

TO: Dockets Management Branch, Food and Drug Administration
Department of Health and Human Services
Room 1-23, 12420 Parklawn Drive, Rockville, MD 20957

RE: Statement of expert opinion in support of the Buchanan Ingersoll Citizen
Petition regarding Generic Desmopressin

FROM: Gary L. Robertson, MD
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Consultant, Ferring Pharmaceuticals

I hereby submit my considered expert opinion on the scientific rationale for the above referenced Citizen Petition requesting the FDA to establish specific bioequivalence requirements for oral products containing desmopressin.

BACKGROUND. I am currently Emeritus Professor of Medicine at the Feinberg Medical School of Northwestern University in Chicago, Illinois. I received my AB and MD degrees from Harvard University in 1957 and 1961, respectively. Subsequently, I completed 3 years of medical residency at the University of Louisville Hospital, 3 years of speciality training in Endocrinology and Metabolism at the Peter Bent Brigham Hospital of Harvard Medical School from 1964 to 1967 and 2½ years of sub-specialty training in the antidiuretic hormone, arginine-vasopressin at the Metabolic and Kidney Disease Branch of the National Institute of Health in Bethesda, Maryland. In 1969, I received the first of several full-time academic appointments that took me from Assistant Professor of Medicine at the University of Illinois in Chicago to Associate and Full Professor of Medicine with Tenure at the University of Indiana Medical School in Indianapolis, to Professor of Medicine and Director of the General Clinical Research Center at the University of Chicago and finally to Northwestern University in 1990 where I also held the rank of Professor of Medicine and Director of the General Clinical Research Center. During my 33 years in academia, I was

continuously engaged in teaching, administration and patient care but devoted most of my time to clinical and basic research into the regulation of vasopressin function and thirst in health and disease. Some of my accomplishments include development of the first clinically useful radioimmunoassay for vasopressin, characterization of the various systems that regulate antidiuretic function and thirst, delineation of their respective roles in the regulation of body water, discovery of several previously unrecognized disorders of water balance including a type of diabetes insipidus caused by abnormal thirst and elucidation of the genetic basis and pathogenesis of an inherited deficiency of vasopressin production. These and other findings have been reported in over 350 publications including 132 original papers, 25 reviews and editorials and 80 book chapters. My achievements have been recognized by numerous research grants and frequent invitations to address medical and scientific groups as well as election to membership in select research societies such as the American Society of Clinical Investigation and the American Association of Physicians (curriculum vitae, attached).

COMMENTS. I shall elaborate on three of the scientific reasons that I believe are most important in petitioning the FDA to require ANDAs for products containing desmopressin to provide additional evidence for bioequivalence to the reference listed drug (RLD), DDAVP.

1. Desmopressin (DDAVP, desamino-D arginine-vasopressin) is a drug with certain unusual if not unique properties in terms of its chemistry, absorption from the GI tract, potency and side effects. It is a nonapeptide analogue of the native antidiuretic hormone, arginine vasopressin (AVP). Like the latter it acts on renal V_2 receptors to reduce urine volume by increasing urine concentration (osmolarity). This antidiuretic effect is the basis for its use in the treatment of the pituitary (AVP-deficient form) of Diabetes Insipidus and is probably also the mechanism by which it reduces or

eliminates nocturnal enuresis in children. Desmopressin differs from AVP in two places. It lacks an N-terminal amino group and D-arginine replaces the L isomer normally found at position 8. These changes reduce its susceptibility to metabolic degradation and eliminate its action at V_{1a} (smooth muscle) and V_{1b} (pituitary) receptors without appreciably impairing its antidiuretic potency at V_2 receptors. Studies in healthy adults using the most sensitive immunoassay available have shown that the native antidiuretic hormone, AVP, produces an antidiuretic effect at plasma concentrations less than 1 pg/ml ($< 1 \times 10^{-12} \text{ M}$)¹. As noted in the Petition, internal Ferring data indicate that desmopressin is capable of producing a significant antidiuretic effect at plasma concentrations of less than 2 pg/ml ($< 2 \times 10^{-12} \text{ M}$). This extraordinary potency explains why desmopressin is so effective when given orally even though its bioavailability remains relatively low. Another result, however, is that desmopressin has a significant antidiuretic effect at plasma concentrations below those which can be measured by the most sensitive radioimmunoassay currently available for the analogue. This means that conventional pharmacokinetic data are of limited value for determining duration of action at least when the drug is administered orally. In this situation, extrapolation of the pharmacokinetic decay-curve below the assay detection limit could grossly underestimate the true duration of action of the drug because some formulations may result in prolonged GI absorption of small amounts of desmopressin that continue to exert a significant antidiuretic effect even though they are too low to be detected by the assay.

The inability of conventional pharmacokinetic data to provide reliable information about the duration of action of orally administered desmopressin is particularly critical for this drug because its safety is largely dependent on this property. The main risk of treatment with desmopressin, AVP or any other antidiuretic

drug is dilutional hyponatremia (low serum sodium). This complication is not a direct or immediate effect. Rather, dilutional hyponatremia is an indirect result of excessive water retention that occurs if and only if the antidiuresis cannot be suppressed and the rate of water intake exceeds urinary and insensible loss. If antidiuretic function is normal, even a high rate of intake does not produce hyponatremia because a decrease in serum sodium of as little as 1-2% suppresses secretion of endogenous AVP, resulting in urinary dilution and a marked water diuresis that quickly eliminates the excess water. However, if the antidiuresis cannot be suppressed normally (e.g. during desmopressin therapy), the excess water is retained and dilutional hyponatremia develops and progresses until the abnormal antidiuresis ceases. The level of antidiuresis is less important in this regard than its duration because even a slight increase in urine osmolarity (e.g. to 200 mosmoles/L) markedly reduces urine output and virtually eliminates the ability to rapidly eliminate excess water from the body. Similarly, the rate of intake does not need to be abnormally high because even a mild impairment in the osmotic inhibition of water intake can result in dilutional hyponatremia if the antidiuresis is maintained at a high enough level for several days. The key to whether a given rate of water intake does or does not cause hyponatremia is how long the antidiuresis is maintained before the effect of the drug ceases and a compensatory water diuresis can develop. If the antidiuretic effect of a drug taken once a day lasts only 8 hours (the optimal time for treatment of nocturnal enuresis), the risk of hyponatremia is very low because any excess water that may be retained during the night can be excreted completely the next day as the effect of the drug ceases and normal control of antidiuretic function by AVP resumes. On the other hand, if drug clearance or GI absorption is prolonged, the resultant antidiuresis may last long enough to prevent a full compensatory water diuresis before the next dose is taken the following night. In this

case, body water may increase rapidly or steadily until severe hyponatremia with all its symptoms and potential morbidity develops.

To establish that a generic formulation of desmopressin does not present a greater risk of hyponatremia than the RLD, it is necessary to demonstrate that it does not have a longer duration of action when given at a dose that produces a similar maximum antidiuretic effect. For this purpose, it is not sufficient to show that the two formulations have similar pharmacokinetic profiles because, as noted above, the generic formulation may prolong the GI absorption of desmopressin in amounts too small to be detected by plasma assays but still sufficient to produce a prolonged antidiuresis. To guard against this risk, it is necessary to demonstrate that the doses of generic which produce a pharmacokinetic profile similar to the RLD also produce a similar pharmacodynamic profile – i.e. the duration of action is also similar. In doing so, urine osmolarity as well as flow should be measured (to distinguish between a solute diuresis and a water diuresis) and the studies should be done in water loaded subjects (to minimize interference from the antidiuretic effect of endogenous AVP). Otherwise, the efficacy and safety of the generic can be established only by appropriately designed and monitored large scale clinical trials.

2. Because of its low bioavailability, desmopressin also presents the risk of excessively large subject-to-subject and/or day-to-day variability in total absorption from the GI tract. Depending on its magnitude and direction, this variability can result in large differences not only in efficacy (which is determined by the level of antidiuresis induced during the first 8 to 10 hours after dosing) but also in safety (which, as explained above, is inversely related to its duration of action after the first 8-10 hours). In the case of the RLD, variability can be reduced by taking the drug on an empty stomach but pH and a host of other uncontrolled or unknown influences,

including binding of desmopressin to various inert ingredients in different formulations of the drug may also play a role. Intra-subject (day to day) variability in absorption is much more difficult than simple inter-subject variability to manage because it cannot be obviated by dose titration. Therefore, another requirement for equating the over-all safety and efficacy of a generic formulation to RLD should be to demonstrate that intrasubject, day-to-day variability of the pharmacokinetic and pharmacodynamic profiles is similar for the two drugs.

3. Because children with nocturnal enuresis are the largest therapeutic indication for desmopressin, they should also be included in the expanded bioequivalence studies described above. The results obtained in healthy adult volunteers probably are not applicable because children are known to absorb and/or eliminate some drugs differently than adults and renal sensitivity to AVP may also be reduced in some enuretics. It is also possible that age or development have different impacts on absorption of desmopressin from different formulations. Therefore, even if doses of desmopressin are adjusted for differences in size, their efficacy and/or safety in children are likely to differ in enuretic children and healthy adults. The safety issue is of particular concern in children because they tend to drink more than adults and are less able to recognize or report symptoms of hyponatremia.

Respectfully,

A handwritten signature in cursive script that reads "Gary L. Robertson". The signature is written in black ink and is positioned above the printed name.

Gary L Robertson, MD

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