

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-795

MEDICAL REVIEW(S)

**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 _____

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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

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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/m²

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 Morrisville, NC, 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 AUC_t were within the 90% confidence interval of 80.00 to 125.00. However, the C_{max} just missed the lower bound at 79.8 (see Table 2 & Table 3).

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Table 2

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

PK parameter	MINIRIN		DDAVP		Geometric Mean Ratio, %	90% CI
	N	Geometric Mean	N	Geometric Mean		
AUC (pg-hr/mL)	69	104	69	114	90.9	93.0 - 99.5
AUC ₁ (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

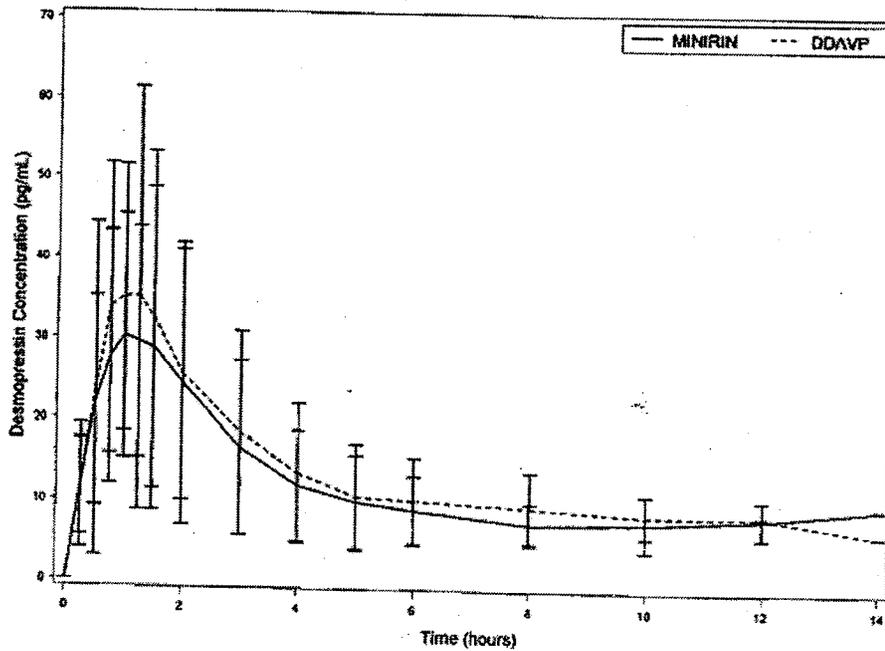
Pharmacokinetic Parameter	MINIRIN (N=69)	DDAVP (N=69)
AUC (hr-pg/mL)		
Mean (SD)	116 (63.2)	132 (83.1)
Median	99.6	104
Range	37.3-454	41.6-529
Geometric mean	104	114
CV%	54.6%	63.1%
AUC ₁ (hr-pg/mL)		
Mean (SD)	98.7 (63.6)	114 (77.1)
Median	76.4	88.7
Range	24.6-439	38.2-486
Geometric mean	85.2	95.9
CV%	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

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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 Vilhardt¹ 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 C_{max} between the two formulations should not impact on clinical efficacy which should correlate best with AUC.

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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 Callreus T, Odeberg J, Lundin S, Höglund P. Indirect-response modeling of desmopressin at different levels of hydration. J Pharmacokinetics 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%
$t_{1/2}$ (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 AUC_t were within the 90% confidence interval of 80.00 to 125.00, for Minirin and DDAVP tablets. The C_{max} 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 that there is no clinical impact from this small difference in C_{max} 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 _____ 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.

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Pediatric Requirements

The sponsor is looking for a new 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.

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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 literature³ 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 though 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

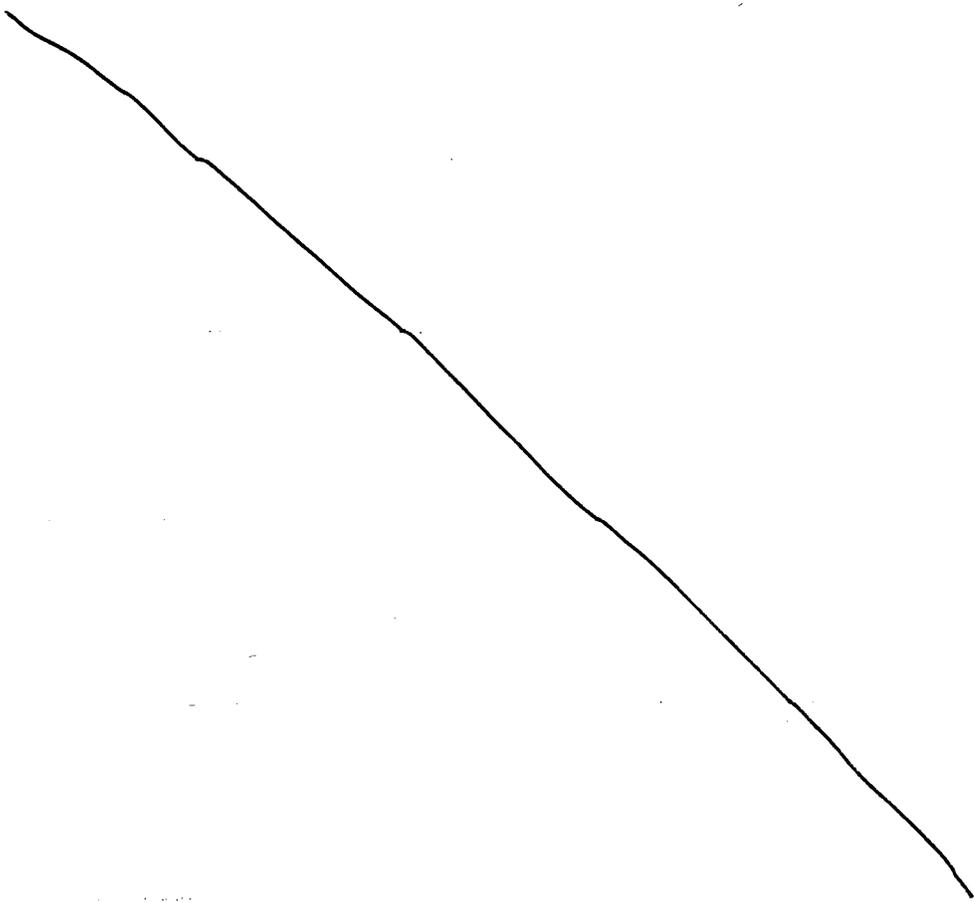
The Division of Medication Errors and Technical Support (DMETS), continues to object to the use of the name Minirin for the tablet formulation, even though the Minirin trade

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.

Labeling

The proposed label is identical to the current label for DDAVP except for the following changes:



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 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Withheld Track Number: Medical- 1

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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 _____

b(4)

3. Approval (AP) for "Management of primary nocturnal enuresis in adults _____"

b(4)

Comments to be conveyed in action letter

b(4)

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

REVIEWED BY:

William Lubas, MD-PhD
FDA/CDER/ORM/ODEII/DMEP
Medical Officer

3/20/2008

Theresa Kehoe, MD
FDA/CDER/ORM/ODEII/DMEP
Medical Team Leader

3/20/2008

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/s/

William Lubas
3/20/2008 03:26:16 PM
MEDICAL OFFICER

Theresa Kehoe
3/20/2008 04:00:19 PM
MEDICAL OFFICER

MEDICAL TEAM LEADER MEMO TO THE FILE

NDA	21-795
Drug name	Minirin® (desmopressin acetate) vasopressin analogue
Applicant	Ferring Pharmaceuticals, Inc.
Indication	<ol style="list-style-type: none"> 1. for single dose use in performing a renal concentration capacity test (RCCT) 2. to treat <u>primary nocturnal enuresis (PNE)</u> in adults

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Background

This new drug application (NDA) is for a synthetic analogue of the neurohormone, vasopressin. Vasopressin is a hypothalamic neuropeptide that is synthesized in the paraventricular and supraoptic nuclei of the hypothalamus and stored in the posterior pituitary where it is released in response to osmotic and non-osmotic stimuli. Vasopressin functions as an antidiuretic hormone (ADH) at physiologic plasma concentrations; vasoconstrictive activity occurs only at higher plasma levels. Release of vasopressin in response to increasing plasma osmolality occurs via stimulation of neurons located in the anterior hypothalamus.

Vasopressin analogues available in the United States include DDAVP tablets, nasal spray, and injections, Minirin nasal spray, and Stimate nasal spray. Save the DDAVP injections, these products are indicated for the treatment of central diabetes insipidus and primary nocturnal enuresis (PNE) in children.

The applicant has submitted a 505(b)(2) application for Minirin® (desmopressin acetate) relying on the Agency's finding of safety and effectiveness for DDAVP tablets (NDA 19-995) via a bioequivalence study to allow "bridging" between the two drug products and to receive an indication for the treatment of central diabetes insipidus and PNE in children ages 6 yrs and older. In addition, clinical studies were conducted with the Minirin tablets to support and indication for single dose use in renal concentration capacity testing (RCCT) and for the treatment of PNE in adults. None of the currently marketed vasopressin analogues has an indication for RCCT; however, Concentraid®, which was approved under NDA 19-776 and has been withdrawn from the market, had an indication for RCCT.

Clinical Studies**Bioequivalence Study**

A BE study was conducted comparing a single dose of Minirin 0.2 mg tablet to DDAVP 0.2 mg tablet in 60 healthy male and female volunteers between the ages of 18 and 55 yrs. This study was reviewed by Dr. Sang Chung from the Office of Clinical Pharmacology and Biopharmaceutics. From his review, bioequivalence was established between the two products with respect to AUC and Cmax (see Table below).

Table 1 Summary of statistical analysis for the BE study (n=60)

Parameter	Geometric Mean (CV%)		Minirin vs. DDAVP
	Minirin	DDAVP	Point estimate (90% CI)
AUC (pg hr / ml)	41.52 (57%)	39.56 (51%)	1.07 (0.97-1.18)
AUCt (pg hr /ml)	36.96 (64%)	34.94 (56%)	1.09 (0.98-1.20)
Cmax (pg/ml)	10.67 (50%)	10.54 (46%)	1.03 (0.95-1.13)

These results, in themselves, would allow Minirin® to be approved for the same indications not protected by exclusivity in the DDAVP label. These indications include treatment of children and adults with central diabetes insipidus and treatment of children 6 years of age and older with primary nocturnal enuresis. However, a DSI audit of this study revealed that the quality control performance was not acceptable as discussed in a memo written by Dr. Sriram Subramaniam dated December 5, 2005. These findings therefore prohibit the division from relying on the data in NDA 19-995, including any non-clinical data, for the approval of Minirin® under a 505(b)(2) application. This application is approvable based on these findings.

Clinical Efficacy Studies

The applicant also conducted clinical studies for Minirin® in the treatment of PNE in adults (ages 18 to 46 yrs) and for RCCT in children. Dr. William Lubas has summarized in his medical review the designs and conduct of these studies and their results. This memo will defer the discussion and conclusions on clinical efficacy and safety until a response to an approvable letter is received.

Labeling

Drs. Sang and Lubas have each included labeling comments in their reviews. These comments will not be conveyed to the applicant in the approvable letter but will be revisited after a response to the action letter has been received.

Regulatory/Legal Issues

CDER policy requires all 505(b)(2) applications to be reviewed by selected team members of OND and the Office of Regulatory Policy and Office of Chief Counsel. During their joint review of this submission, it was noted that the applicant referenced findings of safety and effectiveness for DDAVP tablets (NDA 19-995) and Concentraid® intranasal solution (NDA 19-776). Concentraid was withdrawn from US markets; however, the reasons for this decision have not been made public. Since it is not known whether the drug was withdrawn due to reasons of safety or efficacy, the Agency cannot reference any data from NDA 19-776 to approve NDA 21-795. Dr. Lubas has stated in his review that data from NDA 19-776 were not required to support an approval for Minirin tablets (see Section 4.3 of primary review).

Recommendations

At present, a final decision from the Office of Chief Counsel and Office of Regulatory Policy regarding the approvability of this application based on reference data has not been determined. However, given the deficiency with the BE study, the review division is recommending an approvable (AE) action with the applicant required to conduct another BE study or re-run the stored samples from the previously conducted BE study with an acceptable quality control performance.

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/s/

Mary Parks
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MEDICAL OFFICER

CLINICAL REVIEW

Application Type NDA 21-795
Submission Number 000
Submission Code N

Letter Date March 2, 2005
Stamp Date March 4, 2005
PDUFA Goal Date January 4, 2006

Reviewer Name William Lubas MD-PhD
Review Completion Date December 8, 2005

Established Name desmopressin acetate
(Proposed) Trade Name Minirin®
Therapeutic Class vasopressin analogue
Applicant Ferring Pharmaceuticals Inc.

Priority Designation S

Formulation Oral tablet

(1) Dosing Regimen single dose of 0.6mg
Indication To determine the capacity of
the kidney to concentrate urine
Intended Population Children — with
suspected renal disease

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(2) Dosing Regimen initial dose of 0.2mg at bedtime,
titrate up to 0.6mg to achieve
desired effect

Indication Management of primary nocturnal
enuresis in adults _____

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Intended Population Children > 6 and adults _____
_____ with primary nocturnal
enuresis

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APPEARS THIS WAY ON ORIGINAL

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Approvable.

It is recommended that the quality control issues in bioequivalence study FE992026 CS025 be resolved as described in the PK review before these data can be used to support the 505(b)(2) part of this application.

It is recommended that Minirin tablets (0.6mg dose as a single dose) be approved for renal concentration capacity testing (RCCT) in children 3 to 18 years of age.

It is recommended that Minirin tablets (0.2 to 0.6mg/day) be approved for the treatment of primary nocturnal enuresis (PNE) in adults. Approval of children 6 to 17 years of age is dependant on validation of the data from bioequivalence study FE992026 CS025.

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1.2 Recommendation on Postmarketing Action

None.

1.2.1 Risk Management Activity

Not applicable.

1.2.2 Required Phase 4 Commitments

None.

1.2.3 Other Phase 4 Requests

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1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This NDA submission for Minirin tablets (NDA 21-795) containing desmopressin acetate, a vasopressin analogue, references data from Concentraid (NDA 19-776) an intranasal solution of desmopressin acetate originally approved for renal concentration capacity testing (RCCT) and DDAVP nasal spray, injection and tablets (NDA19-995) approved for treatment of children and adults with central diabetes insipidus and for treatment of children 6 years of age and older with primary nocturnal enuresis (PNE). The clinical program was designed to include the following two new indications to the currently approved indications:

- Use of Minirin tablets (0.6mg) for RCCT in children _____ and
- Management of PNE in adults: _____

Only these new indications will be covered in this review.

The RCCT indication included 3 clinical trials, two open-label trials and one pivotal, double-blind, randomized trial comparing tablet and nasal formulations in nighttime RCCT testing in children between 3 and 18 years of age. Literature citations were included to describe use in infants and children under 3 years of age and in adults up to 75 years of age.

The PNE indication included 5 clinical trials, four open-label trials and one pivotal, double-blind, randomized trial comparing two doses of the tablet formulation (0.2 and 0.4mg/day) in children 12 years of age and older and in adults up to 45 years of age. The pivotal study was designed to look at patients who were responders to nasal spray treatment to see if treatment with Minirin tablets could reduce the number of wet nights per week during 4 weeks of active treatment compared to the baseline observation period. Literature citations were included to describe use in children 7 years of age and older, and use in adults _____

1.3.2 Efficacy

RCCT

In clinical study 45A03-008, Minirin tablets (0.6mg) as a single nighttime dose were not inferior, using a predetermined 7% margin of error, to intranasal Minirin (20µg) in children between 3 and 18 years of age. However, intranasal Minirin (20µg) was statistically superior to Minirin tablets (0.6mg) in terms of increasing urine osmolality. It is not clear if this difference in urine osmolality observed between the Minirin tablet (0.6mg) and the nasal spray (20µg) is of clinical significance.

While there are references that support the use of nasal spray desmopressin in infants up to and including children 3 years of age, the dosing ranged from 10 to 20µg in these studies, and there is not enough information about the relative bioavailability of Minirin tablets in such young patients to recommend use of the 0.6mg dose used in clinical study 45A03-008. In addition, this medical reviewer is concerned about the feasibility of giving three 0.2mg tablets, 8mm in diameter, to infants and young children, because the current study protocol does not permit

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b(4)

crushing of the tablets. Therefore, use in children under 3 years of age is not supported by the current data.

b(4)

PNE

Minirin tablets (0.2 and 0.4mg/day) produced statistically significant reduction in the number of wet nights per week relative to baseline in children 11 years of age and older and in adults up to 45 years of age (Study 45A06-53). There was no statistically significant difference in the efficacy between the two tablet doses though there was a trend in favor of greater efficacy with the higher dose (0.4mg/day). The 0.6mg/day dose was not tested in the double-blind randomized phase of this study, but the sponsor plans to recommend titration up to 0.6mg/day in patients who do not achieve the desired response. Only 13 out of the 95 patients in the PNE safety database were treated with the 0.6mg/day dose suggesting that only a small percentage of patients may require this higher dose (13/95=14%).

The use of Minirin tablets (0.2 to 0.6mg/day) in children 6 to 11 years of age relies on clinical efficacy data submitted under NDA 19-955 (Aventis) for DDAVP tablets.

1.3.3 Safety

RCCT

A total of 204 patients between 3 and 18 years of age were evaluated in the RCCT safety database. There were no serious adverse events associated with the use of Minirin (0.6mg) in these clinical trials. The most common adverse event was vomiting seen in 3% of patients. All other adverse events occurred in less than 2% of the study population.

Literature reports describe three case reports of hyponatremic seizures in infants 1 to 13 months of age treated with nasal DDAVP during RCCT. These occurred in an outpatient setting where parents may have over fed infants to try to increase their urine output to get an adequate urine sample for the testing. Therefore, fluid restriction and extra care is recommended in treating young infants in the DDAVP label. This information will also be included in the WARNINGS section of the Minirin label.

The original protocol recommended that the tablet may be divided into pieces but was not to be crushed prior to ingestion. This could cause a problem with the use of this medication in younger children who cannot swallow tablets. In a response to this concern, the sponsor identified a

recent reference¹ that found crushed and chewed tablets were bioequivalent to tablets swallowed whole as measured by AUC and Cmax in adults. _____

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_____ Information describing how the tablets can be divided or crushed prior to ingestion will need to be addressed in labeling.

PNE

A total of 95 adult patients between 17 and 46 years of age were evaluated in the PNE safety database. No safety information for children enrolled in the PNE trials was submitted in the Integrated Summary of Safety (ISS) as agreed between the sponsor and the Agency at the May 2004 meeting. Desmopressin tablets are already approved in children age 6 years and older (see DDAVP label), and the sponsor is relying on the clinical study data only to support the new indication of treatment in adults. _____

b(4)

Serious adverse events were reported in 4 adult patients (4%) with the following conditions: irritable bowel syndrome, hepatic cirrhosis, urinary retention, and hypertension. Only the case of increased fluid retention and worsening hypertension in a 32 year old female was possibly related to desmopressin. There was a trend for more treatment emergent adverse events at higher doses 8/44=18% (0.2mg), 13/54=24% (0.4mg) and 4/13=31% (0.6mg), but the small number of patients especially at the highest dose affects the ability to conclude a specific dose effect from these data. The most common adverse events in patients taking Minirin tablets were headache (7%), influenza (5%) and nausea (3%). All other adverse events occurred in less than 2% of the study population.

Safety information was also supplied for treatment of nocturia in adults (NIA), which was derived from five clinical trials in the sponsor's Phase III development program. While the sponsor is not currently seeking approval for this indication, this safety analysis provides useful information about the safety risks for elderly patients treated with Minirin tablets. The adult nocturia population differs somewhat from the PNE population as they are older and more likely to have underlying disease, concurrent illness and take multiple medications. In the NIA clinical trials there were 34 cases of hyponatremia. The risk of developing hyponatremia increased with age and declining creatinine clearance/GFR. All but 3 of the 31 patients who developed clinically significant hyponatremia (<130mmol/L), were >65 years of age and all but 4 had a creatinine clearance of < 80mL/min. None of the patients was below 46 years of age. Only 3 of the cases of hyponatremia were considered serious. In the majority of cases hyponatremia occurred in the first two weeks of treatment. All patients recovered after discontinuation of the study medication. Therefore, fluid restriction and extra care is recommended in treating geriatric patients in the DDAVP label. This information will also be included in the WARNINGS section of the Minirin label.

1.3.4 Dosing Regimen and Administration

RCCT

The sponsor proposes a single 0.6mg Minirin tablet dose for all patients.

¹ Argenti et al. 2001, J Urol 165:1446-1451

PNE

The sponsor proposes a nighttime starting dose of 0.2mg in children 6 years of age and older and in adults _____ The dose may be titrated up to a maximum of 0.6mg to achieve the desired response.

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1.3.5 Drug-Drug Interactions

No drug-drug interaction studies were submitted in this submission.

No relationship between response and use of concomitant medications was observed. However, patients in several studies were excluded if they were taking the certain medications (indomethacin, tricyclic antidepressants, chlorpromazine, carbamazepine, chlorpropamide, clofibrate or diuretics) so drug effects with these medications cannot be excluded.

The last Concentraid label, before the drug was withdrawn from the market for business reasons, stated that clofibrate and indomethacin may potentiate while carbamazepine and glibenclamide may decrease its activity.

The current DDAVP label states that while pressor activity is very low compared to its antidiuretic activity, large doses of DDAVP tablets should be used with other pressor agents only with careful patient monitoring.

1.3.6 Special Populations

Pediatric and geriatric patients and patients with declining creatinine clearance/GFR should have fluid intake adjusted downward to decrease the potential of water intoxication and hyponatremia. No clinically relevant gender differences were noted in the pivotal trials. Most of the patients in the clinical trials were Caucasian (85-97%) so no meaningful analysis was possible for other racial groups.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Vasopressin, the naturally occurring antidiuretic hormone, binds to receptors in the collecting duct and distal tubules of the kidney promoting water reabsorption and binds to receptors on smooth muscle cells in arterioles leading to vasoconstriction and an increase in systemic blood pressure. Desmopressin, a synthetic analogue of vasopressin, is modified to increase and prolong the antidiuretic effect while minimizing the effect on smooth muscle vasoconstriction.

Desmopressin is available as a subcutaneous injection, nasal spray, and oral tablets. It has been approved for the following indications:

- treatment of patients with diabetes insipidus who have a deficiency of endogenous vasopressin
- measurement of the kidney's ability to concentrate urine [i.e. renal concentration capacity testing (RCCT)] for patients with suspected renal disease
- treatment of children with primary nocturnal enuresis (PNE)

2.2 Currently Available Treatment for Indications

RCCT

Severe water restriction for greater than 24 hours can be used as an alternative to desmopressin in the RCCT, but it is difficult for some patients to comply with the severe water restrictions.

Vasopressin tannate oil, which was originally used for testing, is no longer available.

PNE

Conditioning treatment with enuresis alarms can be effective as monotherapy or in conjunction with pharmacotherapy.

Tricyclic antidepressants (i.e. imipramine) are approved for the treatment of children 6 years of age and older.

Anticholinergic/antispasmodic agents (i.e. oxybutynin, tolterodine), which increase bladder capacity and diminish involuntary bladder contractions, can be used in children over 5 years of age.

2.3 Availability of Proposed Active Ingredient in the United States

DDAVP tablets containing desmopressin acetate (NDA 19-995) made by Ferring AB and marketed by Aventis Pharmaceuticals are currently available in the US.

2.4 Important Issues With Pharmacologically Related Products

None.

2.5 Presubmission Regulatory Activity

Concentraid® intranasal solution containing desmopressin acetate (NDA 19-776) made by Ferring was approved in December 1990 for RCCT and discontinued in June 2000 for business reasons. DDAVP® tablets containing desmopressin acetate (NDA 19-995) made by Ferring AB and marketed by Aventis Pharmaceuticals were approved 9/6/1995. NDA 21-795 for Minirin tablets containing desmopressin acetate was submitted as a 505(b)(2) application referencing

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data from NDAs 19-776 and 19-995 for the indications of treatment of diabetes insipidus and treatment of children over 6 years of age with primary nocturnal enuresis.

2.6 Other Relevant Background Information

None.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Minirin tablets contain desmopressin acetate as the active drug substance and the following excipients: lactose _____, povidone _____ potato starch _____ and magnesium stearate _____

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Manufacturing changes including new equipment to decrease variations in the manufacturing process and increase production capacity _____, were introduced to the method used to prepare desmopressin tablets under the Aventis NDA 19-955 and are included in this submission. A bioequivalence study was submitted to demonstrate that the Minirin tablets produced under the new method are bioequivalent to the tablets marketed by Aventis Pharmaceuticals (see section 5.1).

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Stability studies performed on drug product prepared using the Aventis manufacturing method support a shelf-life of two years at 25°C. Stability studies performed to date using Minirin tablets manufactured under the new _____ indicate no significant changes in desmopressin content, impurities or water content under accelerated conditions (40°C/75%RH) for six months and under normal conditions (25°C/60%RH) at twelve months.

b(4)

3.2 Animal Pharmacology/Toxicology

Reference is made to NDA 19-955, DDAVP tablets 0.1mg and 0.2mg (Aventis).

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The study reports were submitted in a total of 44 volumes. Volume 1 contained the proposed labeling information and summaries of the Chemistry, PK, and Clinical sections. Volumes 2 through 5 contained the Chemistry data, Volume 6 contained the PK data and Volumes 14 through 28 contained the Clinical information which was reviewed here. There were two electronic submissions:

- the 3/2/05 submission included the package insert, and clinical data from studies CS 025, 45A06_16, 45A06_53, 45A06_62, POL009, 45A06_006, 45A06_008, the RCCT ISE and the PNE ISE
- the 4/27/05 submission included samples of the Minirin bottle and carton labeling

4.2 Tables of Clinical Studies

RCCT

Clinical studies in this submission:

Study No	Study location	Study design	Study population	Treatment regimens	Treatment duration	No of subjects	Report Location Vol.	Report Location Page
45A03-008	Multicentre, Sweden	Cross-over, double-blind, randomized (latin square), double dummy.	Children with an indication for RCCT 3-18 years.	dDAVP tablets 0.6 mg dDAVP spray 20 µg Placebo	2 single doses 1 single dose 1 single dose	ITT: 145 PP: 118	14	23
45A03-006	Multicentre, Sweden	Open-label, cross-over, randomized, stratified	Children with ABU, UTI or renal damage, 3-15 years	dDAVP 1-dose pipette 20 µg	3 single doses	ITT: 58 pp:43	15	167
45A03-04	Multicentre, Sweden	Open-label, cross-over	Healthy adult volunteers, 24-37 years	dDAVP solution for SC injection, 2, 4 & 8 µg dDAVP rhinyle, 20, 40 & 80 µg	6 single doses, one per dose level and adm, form	10	IS	190

RCCT

Clinical studies from the literature:

Authors, year	Study location	Study design	Study population	Treatment regimens	Treatment duration	No of subjects	Report Location Vol.	Report Location Page
Askergren et al). 1981	St. Erik's & Huddinge hosp Stockholm, Sweden	Open label, cross-over	Healthy adult volunteers	dDAVP intranasal solution, 40 µg	2 single doses	11	28	256
Curtis & Donovan 1979	Charing Cross hospital, London. UK	Open label, cross-over	Healthy adult male volunteers Adult hospital in-patients	dDAVP solution for IM injection, 4 µg	1 single dose	16 13	28	260
Delin & Aurell 1986	Sahlgrenska Hospital, Gothenburg, Sweden	Open label, randomized, cross-over	Healthy adult volunteers Patients with renal disease	dDAVP 1-dose pipette, 40 µg	2 single doses	10 9	28	267

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Delin et al. 1978 i)	Sahlgrenska Hospital, Gothenburg, Sweden	Open label, cross-over	Healthy adult volunteers Adult patients	dDAVP rhinyle, 40 µg, and vasopressin tannate in oil for IM injection, 5 IU	1-2 doses, and 1 dose	15 15	28	264
Delin et al. 1978 ii)	Sahlgrenska Hospital, Gothenburg, Sweden	Open label	Healthy adult volunteers	dDAVP rhinyle, 40 µg	2 single doses	14	28	254
Dehn et al. 1979	University of Gothenburg, Sweden	Open label, cross-over	Adult patients	dDAVP rhinyle, 40 µg dDAVP solution for IM injection, 4 µg	2 single doses, 1 of each administration form	24	28	266
Feber et al. 1993	Hôpital Eduard-Herriot, Lyon, France	Open label, cross-over, randomized	Children with an indication for RCCT.	dDAVP spray, 20-40 µg dDAVP solution for IV injection, 2-4 µg	2 single doses, 1 of each administration form	18	28	269
Herbal & Ljunghall 1983	University Hospital of Uppsala, Sweden	Open label, cross-over	Patients with various endocrinological disorders.	dDAVP solution for IV injection, 2 µg pitressin, 5 IU	1 dose	18	28	272
Monnens et al. 1981 i)	University of Nijmegen, The Netherlands	Open label	Healthy infants/children (2mon-15 yrs) 10 pg (infants)(2 mon-15 yrs) 20 pg (children)	dDAVP rhinyle, 10 µg (infants) 20 µg (children)	1 dose	197	28	275
Monnens et al. 1981 ii)	University of Nijmegen, The Netherlands	Open label	Healthy infants/children (2 mon-15 yrs)	dDAVP rhinyle, 10 µg (infants) 20 µg (children)	2 single doses	15	28	275
Monnens et al. 1981 iii)	University of Nijmegen, The Netherlands	Open label	Healthy infants/children (2 mon-15 yrs)	dDAVP rhinyle, 10 µg (infants) 20 µg (children)	1 dose	30	28	275
Nadvornikova et al. 1980	Prague, Czechoslovakia and/or City University of New York, USA	Open label, cross-over	Healthy adult volunteers Adult patients with chronic disease affecting renal function	dDAVP intranasal solution, 10µg	1 dose	45 106	28	279
Sandberg 1991	Ostra Hospital, Gothenburg, Sweden	Open label	Adult patients with fever ≥30°C and negative urine culture	dDAVP solution for Sc injection, 4 µg	2 single doses	18	28	285
Svenningsen & Aronson 1974	University Hospital, Lund, Sweden	Open label, cross-over	term and preterm infants appropriate for gestational age (1-6 wks)	dDAVP 10µg Pitressin tannate in oil 2 µg /6kg bodyweight	2 single doses, one of each	20	28	244

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PNE

Clinical studies in this submission:

Study No	Study location	Study design	Study population	Treatment regimens	Treatment duration	#pts ITT/>17 yrs	Location of report Volume	Li re P: 2:
45A06-53	Multicentre, The Netherlands	run-in open response double-blind, randomized, parallel group open follow-up.	Adolescent and adult PNE patients.	dDAVP spray 20 µg dDAVP tablets 0.2-0.4 mg dDAVP tablets 0.4-0.6 mg	2 weeks 4 weeks 12 weeks	66/35	16	2:
45A06-009	Uppsala University Hospital, Sweden	Screening single-blind dose-titration (double-blind cross-over) open long-term treatment.	Patients with treatment-resistant PNE.	dDAVP tablets 0.2-0.4 mg Placebo	26 weeks 2 weeks	25 / 2	16	1:
45A06-16	Aarhus County Hospital, Denmark	Observation period open dose-titration open (tablet) open (spray)	Patients with PNE	dDAVP tablets 0.2-0.4mg dDAVP spray (IN) 40 µg	6-7 weeks 2 weeks	33**/ 3	25	9:
45A06-60	Multicentre, The Netherlands	observation period open dose-titration open long-term treatment.	Patients with PNE	dDAVP tablets 0.2-0.6mg	Up to 24 months	89/ 51	19	2:
45A06-62	Multicentre, Canada	observation period open dose-titration open long-term treatment.	Patients with monosymptomatic nocturnal enuresis	dDAVP tablets 0.2-0.4 mg	48 weeks	253 / 4	21	1:

PNE

Clinical studies from the literature:

Authors, year	Study location	Study design	Study population	Treatment regimens	Treatment duration	#pts ITT/>17 yrs	Location of report Volume	Li re P: 2:
Belmaker & Bleich 1986	Medical Corps, Israel Defense Forces	Case reports	Primary & secondary enuretics.	dDAVP, IN solution 20-80 µg	6-16 months	4 / 4	28	2:
Ceresoli et al (1993)	University of Milan, Italy	A study of pelvic floor exercise including open label treatment with dDAVP during the 1 st month.	Adult or adolescent patients with PNE and day time urge symptoms.	dDAVP spray 40 µg	28 nights	121 UNK	28	2:
Delaere & Strijbos (1987)	De wever Hospital, Heerlen, The Netherlands	Open label treatment preceded by a baseline period.	Patients with primary or secondary enuresis, refractory to other treatment.	dDAVP, IN solution 20-40µg	Up to 23 months	33/ UNK	28	2:
Hunsballe et al (1998)	Skejby University Hospital, Aarhus, Denmark	Open-label dose-titration preceded by a baseline period and followed by washout and a 24-hour, in-hospital investigation,	Adult and adolescent patients with monosymptomatic PNE; 3 wet nights/week.	dDAVP spray 20-40 µg	3 weeks	24 / UNK	28	2:
Katz et al (1997)	Israel Defense Forces	Open dose-titration preceded by baseline,	Soldiers with PNE, refractory to other treatment.	dDAVP, IN solution 20-40 µg	28 nights	12 / 12	28	3:

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Authors, year	Study location	Study design	Study population	Treatment regimens	Treatment duration	#pts ITT/>17 yrs	Location of report Volume	Li re P: 30
Ramsden et al (1982)	Freeman Hospital, Newcastle & Southern General Hospital, Glasgow, UK	Double-blind, placebo-controlled, cross-over study	Adult patients with >20 wet nights/month, refractory to other treatment.	dDAVP, IN solution 20 µg Placebo	2 weeks 2 weeks	21 / 21	28	30
Robertson et al. (1999)	Northwestern University Medical School, Chicago, USA	Circadian study followed by open-label treatment and a second circadian study (during treatment).	Adult patients with nocturnal enuresis, refractory to other treatment.	dDAVP, IN solution 10-30 µg	Unknown	9/9	28	30
Vanderstoep & Husmann (1999)	Southwestern Medical Centre, Dallas, Texas & Mayo Clinic, Rochester, Minnesota, USA	Dose-titration followed by open-label treatment and dose tapering.	Adult patients with persistent mono symptomatic PNE.	dDAVP, IN solution 10-40µg	8 months	29/29	28	30
Van Kerrebroeck et al (1990)	University Hospital Nijmegen, The Netherlands	Open-label	Adult or adolescent patients with nocturnal enuresis, without daytime incontinence.	dDAVP, IN solution 10 to >20 µg	6-58 months	50 / UNK	28	30

4.3 Review Strategy

Data from the Concentraid NDA (19-776), which describe the use of intranasal administration of desmopressin for RCCT, were not required to support this NDA submission. Data from the DDAVP tablets NDA (19-955) were used to support the following:

- Animal Pharmacology/Toxicology data
- safety and efficacy of desmopressin tablets in the treatment of PNE in children 6 to 17 years of age
- safety and efficacy in the treatment of patients with central diabetes insipidus

The two proposed indications RCCT and PNE were reviewed separately. The efficacy reviews focused on the pivotal trials 45A06-053 (PNE) and 45A03-008 (RCCT), while the safety reviews included data from all of the trials. The clinical and biostatistics reviewers performed independent reviews but collaborated before finalizing their reports.

4.4 Data Quality and Integrity

An audit of the clinical and analytical portions of bioequivalence study FE992026 CS025 found that there was inadequate quality control performance in the study. Therefore these data cannot at this time be used to support the bioequivalence of Minirin and DDAVP tablets and there is insufficient data to support the 505(b)(2) part of this application.

5.3 Exposure-Response Relationships

No exposure-response data were presented in this submission.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The sponsor is proposing the following indication:

“Primary Nocturnal Enuresis (PNE):Minirin Tablets are indicated for the management of primary nocturnal enuresis in children and adults _____ . Minirin may be used alone or as an adjunct to behavioral conditioning or other nonpharmacologic intervention.”

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Desmopressin tablets, DDAVP®, which are also manufactured by Ferring AB, are currently approved for the treatment of PNE based on clinical studies in children 5 to 17 years of age. The

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6.1.1 Methods

The efficacy submission for the PNE endpoint consisted of five studies:

- Study 45A06-53, a randomized, double-blind, multi-center study comparing two doses of desmopressin tablets in adolescent and adult patients with PNE, age 11 to 45 years
- Study 45A06-009, an open-label long term study of desmopressin tablets in the management of treatment-resistant PNE, age 11 to 21 years
- Study 45A06-60, an open-label long term study of desmopressin tablets in adolescents and adults with PNE, age 11 to 39 years
- Study 45A06-62, an open-label long term study of desmopressin tablets in adolescents with primary and secondary nocturnal enuresis, age 6 to 18 years
- Study 45A06-16, an open-label 6-week dose titration study of desmopressin tablets in adolescents with PNE, age 7 to 18 years

This efficacy review was confined to Study 45A06-53, the only randomized, double-blind study submitted for this indication.

6.1.2 General Discussion of Endpoints

The primary endpoint of Study 45A06-053 was reduction in the number of wet nights per week.

6.1.3 Study Design

Study 45A06-053 was a multi-center, randomized, double-blind, parallel group study of two different doses of Minirin tablets (0.2 and 0.4mg/day).

The study was performed in outpatients who kept diaries to document wet nights and adverse events.

Inclusion criteria (included but were not limited to)

- ≥ 12 years and ≤ 45 years of age
- ≥ 6 wet nights during the initial 14 day observation period
- $\geq 50\%$ reduction in wet nights/week during the nasal spray treatment period, i.e. responders
- at least one wet night in the wash out period following the nasal spray treatment i.e. continued enuresis

Exclusion criteria (included but were not limited to)

- Acute UTI
- Concomitant medications which may interact with desmopressin (such as indomethacin)
- Female with known or suspected pregnancy or breastfeeding
- History of diurnal wetting
- Hypertension, heart disease, hepatic disease, urologic malformation, malignant disease or acute illness

A total of 90 subjects began the 2-week observation period to determine baseline rates of enuresis (wet nights/week). Ten patients experienced < 6 wets nights during this observation period and were excluded from the study. The remaining 80 subjects were enrolled in the 2-week treatment period with intranasal desmopressin (20 μ g) to determine treatment responders, followed by a 1-week wash out period to confirm the need for continued therapy. A total of 66 cooperative subjects had $\geq 50\%$ reduction in wet nights/week during the nasal spray treatment period and at least one wet night in the wash out period. These subjects formed the intent to treat (ITT) cohort and were randomized to 4 weeks of active treatment with 0.2mg or 0.4mg tablets of desmopressin. The randomized, double blind, controlled part of the study was followed with a 2-week treatment free period followed by a 3 month open-label extension with 0.4mg of desmopressin to obtain long term efficacy and safety data (57 subjects). A small number of subjects were withdrawn during each of the study phases due to non response, lack of cooperation, or resolution of enuresis (see Table 1).

Table 1						
Reasons for Withdrawal during Study Phases						
	Run-In baseline (n=90)	Nasal Spray (n=80)	Washout (n=68)	Double- blind (n=66)	Washout (n=63)	Open-Label extension (n=57)
<6 wets nights/phase	9	0	0	0	0	0
Non-responder	0	10	0	0	4	1
Completely dry	0	0	2	0	1	0
Adverse event	0	0	0	1 [†]	0	0
Denied consent	1	0	0	0	0	0
Uncooperative	0	2	0	1	1	0
Lost to follow up	0	0	0	1	0	0

Data taken from 45A06-53 Clinical Report Table 1 (Vol.16 pg 273)
[†]This patient was withdrawn due to increased aggression and nervousness while taking Minirin 0.2mg tablets. This episode was of moderate severity and considered possibly related to treatment by the clinical investigator.

Medical Officer's comments:

The withdrawal rate was low for each of the individual phases following subject randomization and as such is not likely to impact on the study results.

Since the study population was preselected for response to Minirin nasal spray the efficacy data can not be extrapolated to patients initially presenting with enuresis.

6.1.4 Efficacy Findings

There was a mean reduction in the number of wet nights per week at the end of treatment relative to the baseline observation period for both Minirin 0.2mg/day (3.1 wet nights per week) and Minirin 0.4mg/day (3.4 wet nights per week) which was statistically significant $p < 0.01$ (see Table 2). There was no significant difference between dose levels.

Table 2						
Mean number of Wet Nights per Week (ITT analysis)						
Observation Period	Subject number		Mean		Range	
	0.2mg	0.4mg	0.2mg	0.4mg	0.2mg	0.4mg
Baseline	34	32	5.5	4.7	3.5-7.0	2.5-7.0
Minirin Nasal Spray	34	32	1.4	0.8	0.0-5.5	0.0-3.0
Washout	34	32	4.7	4.2	1.0-7.0	0.0-7.0
Minirin Tablets	31	32	2.4	1.3	0.0-6.8	0.0-6.8
Washout	29	31	3.9	3.6	0.0-7.0	1.0-7.0
Open-label extension	26	25	1.1	0.8	0.0-4.5	0.0-4.3

Data was derived from PNE/ISSE/Analysis/Efficacy.xpt Jump 5.1 Analysis
 And Study 053 Clinical Trial Report Table 3 Vol. 16 pg. 277

An analysis of the ITT data using Jump 5.1 software (see Figure 1) shows that the 95% CIs (represented by the green extra wide horizontal lines in the figure) for the number of nights per week for both the 0.2mg/day and 0.4mg/day doses do not overlap with the 95% CIs for the baseline period or either of the two wash out periods, confirming the differences are statistically significant. In contrast, the 95% CIs for the nasal spray (20µg) and the two tablet doses (0.2 and 0.4mg/day) overlap, with the 0.4mg/day dose more closely approximating the 20µg nasal spray data. An ANCOVA analysis performed by the FDA statistical reviewer, Dr. Lee-Ping showed the difference between the number of wet nights per week in the 0.4 and 0.2mg/day dose groups was not statistically significant with a p value=0.08, but did show a trend suggesting fewer wet nights with the higher dose primarily in children < 17 years of age.

Medical Officer's comment

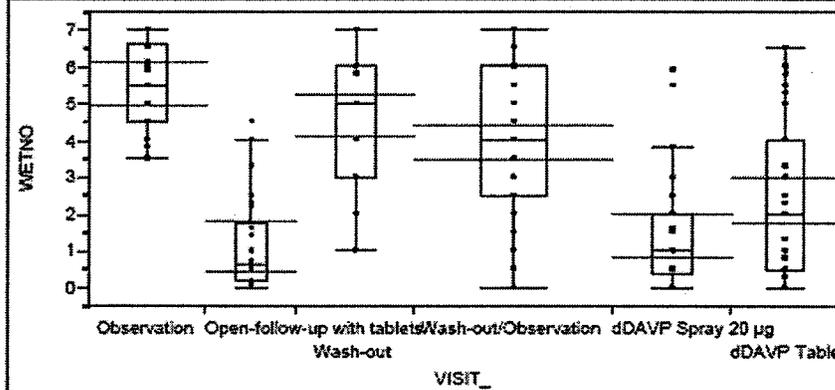
It was important to confirm that the results observed with the tablets were statistically significant relative to the washout periods not just the initial baseline to confirm that the tablet results were not confounded by a carryover effect from the earlier treatment with the nasal spray formulation.

APPEARS THIS WAY ON ORIGINAL

Fig. 1 Number of Wet Nights per Week in the ITT Population-Jump 5.1 Analysis

TRT_ =dDAVP Tablet 0.2 mg

Oneway Analysis of WETNO By VISIT_

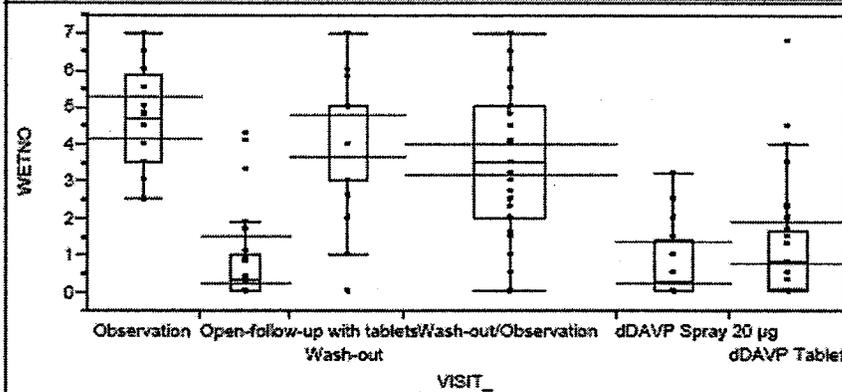


Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
Observation	34	5.5882	1.16003	0.19864	5.1041	5.9136
Open-follow-up with tablets	26	1.11923	1.26651	0.24944	0.6076	1.6309
Wash-out	34	4.67059	1.98637	0.32008	4.0194	5.3218
Wash-out/Observation	57	3.92982	2.04293	0.27059	3.3878	4.4719
dDAVP Spray 20 µg	34	1.42059	1.50449	0.25902	0.8956	1.9456
dDAVP Tablet(0.2 mg or 0.4 mg)	31	2.36452	2.05078	0.36833	1.6123	3.1167

TRT_ =dDAVP Tablet 0.4 mg

Oneway Analysis of WETNO By VISIT_



Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
Observation	32	4.71250	1.44127	0.25478	4.1929	5.2321
Open-follow-up with tablets	26	0.83800	1.27993	0.25599	0.3077	1.3643
Wash-out	32	4.20000	1.72196	0.30440	3.5792	4.8208
Wash-out/Observation	59	3.55424	1.98652	0.25964	3.0365	4.0720
dDAVP Spray 20 µg	32	0.75625	0.96518	0.17080	0.4079	1.1046
dDAVP Tablet(0.2 mg or 0.4 mg)	32	1.21250	1.59992	0.28230	0.7367	1.6883

The green extra wide horizontal lines correspond to the mean 95% confidence intervals.

6.1.5 Clinical Microbiology

No clinical microbiology data was included in this submission.

6.1.6 Efficacy Conclusions

1. Minirin tablets (0.2 and 0.4mg/day) produced a statistically significant reduction in the number of wet nights per week at the end of treatment relative to the baseline observation period.
2. There was no significant difference in reduction in the number of wet nights per week between the two doses of Minirin tablets.
3. Children < 11 years or adults > 45 years were not included in this trial, therefore no conclusions about the adequacy of Minirin tablets for use in PNE in these age groups can be made from this single trial.

6.2 Indication

The sponsor is proposing the following indication

“Renal Concentration Capacity Test (RCCT):Minirin Tablets are used to determine the capacity of the kidney to concentrate urine.”

Desmopressin nasal spray, Concentraid®, was originally approved for RCCT in 1990 as part of a daytime 8 hour urine collection at doses of 20µg for children 1 to 12 years of age, and at 40µg for adults (exact age limits not specified). The sponsor is now proposing the use of the new tablet formulation, Minirin®, during a modified nighttime RCCT.

6.2.1 Methods

The efficacy submission for the RCCT endpoint consisted of three studies

- Study 45A03-008, is a randomized, double-blind study, comparing the tablet formulation to the previously approved nasal formulation
- Study 45A03-004, is an open-label study comparing the nasal formulation to subcutaneous injections of desmopressin in healthy adult volunteers aged 24 to 37 years
- Study 45A03-006, is an open-label study using only the nasal formulation to compare day versus night-time testing

Study 45A03-004 found no further increase in urine osmolality with intranasal doses over 20µg or with subcutaneous doses over 4µg in adults between 24 and 37 years of age.

Study 45A03-006 found that mean concentration capacity was greater with the nighttime test which was better tolerated by children since it did not require fluid restriction. The findings of study 45A03-006 support the use of night-time testing of the tablet formulation in the pivotal trial, study 45A03-008.

The efficacy review will be confined to the pivotal study 45A03-008, the only randomized, double-blind study submitted for this indication.

6.2.2 General Discussion of Endpoints

The primary endpoint of Study 45A03-008 was urine osmolality (mOSm/kg) measured from the first urine obtained at least one hour after drug administration. This endpoint was used to compare efficacy between the intranasal formulation and the tablet formulation of Minirin.

6.2.3 Study Design

Study 45A03-008 was designed as a multi-center, randomized, double-blind, double-dummy, four period cross over trial with four treatments:

- Minirin tablet (0.6mg) and intranasal Minirin (placebo)- 2 treatment periods
- Minirin tablet (placebo) and intranasal Minirin (20µg)- 1 treatment period
- Minirin tablet (placebo) and intranasal Minirin (placebo) – 1 treatment period

A wash out period of at least one night was introduced between each treatment period to try to minimize carry-over effects. The order of the treatment regimens was blinded to the investigator and patient. All tests were finalized within 12 +/- 3 days from the start of the study.

The study was performed in outpatients who stored the labeled urine samples in refrigerators until they were brought to one of the six participating clinics. Diaries were completed at home and case report forms were completed at the clinic.

Inclusion criteria (included but were not limited to)

- ≥ 3 years and ≤ 18 years of age
- candidates for performing a RCCT due to suspected renal disease, urological malformation or anomaly

Exclusion criteria (included but were not limited to)

- Diagnosed or suspected central diabetes insipidus
- URI or allergic rhinitis which could interfere with nasal uptake of medication
- Acute UTI
- suspected pregnancy
- Concomitant medications
 - which may interfere with desmopressin such as tricyclic antidepressants, carbamazepine, chlorpromazine, anticholinergics
 - diuretics

A total of 153 patients, aged 3 to 18 years were allocated to one of four treatment groups by block randomization stratified by the six centers. All doses of medication were taken in the evening just before bedtime. Fluid was restricted to 150mL from one hour before drug administration to 8 hours after dosing. The duration of the night test lasted until the first voided specimen was obtained but not more than 12 hours after drug administration. Any urine sample

taken within one hour of drug administration was discarded. Compliance was monitored by the use of dairy cards. Urine osmolality was measured by freezing point depression.

6.2.4 Efficacy Findings

The intent to treat (ITT) analysis included 145 patients excluding one patient who had no efficacy data recorded, and seven patients who never took their medication. The per protocol (PP) analysis excluded an additional 27 patients who had one or more major protocol violations such as:

Patient number	Protocol Violation
9	missing a urine sample
9	failed to void before drug administration
8	duration of test exceeded 12 hours
7	failed to take oral medication
7	first void after drug intake was not obtained
7	violated inclusion or exclusion criteria
4	no wash out night between drug administrations
3	excess fluid intake >150mL

There were no clear differences between the ITT and PP populations with respect to age, sex, and race. Minirin tablets (0.6mg) and Minirin nasal spray (20µg) produced statistically significant greater mean urine osmolality than placebo i.e. 930.4mOsm/kg and 961.7mOsm/kg, respectively vs. 717.5mOsm/kg in the ITT population (see Table 4). Similar results were observed in the PP population as well i.e. 933.5mOsm/kg and 978.0mOsm/kg, respectively vs. 721.4mOsm/kg (see Table 4).

The pre-specified non-inferiority limit was set at 7%, corresponding to the error in the RCCT method when using 20µg single dose rhinal tube pipettes. The mean urine osmolality with Minirin tablets was 930.4mOsm/kg (ITT) compared to the nasal spray 961.7mOsm/kg (ITT). The 95% lower confidence limit of -58.7mOsm/kg (ITT), was within the prespecified 7% noninferiority limit of -67.3mOsm/kg (ITT), suggesting that 0.6mg of the tablets were not inferior to 20µg of the nasal spray in the night time RCCT. Similar results were obtained in the Per Protocol (PP) population. The ANOVA analysis by the FDA statistical reviewer, Dr. Lee-Ping, also compared the urine osmolality of the nasal spray directly to the tablets not just to placebo and confirmed that the difference in urine osmolality was statistically greater for the nasal spray compared to the tablets (p=0.0003). However, it is not clear if this difference in urine osmolality is of clinical significance.

Table 4					
Urine Osmolality (mOsm/kg) in Minirin Tablets, Nasal Spray and Placebo					
	Tablet (T1)	Tablet (T2)	Tablet mean (T1+T2)/2	Nasal Spray	Placebo (P)
ITT					
N	141	139	137	144	143
Mean	928.6	924.8	930.4	961.7	717.5
SD	180.5	168.5	149.1	187.0	238.0
LCL	898.6	896.6	905.3		678.2
UCL	958.7	953.1	955.6		756.9
Median	952	937	925	988	704
Mm	276	281	279	256	158
Max	1260	1320	1276	1461	1197
Nmiss	4	6	8	1	2
PP					
N	118	118	118	118	118
Mean	938.2	928.7	933.5	978.0	721.4
SD	167.5	170.6	150.0	175.5	245.5
LCL	907.7	897.6	906.1		676.7
UCL	968.7	959.8	960.8		766.2
Median	954	936	930	992	708
Mm	276	281	279	256	158
Max	1259	1320	1276	1461	1197
Nmiss	0	0	0	0	0
ITT - Intention To Treat, PP-Per Protocol N - Number of patients, SD Standard Deviation LCL 95%- Lower Confidence Limit of the 95% two-sided confidence interval for the mean UCL 95%- Upper Confidence Limit of the 95% two-sided confidence interval for the mean Nmiss - Number of patients with missing values Data taken from NDA submission Vol. 14 pg 106-110, Tables 8-12					

6.2.5 Clinical Microbiology

No clinical microbiology data was included in this submission.

6.2.6 Efficacy Conclusions

1. Minirin tablets (0.6mg) and Minirin nasal spray (20µg) produced statistically significant greater mean urine osmolality than placebo.
2. Minirin tablets at a single night time dose of 0.6mg were not inferior to 20µg of the nasal spray in the RCCT using the prespecified 7% noninferiority margin, even though the 20µg nasal spray dose appeared statistically better at increasing urine osmolality than 0.6mg of the tablet in this trial.
3. No dose titration of Minirin tablets was performed in this trial, therefore no conclusions about the efficacy of Minirin tablets at doses other than 0.6mg can be made.

1 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

b(4)

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Minirin® tablets were first approved in 1987 for the treatment of diabetes insipidus, and have been available outside the US since 1989 for the treatment of PNE in children over five years of age. They have also been approved in 38 countries outside the US since 2001 for the treatment of nocturia in adults less than 65 years of age. They are not recommended to treat patients above 65 years of age because of the risk of severe hyponatremia.

The integrated safety summary (ISS) was submitted separately for the two indications, RCCT and PNE. Safety information was also supplied for _____ nocturia in adults (NIA), which was derived from 5 clinical studies in the sponsor's Phase III program. The sponsor is not seeking an indication for this population and so efficacy data from this population were not included in this submission. While the adult nocturia population may differ somewhat from the PNE population as they are older and more likely to have underlying disease, concurrent illness and take multiple medications, they receive similar doses of Minirin and provide useful information about the safety of this medication in the elderly population. Therefore, an analysis of the NIA population is also included in this safety review.

b(4)

In general, desmopressin was found to be well tolerated at daily oral doses up to 0.6mg with the most frequently reported adverse events being nausea, vomiting and headache. There were no cases of hyponatremia in the RCCT and PNE clinical trials. In the NIA clinical trials there were 31 cases of hyponatremia in subjects above 65 years of age and 3 cases in subjects between 46

and 65 years of age. Only 3 of the cases of hyponatremia were considered serious. In post marketing reports only 4 out of 36 reported cases of hyponatremia were in patients below 46 years of age (i.e. 23, 33, 39 and 41).

7.1.1 Deaths

RCCT-No deaths were reported in the clinical trials or publications evaluating desmopressin for RCCT.

PNE- No deaths were reported in the clinical trials or publications evaluating desmopressin for PNE.

NIA-Three patients died following adverse events in the clinical trials that were unlikely to be related to the study medication:

b(4)

Table 5					
Summary of Patients who died in Nocturia Studies					
Age	Gender	Desmopressin dose	Time on Desmopressin	Days between last dose of desmopressin and death	AE leading to withdrawal from study
71	Male	0.2mg	8 days	4 months	bronchitis
76	Female	0.1mg	4 days	3 weeks	Respiratory insufficiency
62	Female	0.2mg	10 days	4 weeks	Pneumonia

Medical Officer's comments-

It is not clear from its mechanism of action how desmopressin would have contributed to these pulmonary adverse events. In addition, the length of time between the date of the last dose of desmopressin and the time of death make it unlikely that desmopressin contributed to the deaths of these patients.

7.1.2 Other Serious Adverse Events

RCCT- No serious adverse events were reported in the clinical trials or publications evaluating desmopressin for RCCT.

PNE- Serious adverse events were reported in 4 adult patients (4%) with the following conditions: irritable bowel syndrome, hepatic cirrhosis, urinary retention, and hypertension. Only the case of increased fluid retention and worsening hypertension in a 32 year old female was possibly related to desmopressin.

Medical Officer's comment-The one serious case of fluid retention and worsening hypertension (130/90->155/100) was most likely the result of a change in the patient's

hypertension/diuretic medications during the study, but a contribution of desmopressin to this adverse event can not be completely ruled out.

NIA-Sixteen patients experienced serious adverse events in the short-term trials (< 2 months). The most common events were headache seen in three patients (<1%) and hyponatremia seen in two patients (<1%). All other events were seen in only one patient each and included: angina pectoris, hypertension, purpura, urinary retention, vertigo, tinnitus, nausea, vomiting, confusion, depression, diplopia, bronchitis, pneumonia and respiratory insufficiency. Only the case of depression was in a patient under 46 years of age.

Twenty six patients experienced serious adverse events in the long-term trials (>10months). The most common events were hypertension and accident/injury, seen in 3 patients each followed by headache, cardiac failure, dyspnea, chest pain, and sepsis seen in two patients each. All other adverse events were seen in only patient each and included: hyponatremia, urinary retention, UTI, pyelonephritis, bladder fibrosis, dyspnea, hemoptysis, nausea, vomiting, ataxia, dizziness, dysaesthesia, peripheral neuropathy, vertigo, Dupuytren's contracture, menorrhagia, back pain, infection, adenocarcinoma, lymphoma, and esophageal, renal and pulmonary carcinomas. Five cases were considered possibly related to the study medication by the clinical investigators. These included one case of chest pain and high blood pressure, one case of nausea, vertigo, headache, and hyponatremia, one case of severe headache and vomiting, one case of cardiac failure and pneumonia associated with a lung tumor, and one case of feeling faint after carpal tunnel surgery. None of these 5 cases was below 46 years of age.

7.1.3 Dropouts and Other Significant Adverse Events

RCCT- Two patients (0.9%) had serious adverse events reported in the RCCT clinical trials just after taking the intranasal desmopressin which resulted in their withdrawal from the trial. One case was a patient with "a stomach flu" with symptoms of fever, cough, vomiting and diarrhea, and the other case was a patient who had a headache. There were no serious adverse events leading to withdrawal from the trial in patients taking the Minirin tablets.

PNE- Four patients, all over 17 years of age, were withdrawn from the study due to adverse events which included: edema, aggression/nervousness, urinary retention and hypertension. Only the case of worsening hypertension was considered a serious adverse event (see 7.1.2 above).

NIA- At least four patients were withdrawn from the studies due to adverse events. These include 3 patients who subsequently died (see 7.1.1, Table 5) and one patient with nausea, headache and hyponatremia who recovered.

7.1.4 Other Search Strategies

None

7.1.5 Common Adverse Events

Because of the low number of patients in these trials, all treatment related adverse events were included in the tables, and they were not separated into common and less common events.

RCCT

Table 6			
Treatment-Emergent Adverse Events in RCCT trials			
AE	Placebo N=146 (100%)	20µg Spray N=204 (100%)	0.6mg Tablet N=144 (100%)
Any AE	3 (2%)	8 (4%)	13 (9%)
EYE DISORDERS	1 (<1%)		1 (<1%)
Conjunctivitis allergic	1 (<1%)		
Eye irritation			1 (<1%)
GASTROINTESTINAL DISORDERS	1 (<1%)	3 (1%)	6 (4%)
Vomiting		1 (<1%)	4 (3%)
Abdominal pain	1 (<1%)	2 (<1%)	
Abdominal pain upper			2 (1%)
Constipation		1 (<1%)	1 (<1%)
Diarrhea		1 (<1%)	
GENERAL DISORDERS AND ADMINISTRATION SIT		1 (<1%)	3 (2%)
Pyrexia		1 (<1%)	2 (1%)
Pain			1 (<1%)
INFECTIONS AND INFESTATIONS		3 (1%)	2 (1%)
Nasopharyngitis		1 (<1%)	1 (<1%)
Bacteriuria			1 (<1%)
Infection		1 (<1%)	
Upper respiratory tract infection		1 (<1%)	
NERVOUS SYSTEM DISORDERS	1 (<1%)	2 (<1%)	1 (<1%)
Headache	1 (<1%)	2 (<1%)	1 (<1%)
RENAL AND URINARY DISORDERS			1 (<1%)
Hematuria			1 (<1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DI		1 (<1%)	1 (<1%)
Cough		1 (<1%)	
Pharyngolaryngeal pain			1 (<1%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		1 (<1%)	
Eczema		1 (<1%)	

Data taken from 36 ISS Vol. 28, pg 156-157

The most common adverse event was vomiting seen in 3% of patients. All other adverse events occurred in less than 2% of the study population. The only AE graded by intensity as severe was abdominal pain/constipation present in one patient in the placebo group and one patient in the 20µg intranasal group. Two AEs were listed as treatment related: Headache present in one patient in the placebo group and two patients in the 20µg intranasal group, and abdominal pain present in one patient in the placebo group and one patient in the 0.6mg tablet group.

Eleven literature citations describing the use of nasal or parenteral desmopressin in excess of 400 subjects between 2 months and 75 years of age were referenced by the sponsor. The only specific adverse events described in these trials were urticaria, hyperkalemia and dehydration.

PNE

Table 7

Treatment-Emergent Adverse Events in PNE trials

AE	Total Tablets N=95 (100%)	0.2mg Tablet N=44 (100%)	0.4mg Tablet N=54 (100%)	0.6mg Tablet N=13 (100%)	20µg Sp N=35 (100%)
Any AE	25 (26%)	8 (18%)	13 (24%)	4 (31%)	6 (17%)
EYE DISORDERS	2 (2%)	1 (2%)	1 (2%)		
Eye pain	1 (1%)		1 (2%)		
GASTROINTESTINAL DISORDERS	8 (8%)	2 (5%)	4 (7%)	2 (15%)	
Abdominal discomfort	1 (1%)		1 (2%)		
Abdominal pain upper	1 (1%)			1 (8%)	
Dry mouth	1 (1%)			1 (8%)	
Esophagitis	1 (1%)		1 (2%)		
Irritable bowel synd	1 (1%)		1 (2%)		
Nausea	3 (3%)	1 (2%)	1 (2%)	1 (8%)	
Vomiting	1 (1%)	1 (2%)			
GENERAL DISORDERS AND ADMINISTRATION SIT	2 (2%)	2 (5%)			1 (3%)
discomfort	1 (1%)	1 (2%)			
edema	1 (1%)	1 (2%)			
Fatigue	1 (1%)	1 (2%)			
Feeling cold					1 (3%)
HEPATOBIILIARY DISORDER	1 (1%)	1 (2%)			
Hepatic cirrhosis	1 (1%)	1 (2%)			
IMMUNE SYSTEM DISORDER	1 (1%)		1 (2%)		1 (3%)
Seasonal allergy	1 (1%)		1 (2%)		1 (3%)
INFECTIONS AND INFESTATIONS	10 (11%)	4 (9%)	3 (6%)	3 (23%)	

Table 7

Treatment-Emergent Adverse Events in PNE trials

AE	Total Tablets N=95 (100%)	0.2mg Tablet N=44 (100%)	0.4mg Tablet N=54 (100%)	0.6mg Tablet N=13 (100%)	20µg Sp N=35 (100%)
Cystitis	1 (1%)	1 (2%)			
GI infection	1 (1%)			1 (8%)	
Herpes simplex	1 (1%)	1 (2%)			
Infection	1 (1%)		1 (2%)		
Influenza	5 (5%)	3 (7%)	1 (2%)	1 (8%)	
Nasopharyngitis	1 (1%)		1 (2%)		
UTI	1 (1%)			1 (8%)	
INJURY, POISONING AND PROC COMPLIC	1 (1%)		1 (2%)		
Patella fracture	1 (1%)		1 (2%)		
MUSCULOSKELETAL AND CT DISORDER	2 (2%)	1 (2%)		1 (8%)	
arthralgia	1 (1%)			1 (8%)	
Back pain	1 (1%)	1 (2%)			
NERVOUS SYSTEM DISORDERS	9 (9%)	3 (7%)	5 (9%)	1 (8%)	3 (9%)
dizziness					1 (3%)
Headache	7 (7%)	3 (7%)	3 (6%)	1 (8%)	2 (6%)
hypertonia	1 (1%)		1 (2%)		
migraine	1 (1%)		1 (2%)		
PSYCHIATRIC DISORDER	3 (3%)	3 (7%)			
aggression	1 (1%)	1 (2%)			
Emotional dis	1 (1%)	1 (2%)			
Nervousness	1 (1%)	1 (2%)			
Sleep disorder	1 (1%)	1 (2%)			
RENAL AND URINARY DISORDERS	2 (2%)		1 (2%)	1 (8%)	
Pollakiuria	1 (1%)			1 (8%)	
Urinary retention	1 (1%)		1 (2%)		
RESPIRATORY, THORACIC AND MEDIASTINAL DI	1 (1%)		1 (2%)		
Cough	1 (1%)		1 (2%)		
VASCULAR DISORDER	1 (1%)			1 (8%)	
hypertension	1 (1%)			1 (8%)	

Data taken from table 48 ISS Vol. 28, PG 167-170

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The most common adverse events in patients taking any dose of the Minirin tablets were headache (7%), influenza (5%) and nausea (3%). All other adverse events occurred in less than 2% of the study population.

The following AEs were listed as treatment related:

- 0.2mg Tablets-edema, headache, aggression and nervousness
- 0.4mg Tablets-eye pain, abdominal discomfort, headache, hypertonia
- 0.6mg Tablets-hypertension
- 20µg Nasal Spray-dizziness

Nine literature citations describing the use of desmopressin in excess of 100 subjects between 7 and 45 years of age were referenced by the sponsor. The only specific adverse events described in these trials were transient headaches, anorexia, increased appetite, daytime polyuria, cough, nasal irritation, and rhinitis.

NIA-incidence of AEs in long-term trials for all doses.

AE	Number	%
URI	35	14
headache	26	10
flu symptoms	24	10
abd pain	18	7
accident/injury	17	7
back pain	17	7
arthralgia	14	6
dizziness	14	6
hypertension	11	4
bronchitis	9	4
dyspnea	9	4
edema	9	4
nausea	9	4
pain	9	4
diarrhea	8	3
sinusitis	8	3
micturition freq	7	3
UTI	7	3

Data taken from ISS Table 75 Vol. 28 pg 222

7.1.6 Less Common Adverse Events

All adverse events were listed in 7.1.5 above.

7.1.7 Laboratory Findings

Overall no clinically significant laboratory parameters were identified in the RCCT or PNE studies.

The only clinically significant laboratory finding in the NIA studies was the occurrence of hyponatremia. The risk of developing hyponatremia increased with age and declining creatinine clearance/ GFR. All but 3 of the 31 patients who developed clinically significant hyponatremia (<130mmol/L), were >65 years of age and all but 4 had a creatinine clearance of < 80mL/min. None of the patients were below 46 years of age. In the majority of cases hyponatremia occurred in the first two weeks of treatment 25/45= 56%. All patients recovered after discontinuation of the study medication.

7.1.8 Vital Signs

Overall no clinically significant findings in vital signs or physical exams were identified in these studies.

7.1.9 Electrocardiograms (ECGs)

No information about ECG measurements between treatment groups was included in this submission.

7.1.10 Immunogenicity

No information regarding immunogenicity was included in this submission.

7.1.11 Human Carcinogenicity

No information regarding carcinogenicity was included in this submission.

7.1.12 Special Safety Studies

No special safety studies were included in this submission.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no evidence of withdrawal phenomena and/or abuse potential with desmopressin. No information regarding withdrawal phenomena and/or abuse potential was included in this submission.

7.1.14 Human Reproduction and Pregnancy Data

Fertility studies have not been done. There are no adequate and well controlled studies in pregnant women. A review of 20 articles describing the use of DDAVP in the management of diabetes insipidus in pregnancy from 1976 to 1997, found it to be safe for both mother and infant, however a few anecdotal cases of congenital anomalies including, low birth weight infants, Down's syndrome and cardiac anomalies were seen⁵. A large database of desmopressin use during pregnancy is needed to clarify the true risk of congenital anomalies.

7.1.15 Assessment of Effect on Growth

No information regarding effect on growth was included in this submission. According to the sponsor no safety data are available concerning a potential effect on growth in children on long-term therapy with desmopressin. Desmopressin has been used clinically for enuresis in children since 1975. A PubMed search of "desmopressin AND growth" by this medical reviewer found no references describing a negative effect on growth rate in children on desmopressin therapy. One reference⁶ describing 15 children with central diabetes insipidus found no effect on growth unless there was preexisting growth hormone deficiency, and DDAVP did not alter growth hormone, cortisol or prolactin levels. In addition, in most cases treatment with desmopressin is short-term and so any effects on growth would likely be limited and reversed after drug discontinuation.

7.1.16 Overdose Experience

Overdose of Minirin tablets leads to a prolonged duration of action with an increased risk of water retention and hyponatremia if fluid restriction is not followed. There is no specific antidote for Minirin. The patient will need to be observed and treated symptomatically for any changes in fluid and electrolyte status, and supportive measures instituted as required.

7.1.17 Postmarketing Experience

As of December 2004, Minirin tablets have been approved in 71 countries for PNE and diabetes insipidus and in 38 countries for nocturia. The estimated exposure is 572 million treatment days. No adverse events have been reported with desmopressin tablets for the RCCT indication.

⁵ Ray JG *Obstet Gynecol Surv.* 1998 Jul; 53 (7):450-5

⁶ Becker DJ, Foley TP *J Pediatr* 1978; 92(6):1011-5

The sponsor reported only adverse events associated with use of desmopressin tablets in adults and for an indication other than diabetes insipidus in this submission. A total of 87 spontaneous reports were identified as of Dec. 6, 2004 of which 39/87=45% were in patients treated for nocturia and 20/87=23% were in patients treated for enuresis. 67% of the reports were in patients over 65 years of age, 16% were in patients between 46 and 64 years of age and 17% were in patients between 18 and 45 years of age. 49 (56%) of the reports were classified as serious and 36 (41%) were associated with hyponatremia. There were 3 deaths in patients 71, 80 and 85 years of age for which a causal relationship could not be excluded. Of the cases of hyponatremia 32/36=89% were classified as serious, 29/36=81% were in patients over 65 years of age and only 4/36=11% were in adults younger than 46 years of age (i.e. 23, 33, 39 and 41 y/o). Most cases 24/36=66% occurred within the first month of therapy.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

RCCT

The majority of the 204 patients in the RCCT safety data set were female 68%, Caucasian 97% (Oriental 3%), with a median age of 8 years and a range of 3 to 18 years of age. Literature citations for two studies⁷ including 55 infants 1 to 12 months of age and one study⁸ with an excess of 100 adults up to 75 years of age using subcutaneous or intranasal desmopressin were also referenced.

PNE

An equal distribution of males 50.5% and females 49.5%, who were primarily Caucasian 85% (Oriental 3%), with a median age of 21 years and a range of 17 to 46 years of age were included in the PNE safety data set of 95 adult patients. Nine literature citations describing treatment of over 140 adults with PNE with a mean age of 20 to 27 in these studies were reviewed by the sponsor (see ISS Vol. 28 pg 126-132 Table 22 of the sponsor's NDA submission and section 4.2 of this review).

No safety information for the children enrolled in the PNE trials was submitted in the ISS as agreed between the sponsor and the Agency at the May 2004 meeting. Desmopressin tablets are already approved in children age 6 years and older (see DDAVP label), and the sponsor is using the clinical study data only to support the new indication of treatment in adults up to 46 years of age.

There were only 13 patients that were titrated up to the maximal dose of 0.6 mg in these clinical studies. The mean period of exposure at the maximal dose was 12 months with a range of 3 to 22

7a Svenningsen NW and Aronson AS 1974; Biol. Neonate 25:230-241

7b Monnens L, Smulders Y, van Lier H and Boo T 1981; Nephron 29:151-154

8 Nadvornikova H, Schuck O and Cort JH1980; Clinical Nephrology 14(3):142-147

months. There were only 22 patients treated with desmopressin for more than one year in these trials. While no safety issues were identified at the highest dose or after long term therapy, the limited amount of exposure in these groups limits the ability to draw conclusive safety assessments from these data.

7.2.3 Adequacy of Overall Clinical Experience

RCCT

There were adequate data for the assessment of safety and effectiveness of Minirin tablets in patients 3 to 18 years of age. There was inadequate data for the assessment of safety and effectiveness of Minirin 0.6mg tablets in children under 3 years of age or in adults over 18 years of age.

There was adequate exposure of children of both sexes but there was insufficient exposure of races other than Caucasian.

b(4)

PNE

There were adequate data for the assessment of safety and effectiveness of Minirin tablets in patients 11 to 45 years of age. Open-label data from study 45A06-16 support the use in children 7 years of age and older, and reference is made to NDA 19-955 (DDAVP tablets) which supports the use in children 6 years of age and older. There was adequate exposure of patients of both sexes but there was insufficient exposure of races other than Caucasian. No clinical data are available for children under 6 years of age.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No special animal and/or in vitro testing was submitted. Reference for preclinical studies is made to data from NDA 19-955 (DDAVP tablets).

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No metabolic, clearance and interaction workup data was submitted. Reference for preclinical studies is made to data from NDA 19-955 (DDAVP tablets).

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{William Lubas MD-PhD}
{NDA 21-795; N-000}
{Minirin® (desmopressin acetate) Tablets, 0.1mg and 0.2mg}

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Clinical studies have been adequate to assess safety in children between 3 and 18 years of age given the RCCT and in children over 6 and adults up to 45 years of age treated for PNE.

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7.2.8 Assessment of Quality and Completeness of Data

Data quality and completeness were adequate to permit review.

7.2.9 Additional Submissions, Including Safety Update

A 4-month Safety Update Report (SUR) was submitted August 9, 2005. No serious adverse events were reported in the two ongoing trials in children (i.e. CS022 and CS002) as of May 2005.

The 4-month SUR contained 35 post marketing reports (11 serious, 24 nonserious) in connection with the use of desmopressin tablets reported between Dec. 7, 2004 to June 6, 2005. The eleven serious case reports included one case of an allergic reaction with edema of the mouth and dyspnea in a 59 year old man, one case of gynecomastia in a 2 year old boy, one case of a severe headache (unknown age), one case of increased aggression in a 7 year old boy and 7 cases of hyponatremia, all in adult patients (ages 58, 75, 82, 84, 85, 86, and 90). In addition, there were 4 cases of hyponatremia that were considered nonserious in subjects aged 43, 67, 72 and 93 years. All but one of the serious cases occurred within 2 weeks of starting the medication and all of the cases except for one nonserious case were in patients over 46 years of age. While desmopressin may be effective at treating nocturia in adult patients over 46 years of age, the safety risk associated with hyponatremia in such patients would need to be evaluated in clinical trials before such an indication could be approved.

Age	Time to Onset	Indication	Lowest sodium (mM)	Severity
58	4 days	Nocturnal enuresis	116	Serious
75	12 days	Nocturia	129	Serious
82	8 days	Nocturia	114	Serious
84	Unknown	Frequent micturition	?	Serious
85	2 weeks	Urinary incontinence	?	Serious

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 {NDA 21-795; N-000}
 {Minirin® (desmopressin acetate) Tablets, 0.1mg and 0.2mg}

Table 9				
Desmopressin-Related Cases of Post Marketing Hyponatremia from Dec. 7, 2004 to June 6, 2005				
Age	Time to Onset	Indication	Lowest sodium (mM)	Severity
86	2 weeks	Nocturia	?	Serious
90	2 years	Nocturia	121	Serious
43	7 months	Urinary disorder	115	Non Serious
67	Unknown	Bladder instability	?	Non Serious
72	Unknown	Unknown	?	Non Serious
93	6 months	Nocturia	125	Non Serious

No new safety issues have been identified in the 4-month SUR that would require changes to the proposed labeling.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

No serious adverse events were seen in the clinical trials submitted for the RCCT (age 3-18 years) and PNE (age 17-46 years) indications. The most common treatment related adverse events were headache, nausea and vomiting. Literature references report the occurrence of hyponatremia, water intoxication and seizure in infants 1 to 13 months of age treated with nasal DDAVP. Clinical data from elderly patients in the nocturia in adult (NIA) trials showed that patients with decreased creatinine clearance and age above 65 years were also at greater risk of hyponatremia. In the NIA trials there were 31 cases of hyponatremia in subjects above 65 years of age and 3 cases in subjects between 46 and 65 years of age. Only 3 of the cases of hyponatremia were considered serious.

There were only 13 patients that were titrated up to the maximal dose of 0.6 mg in these clinical studies. The mean period of exposure at the maximal dose was 12 months with a range of 3 to 22 months. There were only 22 patients treated with Minirin tablets at any dose for more than one year in these trials. While no safety issues were identified at the highest dose or after long term therapy, the limited amount of exposure in these groups limits the ability to draw conclusive safety assessments from these data.

No post marketing reports for children treated for PNE were included in this submission. The adult post marketing reports showed that most adverse events (67%), including three deaths, occurred in adults over 65 years of age. Out of the 36 cases of hyponatremia 32 were classified as serious but only four were in patients under 46 years of age (i.e. 23, 33, 39 and 41 y/o). Most case reports (24/36=66%) occurred in the first month of therapy. This post marketing data suggests that, while the risk of hyponatremia may be low in adults under 46 years of age, use in elderly patients (>65 years of age) is associated with a substantial safety risk.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The studies were all of different design with different study endpoints to preclude any benefit from pooling of the efficacy data. Safety data were pooled prior to review as the numbers of patients in the individual studies were too small to draw independent conclusions from single studies.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The incidence of treatment emergent adverse events increased with increasing dose in the PNE studies i.e. 0.2mg (18%), 0.4mg (24%), and 0.6mg (31%). This was primarily due to an increase in adverse events in males i.e. 0.2mg (2/21=10%), 0.4mg (6/29=21%), and 0.6mg (1/3=33%) compared to females which showed a constant rate between doses i.e. 0.2mg (6/23=26%), 0.4mg (7/25=28%), and 0.6mg (3/10=30%). However, the numbers of patients in each group are too low to conclude specific dose or gender effects.

The incidence of adverse events increased with increasing dose in all patients in the NIA studies as well i.e. 0.2mg (136/575=24%) and 0.4mg (191/524=36%). Here the number of patients are much larger and more suggestive of a true dose effect.

7.4.2.2 Explorations for time dependency for adverse findings

The majority of cases of hyponatremia which occurred in the NIA studies or were obtained from post marketing reports occurred in the first few weeks of therapy.

7.4.2.3 Explorations for drug-demographic interactions

The incidence of treatment emergent adverse events increased with increasing age in the PNE studies. For patients between 17 and 21 years of age it was 5/55=9% and for patients between 21 and 45 years of age it was 20/56=36%.

The number of cases of hyponatremia increased with increasing age in the NIA studies i.e. 0 for patients below 46 years of age, 3 for patients between 46 and 65 years of age and 31 for patients above 65 years of age. The number of patients in each of these age categories was not available in the study report so it was not possible to calculate relative rates.

7.4.2.4 Explorations for drug-disease interactions

The risk of hyponatremia increased with declining creatinine clearance/ GFR in the NIA studies.

7.4.2.5 Explorations for drug-drug interactions

No relationship between response and use of concomitant medications was observed. However, patients in several studies were excluded if they were taking certain medications (indomethacin, tricyclic antidepressants, chlorpromazine, carbamazepine, chlorpropamide, clofibrate or diuretics) so drug effects with these medications cannot be excluded.

7.4.3 Causality Determination

The common adverse events of nausea, vomiting, and headache which were associated with the use of Minirin tablets are likely to be treatment related but direct causality can not be assigned from the available data.

Hyponatremia is likely due to a combination of the pharmacologic effect of desmopressin and inappropriate fluid intake. Limiting fluid intake will likely mitigate the risk of hyponatremia. Infants and the elderly may be at increased risk of water intoxication as their fluid intake may be dependent on others or their thirst center may be less well regulated.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

RCCT

The sponsor proposes a single 0.6mg Minirin tablet dose for all patients.

PNE

The sponsor proposes a nighttime starting dose of 0.2mg in children 6 years of age and older and in adults _____ The dose may be titrated up to a maximum of 0.6mg to achieve the desired response.

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8.2 Drug-Drug Interactions

No drug-drug interaction studies were submitted in this submission.

Use of indomethacin was excluded from PNE study 45A06-053 because the sponsor was concerned it might interact with desmopressin. Use of tricyclic antidepressants, chlorpromazine and carbamazepine was excluded from PNE study 45A06-062 because, according to the sponsor, these drugs have been shown to release antidiuretic hormone. Use of indomethacin, clofibrate, carbamazepine and chlorpropamide was excluded from PNE study 45A06-016 because the sponsor was concerned they might interact with desmopressin. Use of tricyclic antidepressants, chlorpromazine, carbamazepine, anticholinergics and diuretics were excluded from the RCCT study 45A06-008 because the sponsor was concerned they might interfere with the study results.

The last Concentraid label, before the drug was withdrawn from the market for business reasons, stated that clofibrate and indomethacin may potentiate while carbamazepine and glibenclimide may decrease its activity.

The current DDAVP label states that while pressor activity is very low compared to its antidiuretic activity, large doses of DDAVP tablets should be used with other pressor agents only with careful patient monitoring.

8.3 Special Populations

Pediatric and geriatric patients and patients with declining creatinine clearance/GFR should have fluid intake adjusted downward to decrease the potential of water intoxication and hyponatremia. No clinically relevant gender differences were noted in the pivotal trials. Most of the patients in the clinical trials were Caucasian (85-97%) so no meaningful analysis was possible for other racial groups.

8.4 Pediatrics

In all pediatric patients careful fluid intake restrictions should be used to prevent possible hyponatremia and water intoxication.

RCCT

Minirin 0.6mg tablets were studied in children 3 to 18 years of age and found not to be inferior to the currently recommended nasal spray dose of 20µg. Use in children less than 3 years of age was not studied and is not recommended.

PNE

Minirin tablets as doses of 0.2 to 0.6mg/day were studied in children 11 years of age and older and found to be effective for the treatment of PNE. No safety information in children in the PNE trials was submitted in the ISS and so safety in this population could not be evaluated using the sponsor's data.

Ferring has requested a pediatric waiver for further pediatric studies, as Minirin tablets do not represent a meaningful therapeutic benefit over existing pediatric therapies for patients under 6 years of age. This medical reviewer agrees that a tablet formulation is less likely to be useful in this population group compared to the nasal spray and IV formulations which are currently already available (DDAVP®) and so the pediatric waiver for additional pediatric studies is acceptable.

8.5 Advisory Committee Meeting

There was no need for an advisory committee meeting related to this application.

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

[Redacted]

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9.5 Comments to Applicant

This submission supports the use of Minirin tablets (0.6mg) for RCCT in children between 3 and 18 years of age, who can swallow tablets. There is insufficient evidence to support the use of this tablet formulation in children under 3 years of age. There is insufficient evidence to support the use of Minirin tablets (0.6mg) in adults over 18 years of age.

[Redacted]

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This submission supports the use of Minirin tablets (0.2mg to 0.6mg) for PNE in adults up to 45 years of age. Once the bioequivalence data from study FE992026 CS025 can be validated, Minirin tablets can also be approved for the treatment of PNE in children 6 years of age and older. There is a clear increased risk of hyponatremia in elderly patients >65 years of age with chronic use of this medication which would not justify its use as a convenience product for the treatment of nocturia. The risk of hyponatremia in adults between 46 and 65 years of age has not been adequately defined to make recommendations about the use of Minirin tablets for the treatment of PNE or — in this population.

b(4)

10 APPENDICES

10.1 Review of Individual Study Reports

Not applicable.

10.2 Line-by-Line Labeling Review

See labeling review section 9.4.

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REFERENCES

- 1 Argenti D, Ireland D, Heald DL. A pharmacokinetic and pharmacodynamic comparison of desmopressin administered as whole, chewed and crushed tablets, and as an oral solution. *J Urol*. 2001 May;165(5):1446-51.
- 2 Delin K, Aurell M. Hydration affects the result of a desmopressin test in adults. *Scand J Urol Nephrol*. 1986;20(2):143-4.
- 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 Tryding N, Berg B, Ekman S, Nilsson JE, Sterner G, Harris A. DDAVP test for renal concentration capacity. Age-related reference intervals. *Scand J Urol Nephrol*. 1988;22(2):141-5.
- 5 Ray JG. DDAVP use during pregnancy: an analysis of its safety for mother and child. *Obstet Gynecol Surv*. 1998 Jul;53(7):450-5. Review.
- 6 Becker DJ, Foley TP Jr. 1-deamino-8-D-arginine vasopressin in the treatment of central diabetes insipidus in childhood. *J Pediatr*. 1978 Jun;92(6):1011-5.
- 7a Svenningsen NW, Aronson AS. Postnatal development of renal concentration capacity as estimated by DDAVP-test in normal and asphyxiated neonates. *Biol Neonate*. 1974;25(3-4):230-41.
- 7b 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.
- 8 Nadvornikova H, Schuck O, Cort JH. A standardized desmopressin test of renal concentrating ability. *Clin Nephrol*. 1980 Sep;14(3):142-7.
- 9 Koskimies O, Pylkkanen J, Vilska J. Water intoxication in infants caused by the urine concentration test with vasopressin analogue (DDAVP). *Acta Paediatr Scand*. 1984 Jan;73(1):131-2.

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/s/

William Lubas
12/21/2005 12:12:26 PM
MEDICAL OFFICER

Mary Parks
12/21/2005 01:02:13 PM
MEDICAL OFFICER

Approvable recommendation pending resolution of analytical deficiencies in
study. Labeling recommendations to be deferred until review
of the response to clin pharm deficiency is
performed.