

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-143

STATISTICAL REVIEW(S)

OCT 12 1999

Statistical Review and Evaluation

NDA: 21,143
Drug Name: Clotrimazole Vaginal Cream UPS 2%
Applicant: Taro Pharmaceuticals Inc.
Indications: Treatment of vaginal candidiasis
Documents Reviewed: NDA volumes 1.1, dated June 17, 1999
Medical Officer: Winfield, M.D., HFD-590

1. Background

NDA 21-143 is submitted by Taro Pharmaceuticals Inc. for approval of three-day treatment of vaginal candidiasis. The active substance in this drug product is Clotrimazole USP 2%. Gyne-Lotrimin® 3 Vaginal Cream, a drug of Schering-Plough Health Care Products (SPHCP) with a similar formula to Taro's, was approved for 3-day treatment of vaginal candidiasis recently (resubmission of NDA 20-574). The difference in the formulation of two drugs is in their inactive ingredients. The resubmission of NDA 20-574 on 11/25/1997 comprised (1) studies 93-34 and 93-40 combined as a single pivotal study, (2) a new pivotal study, 95-50, of a 2% 3-Day clotrimazole cream that had been conducted by Taro Pharmaceuticals U.S.A. Inc. (3) a bridging study CTZ 97-01 for demonstration of the therapeutic equivalence of the Taro and SPHCP 2% products used for 3 days. A joint Taro and SPHCP decision was made for Taro to file an original NDA which would contain Taro's CMC information and a reference to the safety and efficacy data contained in SPHCP's NDA# 20-574. If Taro's formulation is approved, it will be granted the remainder of SPHCP's exclusivity until November 24, 2001 under the "umbrella policy."

Dr. Stella Machado, a biostatistician of OB/QMR reviewed NDA 20-574. Her conclusions are:

- (i) The SPHCP 3-day 2% and 7-day 1% products are equivalent for Studies 93-34 and 93-40 combined, with respect to therapeutic, clinical and microbiologic cure.
- (ii) The SPHCP 7-day 1% and Taro 3-day 2% products are equivalent in Study 95-50 with respect to therapeutic, clinical and microbiologic cure.
- (iii) The SPHCP 3-day 2% and Taro 3-day 2% products are equivalent in study 97-01 with respect to clinical and microbiologic cure, but the 95% confidence interval is (-0.212, 0.144) for therapeutic cure (rates 62% and 65% for the SPHCP and Taro products, respectively) indicating lack of equivalence.

The Yates correction was used in her calculation of confidence intervals. Equivalence is defined using a 20% delta.

No new clinical efficacy data are submitted with this NDA.

2. Statistical Comments

In Study 97-01, the 95% confidence interval for the difference in therapeutical response rates, SPHCP 3-day 2% minus Taro 3-day 2%, means that with 95% confidence level, the therapeutical rate of SPHCP 3-

day 2% could be as much as 21.2% lower than or as much as 14.4% higher than that of the Taro 3-day 2% regimen. It could also be expressed as such: the therapeutical rate of the Taro 3-day 2% regimen could be as much as 14.4% lower than or as much as 21.2% higher than that of SPHCP 3-day 2% regimen. Note that the two regimens would not be considered bioequivalent. However, as the lower bound of the 95% confidence interval for the difference in rates, Taro's product minus SPHCP's product, is greater than -20%, the Taro 3-day 2% treatment shows that it is equivalent to the SPHCP 3-day 2% treatment, an approved comparator regimen, in Study 97-01.

In summary, Taro 3-day 2% showed it is therapeutically, clinically and microbiologically equivalence to SPHCP 7-day 1% in Study 95-50. It also showed that it is therapeutically, clinically and microbiologically equivalent to SPHCP 3-day 2% in Study 97-01. Because SPHCP 3-day 2% cream is approved for the same indication as is sought in this NDA, the Taro 3-day 2% cream should be considered for approval for the same indication. For further elucidation, please refer to Dr. Machado's review.

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