

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 21-022

APPROVAL LETTER



Food and Drug Administration
Rockville MD 20857

NDA 21-022

Aventis Pharmaceuticals, Inc.
Attention: J. Michael Nicholas, Ph.D.
Director, Regulatory Affairs
10236 Marion Park Drive
P.O. Box 9627
Kansas City, MO 64137

Dear Dr. Nicholas:

Please refer to your new drug application (NDA) dated December 18, 1998, received December 18, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%.

We acknowledge receipt of your submissions dated December 21, 1998; January 22, February 3, 11 and 16, March 8, 9 and 22, April 20, 21 and 23, May 5 and 18, June 25, July 27, August 5 (2) and 19, September 3, 14, 21, 27 (2), 28 and 29 (2), October 5, 7, 15, 25, 27 and 29, November 16, 18, 19 and 24, December 6, 8, 13, 14, 15 (facsimile), 16 (facsimile) and 17, 1999 (facsimile).

This new drug application provides for the use of PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, as a component of a comprehensive management program, for the topical treatment in immunocompetent patients with mild to moderate onychomycosis of fingernails and toenails without lunula involvement, due to *Trichophyton rubrum*. The comprehensive management program should include removal of the unattached, infected nails as frequently as monthly, by a health care professional who has special competence in the diagnosis and treatment of nail disorders, including minor nail procedures.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For

administrative purposes, this submission should be designated "FPL for approved NDA 21-022." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitment specified in your submissions dated December 13 and 16, 1999 (facsimile). This commitment, along with the completion date agreed upon, is listed below:

A commitment to conduct within one year of approval, phototoxicity and photoallergenicity studies with PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, as a condition for inclusion of use of the product on fingernails in the approved product label. The study protocols would be submitted to the Agency for its review prior to the conduct of said studies, to assure that the studies fully serve the needs of the Applicant and the Agency with regard to the use of the product for the treatment of fingernails. The Applicant would submit the Phase 4 final study reports to the Agency within one year of NDA approval and submit the relevant protocols to the Agency for review and comment in advance.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitment, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to this Phase 4 commitment must be clearly designated "Phase 4 Commitment."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until December 2000. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted.

If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, at (301) 827-2020.

Sincerely,

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research