

ORIGINAL

NDA 19-955
DDAVP Tablets

Rhône-Poulenc Rorer Pharm
9 August 1993

Group Leader's Comments on NDA and EIR

This NDA is submitted to secure approval for the first oral dosage form for any peptide intended for absorption and systemic action. Because this is such a novel dosing form for a peptide, we have insisted that the data be very clean and clear cut on the bioavailability of the drug. Only a very small fraction (0.7 to 1%) of the drug dose is expected to be absorbed, but demonstration of even this small absorption has been very difficult. When the NDA was first submitted, DSI audit failed to obtain data for review. We were told this was because the data were lost. We agreed to accept repeat of the bioavailability studies, and only the bioavailability studies, because bioavailability seemed to be the crucial issue. However, the DSI audit of the repeat bioavailability study tells us that the data are not acceptable because of serious irregularities in the data. Standard curves were prepared differently from plasma samples, samples' results were accepted even when controls failed, 65% of the total data points were determined at or below a level that was found to have an interassay coefficient of variation of 49%, and "blank" plasma samples contained high concentrations of DDAVP. In addition, repeated data points were apparently selected to fit the desired profile. DSI recommends that the data from these studies not be used in our evaluation of the bioavailability of the drug.

Dr. Herman has looked at the available data on urinary output and osmolality and finds little there to support an approval. The studies were very small, short-term and done in a population of normal patients given a water load.

I conclude that this application is not approvable.


Gloria Troendle