CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20-649

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-649

JUN 12 1997

Schwarz Pharma, Inc.
Attention: Mr. Steven Pollock
Director, Regulatory Affairs
P.O. Box 2038
Milwaukee, WI 53201

Dear Mr. Pollock:

Please refer to your new drug application dated November 7, 1995, received November 8, 1995, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Edex™ (alprostadil for injection).

We acknowledge receipt of your submissions dated November 20, December 17 and 20, 1996, and March 21 and May 8, 13, and 28, and June 4, 9, and 10, 1997, in response to our approvable letter dated November 8, 1996. The User Fee goal date for this application is June 18, 1997.

This new drug application provides for the treatment of erectile dysfunction due to neurogenic, vasculogenic, psychogenic, or mixed etiology.

We have completed the review of this application, including the submitted draft labeling, 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 draft labeling in the submissions dated December 17, 1996, May 28, and June 10, 1997. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on June 10, 1997. Marketing the product with FPL that is not identical to this draft labeling 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 "FINAL PRINTED LABELING" for approved NDA 20-649. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submission dated December 17, 1996. These commitments, along with any completion dates agreed upon, are listed below.

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. Should an IND not be required to meet your Phase 4 commitments, please submit protocols, data, and final reports to this NDA as correspondences. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to this application, a status summary of each commitment. 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 these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional material 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 material and the package insert directly to:

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

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.

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 contact Terri F.Rumble, B.S.N., Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-649
HFD-580/Div. files
HFD-580/CSO/T.Rumble
HFD-580/Rarick/Jolson/Fourcroy/Srinivasachar/Rhee/El-Hage/Jordan
HFD-870/Dorantes/Chen
HFD-715/Taneja/Kammerman
HFD-160/Cooney/Stinavage
HFD-002/ORM (with labeling)
HFD-102/Office Director
HFD-101/L.Carter
HFD-820/ONDC Division Director
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.
HFI-20/Press Office (with labeling)

APPROVAL (AP) [with Phase 4 Commitments]

Drafted by: 7May 22, 1997/wpfiles/nda/letters/20649ap.ltr
Concurrences: See Page 4
final: Rumble, June 11, 1997

Concurrences:

~~Name~~	Title	Signature	Date
Lisa Rarick, M.D.	Division Director,		6/12/97
Heidi Jolson, M.D., M.P.H.	Deputy Director, Medical Team Leader		6/6/97
Jean Fourcroy, M.D., Ph.D.	Medical Officer		5/28/97
Moo-Jhong Rhee, Ph.D.	Chemistry Team Leader		5/28/97
Kasturi Srinivasachar	Chemistry Reviewer	K. Srinivasachar	5/27/97
Alex Jordan, Ph.D.	Pharmacology Team Leader		5/27/97
Jeri El-Hage, Ph.D.	Pharmacology Reviewer		5/27/97
Angelica Dorantes, Ph.D.	Biopharmacuetics Team Leader		5/28/97
Tien Mien Chen	Biopharmaceutics Reviewer	For	5/28/97
Lisa Kammerman, Ph.D.	Statistical Team Leader		5/25/97
Baldeo-Taneja, Ph.D.	Statistical Reviewer		05/23/97
Peter Cooney, Ph.D.	Microbiology Team Leader	for PHC	23 May 1997
Paul Stinavage, Ph.D.	Microbiology Reviewer		23 May 1997
Lana Pauls, M.P.H.	Chief, Project Management Staff		5/28/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-649

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-649

NOV 8 1996

Schwarz Pharma, Inc.
Attention: Mr. Steven Pollock
Director, Regulatory Affairs
P.O. Box 2038
Milwaukee, WI 53201

Dear Mr. Pollock:

Please refer to your November 7, 1995, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Edex™ (alprostadil for injection).

We acknowledge receipt of your amendments dated February 12, March 1, 14, 15, 20 and 28, April 19 and 29, May 13 and 24, June 19, July 12, August 1 and 7, September 16, 20 and 27, October 2, 7, 14, 25 and 29, and November 6 (telefacsimile), 1996.

We have completed the review of this application as submitted with draft labeling (Package Insert, October 25, 1996, Vial and Carton Labels, October 29, 1996 and Patient Information, October 14, 1996), and it is approvable. Before this application may be approved, however, it will be necessary for you to submit the following information or make the indicated changes, as appropriate:

Biopharmaceutics

An inter-study comparison was carried out for the pharmacokinetic data obtained in studies PHAKI 830 and PHAKI 841, which were conducted using the same dose, IV-infusion rate, and assay methodology. There was a difference between these studies in mean AUC values for PGE_1 in healthy volunteers. Please explain this discrepancy. Possible sources of differences such as pharmacokinetic calculations, analytical site, and analytical operating procedures should be investigated.

Therefore, we request that you a) verify that the analytical methodology (including analytical sites, procedures and data) and pharmacokinetic calculations were properly evaluated, and b) submit the results and descriptions of any discrepancies found.

Chemistry, Manufacturing and Controls

Drug product:

1. The stated overage of % for alprostadil is not permissible for stability assurance for potency and should be eliminated. The assay limits in the USP for alprostadil injection %) cannot be interpreted to mean that an overage is permissible. The monograph

article is for an injectable solution of alprostadil in alcohol and is irrelevant to the dosage form in this NDA.

Additionally, it is not clear what is meant by "theoretical claim" for lactose, as the actual amount of lactose in the vial is mg and after reconstitution with 1.2 mL of diluent, each mL will contain mg of lactose.

2. The regulatory specifications for PGA_1 and PGB_1 are not acceptable. (See comment #5 regarding stability.)

3. The violet color cap is only for the 5 mcg strength. Please revise the table to include the color coding of the vial caps for all strengths of drug product.

4. Regarding the specifications next to the 0 time point data in the stability data tables:

   In the amendment dated September 16, 1996, there are two sets of specifications; the first set in front of the 0 time point data and the other set in front of data at other time point intervals. The set of specifications before the 0 time point data is neither the product release specification nor the end of shelf-life specifications. The origin of this set of specifications must be clarified.

5. Clarify why the specifications for pH and PGA_1 (NMT %) are tighter for Vasoprost than for Edex™. Vasoprost seems to exhibit better stability than Edex in the long-term controlled room temperature studies.

6. The most recent stability data, presented in the amendment dated October 29, 1996, do not justify broadening the specifications for PGA_1 and PGB_1 tc % and %, respectively. The Regulatory (end of shelf life) Specifications for related substances in the drug product should be revised as previously suggested:

   PGA_1 NMT %
   PGB_1 NMT %
   15-keto PGE_1 NMT %
   8-iso-PGE_1 NMT %
   Total %

   The 5 mcg strength of drug product exhibits marginal stability and a 12-month expiration date can be granted only on a tentative basis for this formulation. If stability problems are also encountered with additional lots or if data from ongoing studies are unsatisfactory, it may be necessary to withdraw approval for this strength of Edex™.

   Stability data for lots of the 20 mcg strength of drug product should be provided. The original proposal, agreed to by the Agency, was to place two lots each of the 5 and 40 mcg strengths and one lot each of the 10 and 20 mcg strengths on stability. This protocol should also be followed for lots manufactured with an increased fill volume.

In the absence of primary stability data, a tentative expiration date of 12 months can be granted for the 20 mcg strength of Edex™.

For 10 and 40 mcg strengths of Edex™ an expiration date of 18 months can be provisionally granted pending submission of complete, real time, controlled room temperature data.

Labeling

Package Insert

DESCRIPTION Section

CLINICAL PHARMACOLOGY Section

WARNINGS Section

PRECAUTIONS Section

ADVERSE REACTIONS Section

OVERDOSAGE Section

DOSAGE AND ADMINISTRATION Section

Vial Label

Carton Labels

Patient Information For Edex™ Kit

Specific comments

Erectile Dysfunction: Causes and Treatments section:

Who should NOT use Edex™ section:

What are the risks of using Edex™? section:

Storage and handling section:

Self-injection procedure section:

Prepare Edex™ solution section:

Phase 4 commitments:

Due to the lack of a preservative in the current diluent and because of concerns raised about the possibility of bacterial contamination if the product is not used as labeled, we acknowledge your November 6, 1996, commitment to address the following issues in Phase 4:

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. Should an IND not be required to meet your Phase 4 commitments, please submit protocol, data and final reports to this NDA as correspondences. In addition, we request under 21 CFR 314.81(b)(ivv) that you include in your annual report to this application, a status summary of each commitment. 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 these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

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:

1. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted vs now will facilitate review.

2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Provide details of any significant changes or findings, if any.

4. Summarize worldwide experience on the safety of this drug.

5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. 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.

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.

In addition, please submit three copies of the introductory promotional material 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 material and the package insert directly to:

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

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 such action FDA may take action to withdraw the application.

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

Should you have any questions, please contact:

Terri F. Rumble, B.S.N.
Regulatory Health Project Manager
Telephone: (301) 827-4260

Sincerely yours,

Heidi Jolson M.D. for L.R.

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-649
HFD-580/Div. Files
HFD-2/M.Lumpkin
HFD-80
HFD-580/LRarick/HJolson/JFourcroy/MRhee/KSrinivasachar/AJordan/JElHage/BTaneja/ADorantes/TChen/LPauls/TRumble
HFD-160/PCooney/PStinavage
HFD-102/L.Ripper
HFD-101/L.Carter
DISTRICT OFFICE
HFD-40/DDMAC (with draft labeling)

drafted: TRumble/October 23. 1996/20649.ae3
Final:

APPROVABLE (AE)

Concurrence: See page 10

NDA 20-649

Name	Title	Signature	Date
Lana Pauls, M.P.H.	Chief, Project Management Staff		
Jean Fourcroy, M.D.	Medical Officer		11-7-96
Heidi Jolson, M.D.	Acting Deputy/ Medical Team leader		11/8/96
Kasturi Srinivasachar, Ph.D.	Chemist		11-7-96
Moo-Jhong Rhee, Ph.D.	Acting Chemistry Team Leader		11/7/96
Jeri El-Hage, Ph.D.	Pharmacologist		11-7-96
Alexander Jordan, Ph.D.	Pharmacology Team Leader		11/7/96
~~Baldeo Taneja~~, Ph.D. Tien-Mien Chen	Biopharmaceutics Reviewer		11/07/96
Angelica Dorantes, Ph.D.	Biopharmaceutics Team Leader		11/08/96
Lisa Rarick, M.D.	Division Director		11/8/96