CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW
April 14, 1998

ANDA 75-265

PRODUCT: Tretinoin Cream USP 0.05%

SPONSOR: Spear Pharmaceuticals, Inc.

REFERENCE LISTED DRUG: Retin-A (Tretinoin USP) Cream 0.05%, Ortho Pharmaceuticals, Inc.

REGULATORY HISTORY

ANDA 74-666 was initially filed for the Tretinoin 0.05% strength and included a bioequivalence study with clinical endpoints. The company then had a major manufacturing and testing site change to Therefore, a new acne-bioequivalence study with clinical endpoints was required. The firm was advised by the Office of Generic Drugs to conduct the study using the highest strength, 0.1% and submit this as a new ANDA. They have three product strengths, 0.1% (ANDA 75-213), 0.05% (ANDA 75-265), and 0.025%. A bioequivalence study with clinical endpoints has also been required for their application for the lowest strength, 0.025%. The firm was advised by the Office of Generic Drugs, in a letter from Douglas Sporn, dated October 15, 1997, that they could request a waiver of evidence of *in vivo* bioequivalence for the intermediate strength, 0.05%, provided the following criteria were met:

1. The proposed product's active and inactive ingredients are qualitatively and quantitatively the same as the reference listed drug.

2. The firm conducts acceptable *in vivo* bioequivalence studies with clinical endpoints for both tretinoin cream, 0.1% and tretinoin cream , 0.025%, comparing the test product to the reference listed drug and placebo (vehicle), evaluating both safety and efficacy. The safety studies should include comparative skin irritation and sensitization tests for both strengths.

3. The firm provides additional comparative data, (e.g., *in vitro* release testing, physico-chemical properties comparison, etc.) for each strength of the proposed product

and the reference listed drug, and the data are acceptable.

The current submission for the intermediate strength product contains information pertinent to the first and last requirements listed above. The in vivo bioequivalence studies with clinical endpoints for the highest and lowest strengths were submitted to their respective applications and are cross referenced in this application. This review will address the *in vivo* bioequivalence requirements for this product.

BIOEQUIVALENCE STUDIES WITH CLINICAL ENDPOINTS

Bioequivalence studies with clinical endpoints, carried out in patients with greater than Grade 2 acne, have been submitted for Tretinoin 0.1% (ANDA 75-213) and for Tretinoin 0.025% (ANDA 75-264). These studies are identified below.

I. ANDA 75-213

Protocol Number, Sponsor:
Study Site:
LRC Study Number: 0205-001

TITLE: Efficacy Bioequivalence Study of 0.1% Tretinoin Cream

II. ANDA 75-264

Protocol Number, Sponsor:
Study Site:
LRC Study Number: 97-235-001-L01

TITLE: Efficacy Bioequivalence Study of 0.025% Tretinoin Cream

Conclusions:

The study conduct and design of both studies are similar to each other and acceptable. Provided the endpoints measured are acceptable to the Division of Dermatologic and Dental Drug Products, and the statistical analysis is approved by the consultant statistician, the results show that the two treatment products (either Tretinoin 0.1% cream and Retin-A 0.1% cream or Tretinoin 0.025% cream and Retin-A 0.025% cream) had an effect greater than placebo and that the test and reference drugs were equivalent in therapeutic effect. The test and reference products

at the 0.025% strength were equally irritating in terms of erythema/peeling. However, the 0.1% strength reference product was more irritating in terms of erythema/peeling than the test product (0.1% strength) at week 2, 8, and 12. There were no differences noted in other adverse events.

Recommendation:

These studies demonstrate clinical equivalence between Spear Pharmaceutical's Tretinoin 0.025% Cream and its reference listed drug, Retin-A Cream 0.025% as well as Spear Pharmaceutical's Tretinoin 0.1% Cream and its reference listed drug, Retin-A Cream 0.1% pending approval by the Division of Dermatologic and Dental Drug Products as well as the consultant statistician.

The requirements outlined in the 10/15/97 letter also specify that the safety studies should include comparative skin irritation and sensitization tests for both strengths. While a comparison of erythema/peeling has been done during the course of treatmetn in each trial, this does not represent a formal test for skin irritation. The requirements for skin irritation and sensitization testing could be met by a sensitization study that measured irritation during the three week initial induction phase.

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