

Exhibit A

Statement of Marvin C. Meyer, Ph.D.

To: Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061, Rockville, MD 20852

From: Marvin C. Meyer, Ph.D.
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Re: Statement of Expert Opinion in Opposition To Ferring Pharmaceuticals, Inc.'s 2/2/04
Citizen Petition Regarding Generic Desmopressin (Docket No. 2004P-0068)

I hereby submit this opinion in response to Ferring Pharmaceuticals, Inc.'s Citizen Petition dated February 2, 2004, in which Ferring requests that FDA impose additional bioequivalence requirements on ANDA applicants seeking approval for generic desmopressin acetate formulations.

Background

I am Emeritus Professor and former Chairman of the Department of Pharmaceutical Sciences and Associate Dean for Research and Graduate Programs at the College of Pharmacy at the University of Tennessee Health Science Center in Memphis, Tennessee. I received B.S. and M.S. degrees in pharmacy from Wayne State University, in 1963 and 1965, respectively. I received a Ph.D. in Pharmaceutics from the State University of New York at Buffalo in 1969. I am a registered pharmacist in Michigan and Tennessee.

Until my retirement in June 2001, I was a faculty member at the University of Tennessee for 32 years. I served as Assistant, then Associate Professor of Medicinal Chemistry and Pharmaceutics until 1976, when I became a full Professor. I became the Director of the Division of Drug Metabolism and Biopharmaceutics in 1972, then Vice Chairman and Director of the Division of Biopharmaceutics and Pharmacokinetics in 1978. I was appointed Director of Graduate and Research Programs in 1980, Assistant Dean in 1981 and Associate Dean in 1984. I became Chairman of the Department of Pharmaceutical Sciences in 1991 and held that position until I retired in 2001.

I have conducted research in the areas of bioavailability, pharmacokinetics and assay methodology, which is reflected in over 110 publications in those areas. I recently completed a three-year term as a member of the FDA's Pharmaceutical Sciences Advisory Committee and provide consulting services for a number of pharmaceutical companies.

Comments

I thoroughly reviewed Ferring's Citizen Petition and the statement of Dr. Gary L. Robertson in support of that petition. I also reviewed portions of the DDAVP NDA and various literature references discussing desmopressin. Based upon my extensive knowledge and experience in the areas of pharmacokinetics, bioequivalence, and bioavailability, I conclude that the Citizen Petition has no merit. I believe that neither Ferring nor Dr. Robertson raises any significant issue concerning desmopressin that would suggest that FDA should require additional studies beyond the pharmacokinetic (PK) studies ordinarily sufficient to establish bioequivalence. There is no reason to expect that a bioequivalence study conducted using a properly validated analytical method will

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not provide acceptable evidence of the bioequivalence of a generic and innovator dosage form of desmopressin.

I address, and rebut, each of Ferring's and Dr. Robertson's arguments in favor of additional testing as follows:

A. Ferring's Concerns That Desmopressin's Properties Counsel In Favor Of Requiring Additional Studies To Establish Bioequivalence Are Misguided.

Ferring cites a number of purported concerns about desmopressin's properties that, according to Ferring, recommend that FDA require studies beyond PK studies to establish bioequivalence. I disagree with Ferring that any of these purported concerns render a PK study inadequate in the case of desmopressin to establish bioequivalence.

1. Desmopressin's Duration of Action: Ferring argues that different formulations of desmopressin may cause variations in desmopressin's duration of action and that these variations can create a risk of hyponatremia. (Ferring Pet. at 6-7). I disagree with Ferring's assessment that a different formulation would increase the risk of hyponatremia.

First, under the statutory scheme, if an ANDA drug product is a duplicate of the reference listed drug (RLD) and is bioequivalent, it is considered to be therapeutically equivalent. Indeed, the whole statutory structure is premised on this idea. This means that a duplicate desmopressin acetate product that is established as bioequivalent to the RLD through a PK study is expected to have the same onset, maximum effect, and duration of action as the RLD. Ferring offers no evidence to conclude otherwise.

Second, I do not agree with Dr. Robertson's assessment of the risk of hyponatremia. Dr. Robertson states that if the clearance of a dose of desmopressin is prolonged more than 8 hours, the patient might not have sufficient time to excrete any excess water retained during that time due to the antidiuretic effects of the drug. This may cause body water to increase, in turn, causing hyponatremia. (Robertson Stmt. at 4-5). Ferring provides no evidence that the absorption of desmopressin can be delayed long enough for hyponatremia to be possible from a single dose. In order for this to happen, a significant proportion of the desmopressin would have to be delivered many hours later than for the RLD. If this were the case, it would be readily detected in the bioequivalence study. Further, the delivery of a significant portion of desmopressin many hours later than the RLD does not seem to be physiologically possible. A study by d'Agay-Abensour, *et al.*, indicates that absorption of desmopressin from the lower regions of the gastrointestinal (GI) tract (where absorption necessarily would have to take place in order to have such a prolonged effect as to present a hyponatremia risk for a once daily dose) is much lower than from the upper GI tract. d'Agay-Abensour, *et al.*, *Absolute bioavailability of an aqueous solution of 1-deamino-8-D-arginine vasopressin from different regions of the gastrointestinal tract in man*, Eur. J. Clin. Pharmacol. (1993) 44:473-476. The fraction absorbed from the upper GI tract (stomach, duodenum, and jejunum) was 0.19-0.24%, whereas the fraction absorbed from the lower GI tract (ileum, colon, and rectum) was only 0.03-0.04%. d'Agay-Abensour at 475.

Third, there is evidence that formulation factors have little effect on desmopressin's absorption and bioavailability. The NDA-holder for DDAVP tablets, Aventis, sponsored a study

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that investigated the differences in bioavailability among whole, chewed and crushed desmopressin products and desmopressin in oral solution. Argenti, D., *et al.*, *A Pharmacokinetic and Pharmacodynamic Comparison of Desmopressin Administered as Whole, Chewed and Crushed Tablets, and as an Oral Solution*, J. Urology, Vol. 165, 1446-1451 (May 2001). The authors of that study concluded that desmopressin has the same effect on urine volume and osmolality whether absorbed from whole, chewed, crushed tablet or oral solution formulations. Argenti at 1451. This suggests to me that desmopressin is not sensitive to differences in formulations.

2. Dose Titration: Ferring's alleged concerns about the careful dose titration required for desmopressin are not relevant to bioequivalence. (Ferring Pet. at 3, 13). Again, the requirement of bioequivalence is used to establish that a generic product would have the same therapeutic effects as the RLD. If the dosing of the RLD has been determined to be safe and effective, then the determination of a proper dose of desmopressin should be the same whether the physician is prescribing the RLD or a bioequivalent generic. This is true for both adults and children. Thus, Ferring's argument that one cannot extrapolate a child's dose from an adult dose is also irrelevant. (Ferring Pet. at 15). The issue of what dose to employ in a child is not a bioequivalence issue.

In addition, FDA has not, to my knowledge, imposed special bioequivalence requirements for other drugs that require careful dose titration. Some drugs, such as warfarin, require even more careful dose titration than desmopressin. FDA has nonetheless permitted generic warfarin manufacturers to use plasma concentrations of the active drug to establish bioequivalence. Given that FDA deemed PK studies sufficient for warfarin (a drug that does require careful dose titration), the same should be true here – ANDA applicants should be able to rely on PK studies to establish bioequivalence in the case of desmopressin.

3. Subject Variability: I also disagree with Ferring's concern that inter- and intra-subject variability could present bioequivalence problems in desmopressin that would require additional studies.

First, whether the drug exhibits substantial inter- and intra-subject variability does not preclude the use of a PK study to establish bioequivalence, as Ferring suggests. (Ferring Pet. at 5; Robertson Stmt. at 5-6). High subject variability, if it exists, may make it more difficult to obtain acceptable confidence limits for a PK study. But that simply would mean that bioequivalence was not established. It does not prove that the PK study is an unacceptable method for determining bioequivalence in the first instance.

Second, the labeling on Ferring's DDAVP tablets says nothing about food effect on the drug's absorption. Thus, I am skeptical about Dr. Robertson's unsupported contention that variability may be reduced if the drug is taken on an empty stomach. (Robertson Stmt. at 5-6).

Finally, I think Ferring's concern about subject variability conflicts to some extent with its concern about dose titration and duration of action. Ferring seems to suggest that desmopressin has a "narrow therapeutic index" (NTI) because it presents safety risks if the dose is not carefully titrated and if the duration of action is not within a specific range. Desmopressin's purported high AUC variability, however, indicates that subjects are not particularly sensitive to the level of desmopressin in the body. This, in turn, suggests that desmopressin does not have a NTI.

4. FDA's Bioequivalence Regulations: I disagree with Ferring's suggestion that 21 C.F.R. § 320.33 mandates any unique bioequivalence requirements for specific kinds of drugs. (Ferring Pet. at 12-13). Section 320.33 simply summarizes reasons for requiring *in vivo* bioavailability and bioequivalence data instead of permitting applicants to rely only on *in vitro* data. Section 320.33 has no bearing on the issue of how to determine bioequivalence.

5. Bioequivalence Requirements for Drug Products Not Intended for Delivery Into the Bloodstream: I do not find Ferring's reference to drug products that are not intended to act systemically to be pertinent to the issue of whether FDA should require additional bioequivalence studies for desmopressin. (Ferring Pet. at 13-14). Ferring relies primarily on FDA's decision to create special guidelines for metered dose inhalers (MDI) to establish bioequivalence for drug products using that dosage form. Those MDI guidelines concern drug products that act locally at the site of administration, and not via the systemic circulation. (Draft Guidance for Industry, *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products: Chemistry, Manufacturing and Controls Documentation*, at 3 (1998)). Desmopressin, on the other hand, does not act locally in the gastrointestinal tract, but rather is absorbed into the bloodstream and acts systemically, which is why a PK study, which determines the level of active drug in the bloodstream, is FDA's most preferred method for establishing bioequivalence.

B. The Additional Studies Ferring Requests Should Not Be Required.

Ferring requests that FDA require a number of studies to establish bioequivalence in addition to PK studies, including pharmacodynamic (PD) studies, clinical endpoint studies, multiple dosing studies, studies on enuretic children, and studies for both approved doses of desmopressin. In my opinion, none of these additional studies are necessary.

1. Sensitivity of Pharmacokinetic Studies: Ferring's main complaint about the sufficiency of PK testing for desmopressin centers on the level of sensitivity of PK testing. Specifically, Ferring expresses concern that desmopressin levels in the blood may be high enough to have a clinical effect, but too low for conventional PK testing to detect. (Ferring Pet. at 6-7; Robertson Stmt. at 3). Ferring's concern about assay-sensitivity, however, is limited to radioimmunoassay alone. (Ferring Pet. at 6, 14-15; Robertson Stmt. at 3). Neither Ferring nor Dr. Robertson discuss more sensitive assays, such as LC/MS/MS, which can detect blood levels of desmopressin below the effective level cited by Ferring. This type of assay is sufficiently sensitive to do an accurate PK assessment for purposes of establishing bioequivalence.

Moreover, I disagree with Ferring's assessment of the import of Ms. Troendle's statement concerning the difficulty of demonstrating drug absorption due to the fractional amount expected to be absorbed. (Ferring Pet. at 14-15). Ms. Troendle's statement was limited to Ferring's own difficulties in establishing bioavailability due to an assay with insufficient sensitivity, which was not properly validated. (NDA 19-955, Troendle, Gloria, Group Leader's Comments on NDA and EIR, filed 8/9/93). Ms. Troendle's statement does not, in my opinion, call into question the ability of PK studies in general to establish bioequivalence.

Because there are assays in use today that are sufficiently sensitive to detect blood levels of desmopressin below effective levels, in my opinion, Ferring offers no reason for FDA to require studies in addition to a PK study.

2. Pharmacodynamic Testing: Based on the NDA studies, I am skeptical that PD testing would be effective in establishing bioequivalence. First, Ferring concedes that the biomarkers of urinary osmolality and urine output have not been validated against clinical endpoints. (Ferring Pet. at 10). Ferring also states that no correlation has been established between increased urine osmolality and clinical response to desmopressin in primary nocturnal enuresis (PNE). (Ferring Pet. at 11).

Moreover, I have reviewed some of the desmopressin NDA studies, at least one of which indicates that a PD test would not be very sensitive to differences in bioavailability. Specifically, in Study 1, reviewed by Dr. Tien-Mien Chen, there was only a 10-15% difference in urine flow rate and osmolality, despite a doubling of dose between the 0.2 mg and 0.4 mg groups. (NDA 19-955, Chen, Tien-Mien, Ph.D., Review of Two Pharmacokinetic Studies in a New NDA, at 17, filed 4/20/93). The PD test thus did not demonstrate as large an effect as would be expected with such a significant dose increase, indicating that a PD test is insufficiently sensitive to assess bioequivalence.

3. Clinical Studies: Ferring does not offer any evidence or data showing that clinical endpoint studies are or would be superior to PK studies for establishing bioequivalence of a generic desmopressin acetate product. (Ferring Pet. at 4, 10). FDA has concluded that clinical endpoint studies are not and that they should only be used when no other testing options are available. (Guidance for Industry, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations*, at 9-10 (March, 2003)). As I discussed above, a PK study would be sufficient to establish bioequivalence and thus clinical studies should not be used.

4. Repeated Dosing Studies: I do not believe that repeated dosing PK and PD studies are necessary to establish bioequivalence, as Ferring requests. (Ferring Pet. at 15). FDA, for example, does not recommend or require multiple-dose PK studies because they are less sensitive to formulation differences than single-dose studies, and thus recommends only single-dose studies for immediate release drug products. Because desmopressin acetate tablets are an immediate release drug product, a single-dose study, in my opinion, should be sufficient to establish bioequivalence.

5. Studies on Enuretic Children: I do not believe that the differences Ferring cites between adults and children would preclude the use of adults as subjects in bioequivalence testing. Ferring offers no data that would demonstrate that testing on children is necessary, and has itself used adults to establish bioequivalence and bioavailability for the RLD.

Ferring argues that children have different PK, metabolism, distribution, and excretion from adults. (Ferring Pet. at 8, 15-16). I do not think those factors, if true, are relevant to bioequivalence. Ferring offers no data to demonstrate that a test and reference product will be bioequivalent in adults but not in children. Even if Ferring established that the metabolism, distribution, and excretion of desmopressin are different in children compared to adults, this would not be relevant to a bioequivalence study with a crossover design. A number of drugs are indicated for use in children, but FDA does not require bioequivalence studies on those drugs to be conducted in children despite the differences in metabolism and PK.

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Ferring also contends that adults and children “may” differ in gastrointestinal absorption of desmopressin, depending on formulation. (Ferring Pet. at 8). Ferring offers no data to support its contention, nor is it clear how this would be relevant to bioequivalence.

I also believe it is significant that Ferring and the NDA-holder, Aventis, have relied on studies conducted using healthy adult subjects to establish bioequivalence and bioavailability. For instance, Studies 1 and 2 in the NDA were studies submitted to FDA and reviewed by Dr. Tien-Mien Chen to determine the bioavailability of the RLD. Both studies used healthy adult males. Dr. Chen concluded that those studies were “acceptable” to establish the RLD’s bioavailability. (Chen Review at 2-4).

In addition, the published Argenti study, which Aventis sponsored, also used healthy adult males as subjects. In that study, the subjects were given 0.6 mg doses as whole, chewed, and crushed tablets, as well as a solution. The investigators collected the subjects’ blood for 12 hours and measured urine volume and osmolality. The paper concluded that the three tablet dosage forms and the oral solution were bioequivalent using this design. The investigators used healthy adult male subjects to reduce variability and render it easier to make comparisons among the four different treatments. In their view, if the treatments are bioequivalent, the results of the studies could then be applied to the general population, regardless of age, gender or disease state. Argenti at 1449. This discussion directly conflicts with Ferring’s position in its petition that adults should not be used to establish bioequivalence for the drug since it is used primarily for treatment of children.

6. Studies On Both Approved Doses: I disagree with Ferring’s assertion that the two approved strengths of desmopressin do not give proportionally similar drug exposure. (Ferring Pet. at 1-2, 7-8). The NDA studies indicate that studies on both doses are not necessary.

Ferring states that the AUC and Cmax of the two strengths of desmopressin acetate tablets do not give proportionally similar drug exposure. Ferring does not explain, however, why AUC or Cmax should be used to show non-linearity, if plasma concentrations are not appropriate for determining bioequivalence.

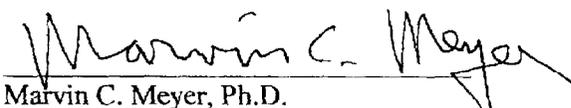
Moreover, based on the FDA review, it appears that the two strengths of desmopressin acetate tablets do give proportionally similar drug exposure. The 0.1 mg tablet biolot actually had about 0.0931 mg of desmopressin (or a content uniformity of 93.1%), while the 0.2 mg tablet biolot had about 0.2046 mg of desmopressin (or a content uniformity of 102.3%). This means the two doses differed in actual strength, relative to their labeled strength, by 9.9%. (Chen Review at 10). If the Cmax and AUC are corrected for strength, the 0.1mg/0.2mg ratios are 97% and 85%, respectively. (Chen Review). Neither 85% nor 97% would be evidence of non-proportionality given the coefficient of variation for AUC of 77-104%. In my opinion, the measurement of Cmax, being less prone to assay sensitivity limitations, may in this case be a more reliable measurement than AUC, particularly given the variability of AUC. A Cmax ratio of nearly 100% indicates that the two strengths of desmopressin acetate tablets yield proportionally similar blood concentrations. Also, the 0.1 mg and 0.2 mg tablets had identical quantities of inactive ingredients and thus would not be expected to exhibit bioavailability differences.

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Conclusion

For the reasons discussed above, I do not believe that FDA should credit any of Ferring's arguments.

Respectfully submitted,


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