CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-212

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-212

Pharmacia & Upjohn
Attention: Terry Reinstein
Regulatory Manager, Regulatory Affairs
700 Portage Road
Kalamazoo, MI 49001

Dear Mr. Reinstein:

Please refer to your new drug application (NDA) dated January 20, 2000, received january 21, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Caverject (alprostadil for injection) .

We acknowledge receipt of your submissions dated December 10, 2001, May 6 and 24, 2002. Your submission of December 10, 2001 constituted a complete response to our November 20, 2000 action letter.

This new drug application provides for the use of Caverject (alprostadil for injection) for the treatment of erectile dysfunction.

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 labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted June 10, 2002). 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 the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no 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 21-212." Approval of this submission by FDA is not required before the labeling is used.

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 are waiving the pediatric study requirement for this action on this application.

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-42
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, please call Eufrecina DeGuia, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ATTACHMENT

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-212

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-212

Pharmacia & Upjohn
Attention: Terry Reinstein
Regulatory Manager, Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001

Dear Mr. Reinstein:

Please refer to your new drug application (NDA) dated January 20, 2000, received January 21, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Caverject (alprostadil for injection) Dual-Chamber Syringe.

We acknowledge receipt of your submissions dated May 2 and 31, June 15 and 21, August 14, 28 and 31, September 6, 14, 15, 18, 21 and 27, and October 2 and 5, 2000.

We also acknowledge receipt of your submission dated November 17, 2000. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following deficiencies.

1. Until actual data are provided to demonstrate that the water content will not significantly affect the drug product during the shelf-life, specifications for water content need to be implemented as follows: NMT [redacted] at release and NMT [redacted] % during the shelf-life.

2. Provide a brief overall description of the sampling plan(s) for production batches and selection of sub-samples for analyses. Evaluation should consider the adequacy of the sampling process (e.g., beginning, middle, end) and the number of samples per production batch.

3. Based on 12 months of stability data at 25°C and 6 months at 40°C, an 18-month expiration period can be granted.

In addition, it will be necessary for you to submit revised draft labeling for the drug. The labeling should be identical in content to the attached labeling (text for the package insert and text for the patient package insert.) Carton labels must be revised to include the statement "Keep out of reach of children".

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the inspector. Satisfactory inspections will be required

before this application may be approved.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Details of any significant changes or findings.

2. Summary of worldwide experience on the safety of this drug.

3. English translations of any approved foreign labeling not previously submitted.

4. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Kim Colangelo, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Susan Allen, M.D.
Director
Division of Reproductive and
Urologic Drug Products (HFD-580)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ATTACHMENT