labeled, Randomized, Two-sequence, Two-treatments, Cross-over Study Determining the Relative Bioavailability of a single 0.6mg Dose of DDAVP Tablets (3 X 0.2mg) compared to a Single 0.6mg Dose of DDAVP Tablets (3 X 0.2mg) in Healthy Male and Female Subjects."

OBJECTIVES OF STUDY

To assess the bioequivalence of a single oral dose of MINIRIN tablets (0.6mg) to DDAVP tablets (0.6mg) in healthy volunteers under fasting conditions.

EXPERIMENTAL DESIGN

STUDY DESIGN

This is an open-label, single-center, randomized, single-dose, two-period, cross-over, bioequivalence study comparing MINIRIN (3 x 0.2mg tablets) to DDAVP (3 x 0.2mg tablets) under fasting conditions. Subjects were randomized to treatment sequence. Dosing periods were separated by a washout period of three to seven days.

Table 1 Study Design

	Screening 2 to 21 days before dosing	**Period 1**	**Washout 3-7 days**	**Period 2**
Sequence 1		MINIRIN		DDVAP
Sequence 2		DDAVP		MINIRIN

INCLUSION CRITERIA

- male or female Caucasians age 18 to 55
- BMI 18 to 30 kg/m^2

EXCLUSION CRITERIA

- history of serious clinical illness, mental illness or allergic reactions to related drugs
- abnormal physical examination, vital signs, ECG or lab screening tests
- hepatitis C antibody, hepatitis B surface antigen or HIV positive
- history of caffeine, alcohol or drug abuse
- pregnancy or breast-feeding
- smoking more than 5 cigarettes per day (subjects had to be willing to abstain from smoking during the residential session of the trial)
- use of prescription drugs or over the counter drugs within 14 days or 5 half lives of the study

TREATMENT

Subjects were admitted to a single center, Phase I Clinic in ------ ------ ----- , on the evening before study dosing. A randomized single dose of MINRIN (3 x 0.2mg tablets) or DDAVP (3 x 0.2mg tablets) was administered with 240mL of water in Period 1 after a 10 hour overnight fast. Blood samples were taken predose and at 15, 30, 45, 60, 75, 90min and 2, 3, 4, 5, 6, 8, 10, 12 and 14 hours post dose. Subjects were discharged at 30 to 36 hours post dose and readmitted 3-7 days later to receive the alternative study medication in Period 2.

STUDY RESULTS

PATIENT POPULATION

A total of 47 males (64%), 27 females (36%) and one patient with missing demographic information received at least one dose of the study medication. Only two of the 75 subjects did not complete both study periods. The age range of the healthy volunteers was between 18 and 53yrs with a mean of 26.3yrs (SD 7.4yrs). Their weight ranged between 49.4 and 104kg with a mean of 77.8kg (SD 12.3kg). BMI was between 18.1 and 30.0 with a mean of 25.7 (SD 3.0).

PHARMACOKINETIC RESULTS

The bioequivalence data was based on 69 subjects who completed the study and for whom there was adequate data to perform a PK analysis for both treatment periods. Both AUC and AUCt were within the 90% confidence interval of 80.00 to 125.00. However, the Cmax just missed the lower bound at 79.8 (see Table 2 & Table 3).

Table 2

MINIRIN 90% Confidence Intervals (Table 9-1, Vol. 1 Clinical Study Report)

	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

Source: EOT-Table 8

Table 3

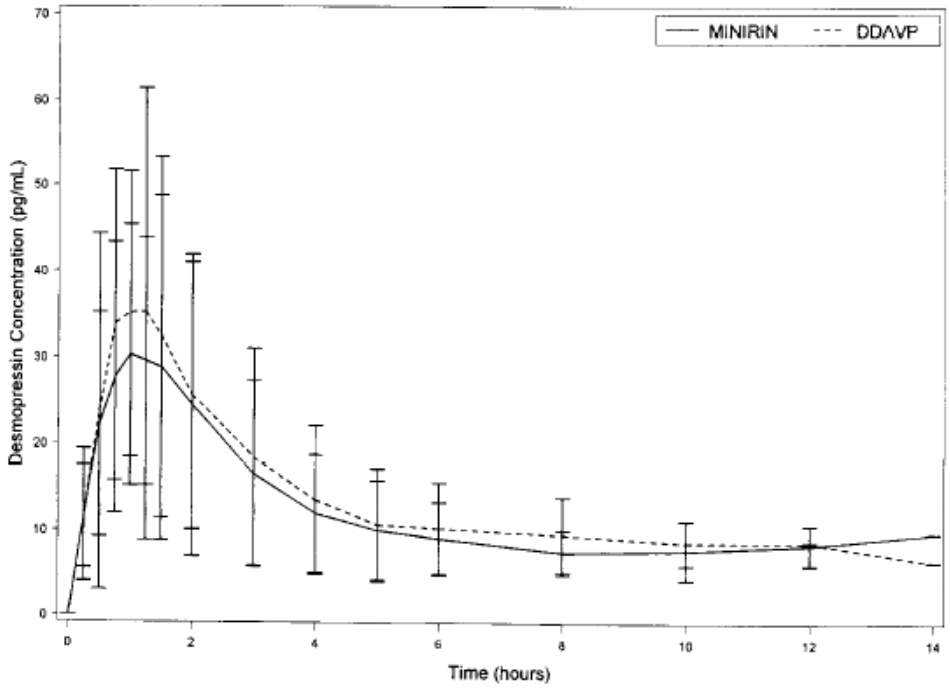
Summary Primary Endpoint PK Data

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%

Source: EOT-Table 7

Figure 1

MINIRIN and DDAVP Mean Concentration Profiles
(Error Bars-standard deviation, Source Fig. 9-1 Clinical Study Report, Vol. 1)



Source: EOT-Figure 2

Medical officer's comment-
Hammer and Vilhardt[1] examined the pharmacodynamic effect of desmopressin in nine patients with diabetes insipidus and found the maximal effect on water permeability on the collecting ducts was reached at 4 to 5pg/mL. Similar results were reported by Callreus et al.[2] in healthy male subjects (e.g. IC 50 = 3.7 ± 1.2pg/mL). Fig. 1 shows that both formulations resulted in serum desmopressin levels above 5pg/mL for almost the entire 14 hours following dosing. Therefore, the minor difference in Cmax between the two formulations should not impact on clinical efficacy which should correlate best with AUC.

1 **Hammer M**, **Vilhardt H**. Peroral treatment of diabetes insipidus with a polypeptide hormone analog, desmopressin. J Pharmacol Exp Ther. 1985 Sep;234(3):754-60
2 **Callréus T**, **Odeberg J**, **Lundin S**, **Höglund P**. Indirect-response modeling of desmopressin at different levels of hydration. J Pharmacokinet Biopharm. 1999 Oct;27(5):513-29.

The data in Table 4 show that the mean times to maximal serum concentration and terminal half lives for desmopressin were also similar for the Minirin and DDAVP tablets.

Table 4

Summary of Secondary Endpoint PK Data

	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%
λ_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%

Source: EOT-Table 7

EFFICACY EVALUATION

No formal analysis of urine output (e.g. wet nights/wk or urine osmolality) was performed in this single dose study.

SAFETY EVALUATION

There were no deaths, no moderate, severe or serious AEs reported in this trial. No subjects withdrew from the study because of a treatment related AE. Five subjects (7%) in the Minirin treatment group and 7 subjects (9%) in the DDAVP treatment group experienced treatment emergent AEs, all of which were gastrointestinal disorders (e.g. abdominal discomfort, emesis, nausea and cramps). In addition, two subjects (3%) in each group had headaches which were considered unrelated to treatment. There were no new safety concerns identified with Minirin tablets in this PK study.

Periodic Safety Updates-

June 7, 2006 to Dec. 6, 2006; Dec. 7, 2006 to June 6, 2007

Minirin is currently approved in 96 countries for the following indications: central DI, RCCT, and PNE. A total of 52 serious and 50 non-serious but unlisted case reports were included in these two submissions. These reports included safety information on all available formulations of desmopressin (e.g. tablet, melt, intranasal and injection).

There were two deaths reported. One was a 47 y/o female who had worsening of her TTP in connection with administration of desmopressin for central DI. One was a 39 y/o female s/p hypophysectomy on desmopressin for central DI who developed hyponatremia secondary to gastroenteritis and then suffered CNS decompensation following too rapid correction of her hyponatremia.

The most common events reported in children were drug ineffective (20 cases) and abdominal pain (10 cases). The most common events reported in the elderly were hyponatremia (12 cases) and headache (4 cases).

Since its approval through Jun 2007 there have been a total of 560 cases of hyponatremia, 63% due to the intranasal formulation, 15% due to the tablet and 12% to the injection. The intranasal formulation accounts for 74% of cases associated with seizure, 70% of cases associated with coma and 77% of cases associated with both seizure and coma. As a result of the excessive number of serious cases of hyponatremia with the nasal formulation the sponsor in conjunction with the EMEA removed the PNE indication from the nasal formulation in countries where an oral alternative (e.g. tablet or melt formulation) was available. In countries where only a nasal formulation was available the sponsor revised the dosing recommendation to include a lower start dose and lower maximum dosage. New labeling about the risk of hyponatremia was also incorporated into the PI for DDAVP tablets in the US, and it is recommended by this medical reviewer that similar language be inserted into the Minirin PI submitted by the sponsor.

New language stating “very rare cases of emotional disorders including aggression in children have been reported” has been added in the UK in response to a request from the UK health authorities to the sponsor to perform a cumulative review of the world wide safety data concerning desmopressin and aggression. The review identified 50 reports worldwide up to Oct. 2006 of cases of aggression, anger, emotional disorder, emotional distress, hostility mood altered and mood swings, with 43 of these events reported in children. It is this medical officer’s recommendation that there is insufficient information at this time to warrant new labeling in the US PI, as pediatric patients with emotional disturbances are more likely to present with bedwetting issues and frustration with an inability to control bedwetting in and of itself could lead to aggressiveness and emotional issues unrelated to the study medication.

In summary, the overall pattern of AEs was similar to what had been previously reported for desmopressin. Labeling changes have recently been approved to remove the PNE

indication from the nasal formulation and to decrease the starting and maximal dosage of the nasal formulation.

PK STUDY CONCLUSIONS

- Both AUC and AUCt were within the 90% confidence interval of 80.00 to 125.00, for Minirin and DDAVP tablets. The Cmax for Minirin just missed the lower bound at 79.8, so technically the Minirin and DDAVP tablets are not bioequivalent. However, since the pharmacodynamic effect of desmopressin is most closely linked to AUC, it is this medical officer's conclusion the there is no clinical impact from this small difference in Cmax and that the two drugs are clinically equivalent.
- It is this medical officer's opinion that there is not enough evidence to prove that the small number of cases of aggression reported in children taking desmopressin in the UK are drug related. These cases may simply represent part of the normal patient profile of pediatric patients with PNE. Therefore, there were no new safety concerns identified with Minirin and DDAVP tablets in the PK study reviewed in this submission or in the other recent studies summarized in the latest two SURs that should be included in the PI.
- Postmarketing reports of an increased risk of hyponatremia associated with nasal formulations of desmopressin have resulted in the removal of the PNE indication from DDAVP nasal spray/rhinal tube and the addition of new safety information to the PI for DDAVP tablets. It is recommended by this medical officer that this new safety information also be included in the Minirin tablet PI.

Other Discipline Review Issues

The clinical biopharmacokinetics review was performed by Dr. Manoj Khurana.
Dr. Khurana confirmed that the data on three subjects (e.g. 013, 040 and 071), which were excluded from the PK dataset in the sponsor's analysis because they did not include data for both treatment periods, did not significantly alter the study results.

Other Administrative Issues

Audits

During the original inspection at the sponsor's central facility in Germany the Division of Scientific Investigations (DSI) found the bioanalytical assay runs to be unacceptable requiring the sponsor to perform a new trial (e.g. FE992026 CS028) with new assays. The DSI inspection of study CS028 identified that the data from subjects 78 (Period 1) and 79 (Period 1) were questionable due to anomalous results and lack of sample sequence verification. Dr. Khurana, reanalyzed the data excluding these subjects and

found no significant affect on the PK results. Therefore, there is sufficient verifiable data in this current submission to support approval.

Financial Disclosure

The sponsor provided a signed form FDA 3454 certifying that no financial arrangements or interests were held by Dr. ---------- - the only clinical investigator for the single study site used for the current study, CS028, reported in this resubmission. Therefore, it appears unlikely that the study results were biased due to financial arrangements.

Pediatric Requirements

The sponsor is looking for a ----- indication, RCCT in children ----------, and is looking to extend the age range for patients with PNE to adults ---- - --- ----- Therefore, these two indications need to address pediatric requirements for labeling.

Pediatric studies were performed for RCCT in patients 3 to 18 years of age. The sponsor is seeking a waiver request for children under 3 years of age. While, there is literature[3] to support the use of the nasal spray/rhinal tube nasal formulations in infants (10µg) and older children (20µg) under 3 years of age neither of the sponsor's who currently market these formulations are interested in seeking an indication to treat RCCT, most likely because of the small patient population for this indication. A nasal formulation of desmopressin (e.g. Concentraid) was originally approved for RCCT in children 1 to 12 years of age but was discontinued because of financial considerations. After review with the PERC committee it was determined that it is acceptable to grant a pediatric waiver in this population as there are too few patients under age 3 who would require RCCT to require that the sponsor develop a new formulation to treat this population.

Nighttime enuresis is normal in infants and decreases with age, so that by age 5 about 15% of children are still affected. Of these, about half (7%) will improve spontaneously by age 8, so pediatricians typically do not recommend treatment with medication until about age 8 even thought the diagnosis of PNE can be made at age 5-6. Desmopressin tablets are currently approved for the treat of children age 6 and older with PNE. Pediatric studies were performed in adolescents aged 12 to 18 with Minirin Tablets, and a bridging study with Minirin and DDAVP® Tablets was used to support the safe use in children 6 to 12. Since the diagnosis of PNE does not exist below age 6 there is no need for the sponsor to do studies in this age group and the sponsor can receive a waiver for additional pediatric studies for this indication.

Tradename

The Division of Medication Errors and Technical Support (DMETS), continues to object to the use of the name Minirin for the tablet formulation, even though the Minirin trade

3 **Monnens L**, **Smulders Y**, **van Lier H**, **de Boo T**. DDAVP test for assessment of renal concentrating capacity in infants and children.. Nephron. 1981;29(3-4):151-4

name is approved for the nasal spray formulation. This medical officer's review of the DMETS consult found the following names to be potentially confused for MINIRIN: MINERIN, MINITRAN, MILRINONE, MIDRIN, MINOCIN and MINIPRESS. However, these products, are not available as tablets, e.g. MINERIN is an OTC cream for dry skin, MINITRAN is a transdermal patch, MILRINONE is an IV infusion, & MIDRIN, MINOCIN and MINIPRESS are capsules, which makes the likelihood of name confusion less likely. The potential doses of the capsules for Minocin (50, 75 and 100mg) and Midrin (65/100/325mg for the three capsule components) are different enough that they are not likely to be confused with the Minirin doses of 0.1 and 0.2 mg. Only the doses of the Minipress capsules (1 and 2 mg) could potentially be confusing. Therefore, it is this medical reviewer's opinion that the risk for name confusion between MINIRIN and other marketed products is low and the sponsor can use the same name which is already marketed as a nasal spray.

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Summary/Conclusion

The PK data from study FE992026 CS028 support the clinical equivalence between Minirin and DDAVP tablets. This application is acceptable, assuming the sponsor and the Agency can agree to the proposed labeling changes.

Recommendations

1. Approval (AP) for "Use of Minirin Tablets for renal concentration capacity testing in pediatric patients 3 to 18 years of age."

2. Nonapproval (NA) for [redacted] "

3. Approval (AP) for "Management of primary nocturnal enuresis in adults [redacted]

Comments to be conveyed in action letter

[redacted]

References

1 Hammer M, Vilhardt H. Peroral treatment of diabetes insipidus with a polypeptide hormone analog, desmopressin. J Pharmacol Exp Ther. 1985 Sep; 234(3):754-60

2 Callréus T, Odeberg J, Lundin S, Höglund P. Indirect-response modeling of desmopressin at different levels of hydration. J Pharmacokinet Biopharm. 1999 Oct; 27(5):513-29.

3 Monnens L, Smulders Y, van Lier H, de Boo T. DDAVP test for assessment of renal concentrating capacity in infants and children.. Nephron. 1981; 29(3-4):151-4

4 Koskimies O, Pylkkänen J, Vilska J. Water intoxication in infants caused by the urine concentration test with vasopressin analogue (DDAVP). Acta Paediatr Scand 1984; 73:131-2

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