

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-228

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA#: 21-228

Name of Drug: Tolterodine — Release Capsules for overactive bladder

Applicant: Pharmacia and Upjohn Company

Document Reviewed: Vol 1.26

Medical Officer: Brenda Gierhart, M.D., HFD-580

The sponsor has submitted one 12 week placebo-controlled, double-blind, parallel group, randomized trial (98-TOCR-007) in support of Tolterodine — once daily capsules for the treatment of overactive bladder. The trial was conducted at 167 centers in Australia, Europe and North America. There were 3 treatment arms: placebo (N=508), tolterodine — (4 mg qd, N=507), and tolterodine IR (2 mg bid, N=514). There was a 14 day washout/run-in period before randomization.

The primary endpoint was the change in the number of incontinence episodes per week. Diaries were filled out daily. For purposes of assessing efficacy, "change" was calculated by the difference between the last 7 days of the baseline period and the last seven days on drug.

The planned sample size of 360 patients/ group was based on 80% power to detect a mean treatment difference of 4.2 episodes/week, assuming a standard deviation of 18.2 for the change in the number of incontinent episodes in the population. Assuming a 20% dropout rate, the total planned sample size was 1350 patients (450/group).

Demographics and baseline clinical variables were well-balanced at baseline with 97% of patients having at least 5 episodes of incontinence in each treatment group during the 7-day baseline period (placebo mean=23.3, tolterodine — mean=22.1). At least 5 episodes during this period was, in fact, an inclusion criterion for randomization.

The overall dropout rate was 12% with reasons for withdrawal evenly balanced among the groups. Adverse events were the most common reason for withdrawal. Withdrawal for lack of efficacy was very rare (1.4%).

The key result for purposes of the comparison of tolterodine — to placebo was that the difference between the groups was 4.8 episodes/week with a p-value of .0001. This reviewer has reproduced that result. Although the PR formulation had a greater mean change from baseline than the IR formulation (4.8 vs 3.7), the comparison was not statistically significant at the .05 level.

Reviewer's Comments

There are no statistical issues regarding the nominal results of the trial demonstrating that tolterodine formulation is statistically significantly different from placebo on the primary endpoint in the mean number of incontinent episodes. Statistical significance was also achieved for number of micturations/day and volume voided /micturation. However, this reviewer suggests that a better measurement of benefit can be described by referring to what could be expected on a daily basis. Examination of the data reveals that 80% of the patients in the trial had between 1 and 5 incontinent episodes per day during the baseline period. The table below displays, in this 80% subgroup, the percentage of patients who achieved either of two categories of change in episodes/day from baseline:

Change in Number of Episodes per Day

	-1 or -2	-3 or -4
Placebo	34.5%	5.0%
PR	43.0%	7.5%

David Hoberman, Ph.D.

Concur: Dr. Kammerman

Dr. Nevius

cc:

Arch NDA# 21-228

HFD-580

HFD-580/BGierhart, EFarinas

HFD-715/DHoberman, DOB2, Chron

**APPEARS THIS WAY
ON ORIGINAL**

Farinas

Memorandum

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

Date:

From: David Hoberman, Ph.D., HFD-715

Subject: Tolterodine labeling supplement

To: File (NDA# 21-228)

The sponsor has submitted trial 98-TOCR-007 as support for a labeling revision concerning the indication of use of tolterodine for overactive bladder. The Clinical Studies section of the package insert contains a table indicating the results for 1) the number of incontinent episodes/week, 2) the number of micturations/day, and 3) the volume/micturation (mL). In addition, confidence intervals for the difference between tolterodine and placebo are illustrated for these three endpoints. This reviewer has reviewed the data and has found the data reported in the label to be accurate. Since the Medical Officer's revisions are taken directly from the sponsor's numbers, further review is not necessary.

ISI
David Hoberman, Ph.D.

Concur: Dr. Kammerman

ISI
ISI 10/23/00

Dr. Nevius

10-23-00

cc:

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HFD-580

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