

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-795

SUMMARY REVIEW

MEDICAL TEAM LEADER MEMO

NDA#: 21-795

Sponsor: Ferring Pharmaceuticals, Inc

Drug: Minirin (desmopressin acetate) 0.1 mg and 0.2 mg tablets

Indication:

- Treatment of central diabetes insipidus
- Treatment of primary nocturnal enuresis in children and adults
- Diagnostic use in assessing renal concentrating capacity

Date of Submission: September 24, 2007

Primary Medical Reviewer: Bill Lubas, M.D., Ph.D.

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I. Introduction and Background

Ferring Pharmaceuticals, Inc. has submitted this complete response to the approvable Action Letter dated 12/22/05. The Sponsor originally submitted a 505(b)(2) application relying on the Agency's findings of safety and effectiveness for DDAVP tablets (NDA 19-955) seeking approval of Minirin (desmopressin acetate) 0.1 mg and 0.2 mg for treatment of central diabetes insipidus and treatment of primary nocturnal enuresis (PNE) in children ages 6 years and older. In addition, clinical studies were submitted in support of an expanded indication of treatment of PNE in adults and for diagnostic use in assessing renal concentrating capacity. The original application included the pivotal bridging bioequivalence study FE992026 CS025. An audit of the clinical and analytical portions of the bioequivalence study was conducted, leading to questionable accuracy of a large number of analytical runs due to unacceptable quality control performance. Based on these findings, the application was found approvable, and the Sponsor was informed that *"it will be necessary for you to conduct another bioequivalence study or rerun the stored samples from Study FE992026 CS025 with acceptable quality control performance"*.

With this submission, Ferring has 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.

Desmopressin acetate is a synthetic analogue of vasopressin, a hormone secreted by the posterior pituitary gland in response to osmotic and non-osmotic stimuli. Currently available formulations of desmopressin acetate include injection (DDAVP: NDA 18-938 and generic preparations), nasal spray (Minirin 10 mcg (40 IU)/spray: NDA 21-333; Stimate 150 mcg (600 IU)/spray: NDA 20-355; DDAVP 10 mcg (40 IU)/spray: NDA 17-922 and generic preparations) and tablets (DDAVP: NDA 19-955 and generic preparations)

Known safety concerns with desmopressin acetate include an increased risk of hyponatremia. Most at risk are pediatric patients, geriatric patients and patients with underlying conditions of fluid and electrolyte imbalance. A recent review of safety data for the desmopressin nasal spray products revealed an increased incidence of reports of hyponatremia with desmopressin nasal

spray use in the pediatric population. This led to the removal of the indication for treatment of primary nocturnal enuresis for all desmopressin nasal spray products. The increased incidence of hyponatremia was not evident in the tablet or injectable formulations; therefore the indication was not removed and an upgraded warning was added.

II. Clinical Efficacy

A new bioequivalence study FE992026 CS028 (Study 028) has been submitted with this complete response and is discussed under Clinical Pharmacology. This study provides the bridge to the efficacy data supporting the indications for treatment of central diabetes insipidus and treatment of paroxysmal nocturnal enuresis (PNE) in children ages 6 years and older. In addition, the sponsor has submitted five studies in support of expanding the indication for treatment of PNE to adult patients and three studies in support of the addition of the Renal Concentrating Capacity Test (RCCT) indication. These studies have been reviewed in depth by Dr. Lubas during the first review cycle. The pivotal trials for each indication are reviewed below. In the original NDA package, the Sponsor included safety information from five studies conducted under their Phase 3 program for nocturia in adults (NIA). The Sponsor is not seeking this new indication and no efficacy data was provided. Therefore, review of these trials is limited to clinical safety.

II.a Expansion of the indication for treatment of PNE to adult patients

Study 45A06-053: This is a multicenter, randomized, double-blind study comparing two doses of desmopressin tablets in adolescents and adult patients with PNE. This study was initiated in October 1993 and completed in December 1995.

Study population: Subjects enrolled in the study were age 12 to 45 years, diagnosed with primary nocturnal enuresis and had demonstrated a response to desmopressin nasal spray.

Study Design: This trial consisted of seven study periods beginning with a two-week observation period without study medication followed by a two-week period of treatment with 20 mcg desmopressin nasal spray. Subjects who demonstrated a response (defined as $\geq 50\%$ reduction in the number of wet nights per week) to the nasal spray had a one week washout period and then were randomized to four weeks of treatment with either 200 mcg or 400 mcg desmopressin tablet at bedtime. After the double-blind study period, subjects underwent a two week wash-out period followed by a 12-week open label follow-up period in which all subjects received desmopressin 400 mcg at bedtime. The open-label period was followed by the closing 2 week final wash-out period.

The primary endpoint of this trial was the reduction in the number of wet nights per week at each of the dosage levels. The secondary endpoints evaluated the number of wet nights per week at the end of the double blind period in comparison to the observation period and the period of nasal spray therapy. Detailed patient diaries were used to record the enuresis events.

Study treatments: All subjects were initially treated with desmopressin nasal spray 20 mcg nightly for two weeks. After a one-week washout period, eligible subjects were randomized 1:1 to receive either 200 mcg or 400 mcg desmopressin tablets at bedtime. All patients received two tablets, a 200 mcg desmopressin tablet and a 400 mcg placebo tablet; or a 200 mcg placebo tablet and a 400 mcg desmopressin tablet.

Results:

Disposition: A total of 90 subjects were enrolled into the initial observation study period. Ten patients were withdrawn from the study at the end of the observation period because they had < 6 wet nights during the two week period (9 subjects) or withdrawal of consent (1 subject). Of the 80 subjects who entered the nasal spray and subsequent wash-out period, 14 subjects did not enter the double-blind portion of the study (10 failed to have an adequate response to the nasal spray, 2 withdrew consent and two who ceased having wet nights during the wash-out period). A total of 66 subjects enter the double blind period and were randomized to receive desmopressin tablets (34 subjects in the 200 mcg group and 32 subjects in the 400 mcg group). Three of the 66 subjects enrolled in the double-blind withdrew during this period (one due to adverse events, one to loss of follow-up and one to noncompliance). During the second wash-out period, 6 subjects discontinued the study. During the open label period, one patient withdrew from the study due to lack of response. Overall, 56 subjects completed the trial.

Demographics: The average age of enrollees was approximately 19.4 ± 7.8 years, with a range of 12 – 45. Fifty nine percent of the study population was male and 92% were Caucasian.

Efficacy: The mean reduction in the number of wet nights per week for the ITT population at each phase of the study is outlined in the table below. During the baseline observation period, the mean number of wet nights per week was 5.5 in the 200 mcg group and 4.7 in the 400 mcg group. Treatment with desmopressin nasal spray resulted in a decrease in mean wet nights per week to 1.4 in the 200 mcg group and 0.8 in the 400 mcg group. After a wash-out period, treatment with desmopressin tablets also resulted in a decrease in mean wet nights per week to 2.3 in the 200 mcg group and 1.3 in the 400 mcg group. During the open label extension period when all subjects received 400 mcg desmopressin, the mean number of wet nights per week was 1.0.

Treatment with 200 mcg (0.2 mg) or 400 mcg (0.4 mg) desmopressin tablets resulted in a significant decrease in the number of wet nights per week, compared to the observation or wash-out periods. Desmopressin 400 mcg was associated with a least square mean (LSM) reduction from baseline of 3.7 wet nights per week and the 200 mcg dose was associated with a LSM reduction of 2.9 wet nights per week. There was no significant difference in the treatment effect between the nasal spray and the oral tablets.

Study 45A06-053: Mean Wet Nights Per Week, ITT		
	200 mcg	400 mcg
Observation Period, n	34	32
mean \pm SD	5.5 \pm 1.2	4.7 \pm 1.4
range	3.5 – 7.0	2.5 – 7.0
95% CI	5.1 ; 5.9	4.2 ; 5.2
Nasal Spray Period, n	34	32
mean \pm SD	1.4 \pm 1.5	0.8 \pm 1.0
range	0.0 – 5.5	0.0 – 3.0
95% CI	0.9 ; 1.9	0.4 ; 1.1
Wash-out Period I, n	34	32
mean \pm SD	4.6 \pm 1.9	4.2 \pm 1.6
range	1.0 – 7.0	0.0 – 7.0
95% CI	4.0 ; 5.3	3.6 ; 4.8
Tablet Period, n	31	32
mean \pm SD	2.3 \pm 2.1	1.3 \pm 1.6
range	0.0 – 6.8	0.0 – 6.8
95% CI	1.6 ; 3.1	0.7 ; 1.9
Open Label 400 mcg Tablet Extension, n	51	

Study 45A06-053: Mean Wet Nights Per Week, ITT		
	200 mcg	400 mcg
mean ± SD	1.0 ± 1.3	
range	0.0 – 4.5	

II.b Renal Concentrating Capacity Test

Study 45A03-008: This is a randomized, double-blind, double-dummy study evaluating desmopressin tablet and desmopressin nasal spray for evaluation of renal concentrating capacity.

Study population: Subjects enrolled in the study were age 3 to 18 years with underlying renal disease.

Study Design: This was designed as a four period, four sequence cross-over study with three treatment arms:

- Desmopressin tablet 600 mcg (0.6mg) and placebo nasal spray
- Placebo tablet and desmopressin nasal spray 20 mcg
- Placebo tablet and placebo nasal spray

Study subjects received the desmopressin tablet treatment arm twice, the desmopressin nasal spray once and the all placebo once. A wash-out period of at least one night occurred between treatment periods to minimize the carryover effect. Each patient was randomized to one of four study drug sequences:

- A: placebo, nasal spray, tablet 1, tablet 2
- B: tablet 2, placebo, nasal spray, tablet 1
- C: tablet 1, tablet 2, placebo, nasal spray
- D: nasal spray, tablet 1, tablet 2, placebo

The primary endpoint of this trial was the urine osmolality, measured from the first urine obtained after study drug administration. It should be noted that the active comparator is desmopressin nasal spray. This formulation is currently not approved for RCCT. The desmopressin nasal spray, Concentraid (NDA 19-776) was approved for the RCCT to determine the extent of renal impairment in children with urinary tract disorders in 1990. However, it is no longer marketed and is not available in the US.

Study treatments: All subjects received all three treatment arms in this crossover study. All medications were dosed in the evening before bedtime. Fluid was restricted to 150 mL from 1 hour before dosing to 8 hours after dosing.

Results:

Disposition: A total of 153 subjects were enrolled into the study and 145 subjects are included in the ITT analysis. Of the eight subjects excluded from the ITT analysis, seven did not receive study drug, and one had no efficacy measurement. Overall, eleven subjects did not complete the study.

Demographics: The mean age of the enrolled population was 9.5 years, with a range of 3.5 – 17.2 years. Sixty eight percent of the study population was female and 98% were Caucasian.

Efficacy: The primary endpoint of this trial was the urine osmolality of the first void urine at least one hour after study drug administration at bedtime. Results are outlined in the table below. The mean results of the two periods of dosing for the 600 mcg tablet are presented. The prespecified non-inferiority margin was -7% of the nasal spray which calculates to be -67.3. The LSM difference between the nasal spray and the tablet was -40.7, with the lower bound of the confidence interval of -62.2, which is within the noninferiority margin. As outlined in Dr. Pian's statistical review, the LSM difference between desmopressin tablets and placebo was 227 ± 213.7 mosm/kg was statistically significant ($p < 0.000005$). No treat-by-gender or treatment-by-age effects were noted.

Study 45A03-008: Urine osmolality following study drug, ITT			
	placebo	600 mcg tablet	20 mcg nasal spray
N	141	137	144
mean \pm SD	718.3 \pm 239.4	930.4 \pm 149.1	961.7 \pm 187.0
LSM difference vs NS (95% CI)		-40.7 (-62.2, -19.2)	
p value		0.0003	
LSM difference vs placebo	227 \pm 213.7		
p value	<0.000005		

II.c. Efficacy Conclusions:

Expansion of the indication for treatment of PNE to adult patients: For the expansion of the treatment of PNE indication to adults, desmopressin was effective in decreasing the number of wet nights per week in patients aged 12 – 45 years. Minirin 0.2 mg was associated with a least square mean reduction from baseline of 2.9 wet nights per week and the 0.4 mg dose was associated with a least square mean reduction of 3.7 wet nights per week. There was no significant difference in the treatment effect between the nasal spray and the oral tablets.

Renal Concentrating Capacity Test: For the new indication of testing for renal concentrating capacity, the submitted studies provided adequate evidence that desmopressin 600 mcg in tablet form is effective in demonstrating urinary concentration in patients age 3 to 17 years when compared to placebo. When compared to 20 mcg desmopressin nasal spray, desmopressin 600 mcg tablets were noninferior to the nasal spray with regard to concentrating capacity. The highest age group tested in the pivotal trail was 18 years.

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III. Clinical Safety

This safety review will focus on the clinical trials for proposed indications, PNE and RCT. In addition, safety data from the Phase 3 program for nocturia in adults (NIA) is reviewed. The NIA program safety data is discussed in terms of short-term trials, lasting 2 months or less; and long-term trials which were over 10 months in duration.

Exposure: The overall safety database includes 494 subjects (146 in the placebo group, 204 in the desmopressin 20 mcg nasal spray group, and 144 in the desmopressin 600 mcg (0.6 mg) tablet group) enrolled in the RCCT trials; 95 subjects in the PNE trials; 632 subjects in the short-term NIA trials; and 249 subjects (44 in the 100 mcg group, 108 in the 200 mcg group, and 132 in the 400 mcg group) in the long-term NIA trials.

Deaths: No deaths occurred during any of the clinical trials for PNE, RCCT or bioequivalence studies.

In the NIA short-term trials, three deaths occurred. A 76 year-old woman who received desmopressin 0.1 mg daily for 4 days, died of respiratory insufficiency 3 weeks after the last desmopressin dose. A 62 year-old woman who received desmopressin 0.2 mg daily for 10 days, died of pneumonia 4 weeks after the last desmopressin dose. A 71 year-old man who received desmopressin 0.2 mg daily for 8 days, died of bronchitis 4 months after the last desmopressin dose. Given the rapidity of clearance of desmopressin and the length of time between the last desmopressin dose and the event, it is unlikely that desmopressin therapy played a role in these deaths.

No subjects died during the NIA long-term trials.

Serious adverse events: No serious adverse events occurred in the RCCT or bioequivalence trials. Four serious adverse events occurred in the PNE trials. As outlined in Dr. Lubas's review, the SAE of one patient, a 32 year-old woman with fluid retention and worsening hypertension, is likely due to desmopressin treatment.

In the NIA short-term trials, 16 subjects experienced serious adverse events, with the most common events being headache in three patients and hyponatremia in two patients.

In the NIA long-term trials, 26 subjects (4 in the 0.1 mg group, 11 in the 0.2 mg group and 11 in the 0.4 mg group) experienced serious adverse events. The most common events were hypertension and accidental injury, each occurred in three subjects (one in each treatment group for both events). Other SAEs occurring in more than one subject included cardiac failure, dyspnea, chest pain, headache and sepsis.

Adverse events leading to withdrawal from study: No patients withdrew from the bioequivalence trials due to adverse events. In the RCCT trials, two patients withdrew from the trial due to adverse events. Both of the events, headache and flu-like symptoms were reported as SAEs.

In the PNE trials, four patients withdrew due to adverse events. All were over age 17 years and the events included edema, aggression/nervousness, urinary retention and hypertension.

In the NIA short-term trials, four subjects withdrew from the study due to adverse events, including the three patients who died (discussed previously). A fourth patient withdrew due to nausea, headache and hyponatremia.

In the NIA long-term trials, 25 subjects (2 in the 0.1 mg group, 10 in the 0.2 mg group and 13 in the 0.4 mg group) withdrew from the trial due to adverse events.

Adverse events: In the bioequivalence trial, 5 subjects (7%) in the Mimirin treatment group and 7 subjects (9%) in the DDAVP treatment group experienced gastrointestinal adverse events (e.g.

abdominal discomfort, emesis, nausea and cramps). Two subjects in each treatment group experienced headache.

In the RCCT trials, the most common adverse events were vomiting (5 subjects), and headache (four subjects).

In the PNE trials, the most common adverse events were headache (7%), influenza (5%), and nausea (3%). All other adverse events occurred in less than 2% of the study population.

In the NIA trials, 182 subjects (27 (61%) in the 0.1 mg group, 71 (66%) in the 0.2 mg group and 97 (73%) in the 0.4 mg group) experienced at least one adverse event. The most common events were upper respiratory symptoms (15%), headache (10%), and flu symptoms (10%). Hypertension and accidental injury, each occurred in three subjects (one in each treatment group for both events).

Adverse events of special interest

Hyponatremia: Hyponatremia is a known side effect of desmopressin therapy. Serum sodium levels were not evaluated in the RCCT trials. In the PNE trials, one subject developed a sodium level of 128 mmol/L at Week 6 of the study. The patient was continued in the trial and serum sodium was 141 at Week 8 and 138 at Week 10. The mean serum sodium levels were 140.8 ± 1.2 at baseline, 140.2 ± 1.9 at Week 4, 140.3 ± 3.5 at Week 6, 140.7 ± 2.4 at Week 8, 140.6 ± 2.4 at Week 10, and 141.4 ± 2.0 post therapy.

In the NIA trials, 45 patients developed at least one sodium level below normal and 31 subjects developed "clinically relevant" hyponatremia (< 130 mmol/L). The risk of developing hyponatremia increased with age and declining creatinine clearance/GFR.

Safety Update: As outlined in Dr. Lubas's review, a total of 101 cases adverse events, including 2 deaths, 52 serious case reports and 50 non-serious but unlisted reports were listed in the safety updates. These reports encompass all available formulations of desmopressin (e.g. tablet, melt, intranasal and injection). The two deaths included a 47-year-old woman who had worsening of her thrombotic thrombocytopenia purpura in connection with administration of desmopressin for central DI; and a 39-year-old woman s/p hypophysectomy on desmopressin for central DI who developed hyponatremia secondary to gastroenteritis and then suffered CNS decompensation following a 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.

III.b. Safety Conclusions

The safety profile of Minirin (desmopressin acetate) tablets is similar to the other formulations of desmopressin. Hyponatremia is the predominant clinical safety concern with desmopressin use. Because of the increased incidence of hyponatremia in children noted postmarketing, the indication treatment of PNE has been removed from the desmopressin nasal spray products. With the tablet formulation, there were no incidences of hyponatremia in children reported in the submitted clinical trials. However, it should be noted that most of the trials submitted were conducted in patients over age 12 and serum sodium was not specifically monitored in the RCCT

trials which provide the bulk of the new pediatric data. The risk of developing hyponatremia increased with increasing age and decreasing renal function (creatinine clearance/GFR).

IV. Pharmacology/Toxicology

No new Pharmacology/Toxicology information is included in this submission.

V. Clinical Pharmacology

Please refer to Dr. Khurana's review for complete details. In response to the Approvable Action Letter, the Sponsor conducted a new bioequivalence study FE992026 CS028, a open-label study comparing the bioequivalence of three 200 mcg tablets (total dose 600 mcg) Minirin tablets to three 200 mcg tablets (total dose 600 mcg) DDAVP tablets. As outlined in the table below, the lower bound of the 90% confidence interval for Cmax was below 80.0, by both the Sponsor's analysis and Dr. Khurana's analysis. As noted in his review, Dr. Khurana disagreed with the Sponsor's exclusion of certain subjects from the analyses as these exclusions were not in agreement with the prespecified definitions of the analysis populations. In FDA analysis of all evaluable subjects, the lower bound of the 90% confidence interval for AUCt was also below 80.0.

A DSI audit of the analytical portions of study FE992026 CS28 did not find any serious deficiencies that might affect the outcome of the study. However, questions were raised regarding the accuracy of data from subjects 078 and 079, in light of the anomalous results for subjects 78 and 79 and the lack of investigation and sample sequence verification. Based on these results, Dr. Khurana conducted a reanalysis of the bioequivalence data from study CS28, excluding Period one data for subjects 078 and 079. As outlined, upon this reanalysis, the lower bound of the 90% confidence interval again falls below 80.0 for both Cmax and AUCt. Therefore, it can be concluded that the two tablets are not strictly bioequivalent.

Study FE992026 CS028: Pharmacokinetic Results				
PK Parameter	Minirin	DDAVP	GMR (%)	90% CI
Sponsor's analysis, excluding subjects 013, 040, 071, 076 (n=67)				
AUCinf (pg.hr/mL)	104	114	90.9	93.0 , 99.5
AUCt (pg.hr/mL)	85.0	86.2	80.4	80.1 , 97.5
Cmax (pg/mL)	32.7	37.2	88.0	79.8 , 97.0
FDA Clinical Pharmacology analysis, excluding subjects 071 and 076 (n=69)				
AUCinf (pg.hr/mL)	105.90	114.40	92.57	83.97 , 102.06
AUCt (pg.hr/mL)	79.55	90.40	87.99	79.51 , 96.96
Cmax (pg/mL)	32.35	36.70	87.96	79.79 , 97.37
FDA Clinical Pharmacology analysis, excluding additional subjects 078 and 079				
AUCinf (pg.hr/mL)	105.34	114.31	92.16	83.35 , 101.91
AUCt (pg.hr/mL)	78.96	90.36	87.39	78.78 , 96.93
Cmax (pg/mL)	31.72	36.78	86.23	78.44 , 94.79

Study FE992026 CS028 provides the bridge to the indications treatment of central diabetes insipidus and treatment of primary nocturnal enuresis (PNE) in children ages 6 years and older. While this study reveals that Minirin and DDAVP tablets are not strictly bioequivalent based on Cmax or the more relevant AUCt, there is clinical data from Study 45A03-008 that adequately shows that treatment with Minirin tablets does result in increased urine osmolality in children as young as three years of age. In addition, results from Study 45A06-053 clearly show that treatment with Minirin tablets will decrease urine volume, as evidenced by the number of wet

nights. Therefore, the clinical data available support the clinical anti-diuretic effectiveness of Minirin tablets. Because the biologic action of desmopressin is the same, regardless of the indication, there is no reason to believe that Minirin would not be effective for treatment of central diabetes insipidus, or treatment of PNE in children age 6 to 12 years.

VI. Chemistry, Manufacturing and Control (CMC)

No new CMC information is included in this complete response. As outlined in the CMC Summary Basis of Approval of the original submission, the drug substance was acceptable, the drug product was satisfactory, the EER status was acceptable, and the application was recommended for approval. The Office of Compliance completed their evaluation of the manufacturing facilities on March 26, 2008 and the overall recommendation is acceptable.

VII. Medication Error Prevention

The Division of Medication Error Prevention was consulted regarding the use of the Minirin tradename for the tablet formulation. As outlined in Ms. Duffy's review, objections have been raised regarding the use of the proposed tradename Minirin for desmopressin acetate tablets. Minirin is currently marketed as a nasal spray formulation. The objection to Minirin is based on the potential for name confusion with Minirin (nasal spray), Minocin, Minitran, Minerin and Niravam. As outlined in Dr. Lubas's review, Minitran is a transdermal patch, Minocin is a capsule formulation, and Minerin is an over-the-counter lotion, making the potential for name confusion for these preparations less likely.

Niravam, an orally disintegrating benzodiazepine (alprozalolam), is a tablet preparation available in dosage strengths of 0.25mg, 0.5 mg, 1 mg and 2 mg. There is orthographic similarity between Minirin and Niravam and numerically similar dosage strengths. Because of Minirin's high usage in children, the potential for medication errors resulting in the administration of a central nervous system depressant medication like a benzodiazepine is particularly concerning. Due to the concerns raised, it would be prudent to require the Sponsor to submit alternative proprietary names.

VIII. Other Regulatory Requirements

VIII.a. Financial Disclosure

Dr. Lubas has reviewed the financial disclosure information and found them acceptable.

VIII.b. Pediatrics

This Sponsor has requested a waiver of pediatrics studies for children under age 6 years. For the PNE indication, this waiver is appropriate because there will be a very limited population of children under age 6 years diagnosed with PNE in whom to conduct studies. For the RCCT indication, the Sponsor has conducted a study including children age 3 years and above. There will be a very limited population of children under age 3 years who will require an RCCT. Therefore, a waiver of pediatrics studies for children under age 3 years appears appropriate.

VIII.c. Clinical Audits/Inspections

A DSI audit was conducted of the analytical portion of the submitted clinical pharmacology study FE992026 CS28. DSI found that the accuracy of data from subjects 78 and 79 was questionable, in light of the anomalous results for subjects 78 and 79 and the lack of investigation and sample

sequence verification. Based on these results, Dr. Khurana conducted a reanalysis of the bioequivalence data from study CS28, as discussed in the Clinical Pharmacology section of this review.

IX. Conclusions and Recommendations

IX.a. Conclusions

The Sponsor is seeking approval of three indications, treatment of central diabetes insipidus, treatment of primary nocturnal enuresis in children and adults _____ and for diagnostic use in assessing renal concentrating capacity. b(4)

No new clinical efficacy data has been submitted in support of treatment of central diabetes insipidus. Instead, the Sponsor is relying on the demonstration of bioequivalence to the approved desmopressin tablet, DDAVP. As outlined, the two tablets are not strictly bioequivalent. However, there is sufficient clinical data to support the anti-diuretic effectiveness of the Minirin tablet and there is no reason to believe that this effectiveness would not be demonstrated in patients with central DI.

The Sponsor has provided clinical data supporting the efficacy of Minirin for the treatment of PNE in patients aged 12 – 45 years. Minirin 0.2 mg was associated with a least square mean reduction from baseline of 2.9 wet nights per week and the 0.4 mg dose was associated with a least square mean reduction of 3.7 wet nights per week. Similar to the central DI indication, no new clinical efficacy data has been submitted in support of treatment of PNE in patients aged 6 – 12 years. For that age group, the Sponsor is again relying on the demonstration of bioequivalence to the approved desmopressin tablet, DDAVP. Based on the clinical efficacy noted in the RCCT trials conducted in patients as young as three years, there is no reason to believe that the clinical effectiveness in the treatment of PNE would be altered in children aged 6 – 12 years.

Clinical trial data has been provided and shows adequate evidence that desmopressin 600 mcg in tablet form is effective in increasing urine osmolality and concentrating urine in patients aged 3 to 18 years when compared to placebo. When compared to 20 mcg desmopressin nasal spray, desmopressin 600 mcg tablets were noninferior to the nasal spray with regard to concentrating capacity in this age group. The highest age tested in the pivotal trial was 18 years. _____ b(4)

The safety profile of Minirin (desmopressin acetate) tablets is similar to the other formulations of desmopressin. Hyponatremia is the predominant clinical safety concern with desmopressin use. Because of the increased incidence of hyponatremia in children noted postmarketing, the indication treatment of PNE has been removed from the desmopressin nasal spray products. With the tablet formulation, there were no incidences of hyponatremia in children reported in the submitted clinical trials. The data presented do indicate that the risk of developing hyponatremia increased with increasing age and decreasing renal function (creatinine clearance/GFR).

One remaining unresolved issue is the tradename. Niravam, orally disintegrating alprozalolam, is orthographically similar to Minirin and the dosage strengths are numerically similar. Because of Minirin's high usage in children, the potential for medication errors resulting in children receiving a benzodiazepine, a central nervous system depressant medication, raises a concern.

The Sponsor has been informed about our concern and they admit that they recognize the basis for it. However, at this time, both Niravam and Minirin tablets are available in the European Union. The Sponsor proposes to further address our concerns by providing data regarding medication error data from countries where these two products are already marketed. While the concerns raised make it prudent to require the Sponsor to submit alternative proprietary names, if data support that medication errors are not occurring, then further consideration could be given to allowing the trade name Minirin.

IX.b. Recommendation

Approve, with agreed upon labeling revisions but without a trade name at this time.

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