CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-649

ADMINISTRATIVE DOCUMENTS

Item 13

PATENT INFORMATION

1.	ACTIVE INGREDIENT	alprostadil (used as 1:1 clathrate complex with alfadex)
2.	STRENGTHS	5, 10, 20, and 40 mcg
3.	TRADE NAME	SPM 691
4.	DOSAGE FORM, ROUTE OF ADMINISTRATION	Sterile lyophilized powder Intracavernous
5.	APPLICATION FIRM NAME	SCHWARZ PHARMA, INC.
6.	APPLICABLE PATENT NUMBER AND EXPIRATION DATE	None

Item 14

PATENT CERTIFICATION

SCHWARZ PHARMA, INC. (a wholly owned independent subsidiary of SCHWARZ PHARMA AG) is not aware of the existence of any patent rights at the present time which would be infringed upon by the approval of this application. To the best of our knowledge, we do not infringe on any existing pharmaceutical patent, nor are we aware of any pending indication patent.

SCHWARZ
PHARMA

CERTIFICATION STATEMENT

As Required By The

GENERIC DRUG ENFORCEMENT ACT of 1992

For SPM 691 (alprostadil for injection) NDA 20-649

On behalf of SCHWARZ PHARMA, INC. (SPI), we hereby certify SPI did not employ and did not use in any capacity the services of any individual, partnership, corporation or association debarred under subsection (a) or (b) of Section 306 of the Federal Food, Drug and Cosmetic Act in connection with the above-referenced New Drug Application.

Wendy L. Fritz, Director
Human Resources

Peter Gottsacker, President

cc: SPM 691 (alprostadil for injection) NDA 20-649 File

Mail P.O. Box 2038 · Milwaukee, WI 53201 · 5600 W. County Line Road · Mequon, WI 53092
Phone 414 354 4300 · Telex 4311043 · Fax 414 354 4309

SCHWARZ
PHARMA

CERTIFICATION STATEMENT

As Required By The

GENERIC DRUG ENFORCEMENT ACT of 1992

For SPM 691 (alprostadil for injection) NDA 20-649

On behalf of SCHWARZ PHARMA AG, D-40789 Monheim, Germany, I hereby certify that SCHWARZ PHARMA AG did not and will not use in any capacity the services of any individual, partnership, corporation, or association debarred under subsections (a) or (b) of Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with NDA 20-649 SPM 691 (alprostadil for injection).

To the best of my knowledge, I am not aware of any relevant convictions of any affiliated persons responsible for the development of submission of the application.

Dr. Hans-Werner Huppert
Director Drug Regulatory Affairs
SCHWARZ PHARMA AG

Mail P.O. Box 2038 · Milwaukee, WI 53201 · 5600 W. County Line Road · Mequon, WI 53092
Phone 414 354 4300 · Telex 4311043 · Fax 414 354 4309

NDA 20-649
Edex(alprostadil-α-cyclodextrin for injection)
Schwarz Pharma, Inc.

This application will be signed off at the division level, therefore, a Division Director Memo is not needed.

NDA 20-649
Edex™ (alprostadil-α-cyclodextrin for injection)
Schwarz Pharma, Inc.

No Advisory Committee Meeting was held to discuss this drug product.

NDA 20-649
Edex™ (alprostadil-α-cyclodextrin for injection)
Schwarz Pharma, Inc.

No Federal Register Notice, OTC, or DESI documents are applicable.

NDA 20-649
Edex™ (alprostadil-α-cyclodextrin for injection)
Schwarz Pharma, Inc.

No advertising material was provided at this time for review.

NOV 8 1996

Group Leader Memorandum

NDA:	**20-649**
Drug and indication:	**Alprostadil for injection (Edex) for the treatment of erectile dysfunction**
Applicant:	**Schwarz Pharma, Inc.**
Submission received:	**November 9, 1995**
Date of MO review:	**November 7, 1996**
Date of Memorandum:	**November 8, 1996**

In this application, the sponsor requests approval for alprostadil, formulated in an alfadex inclusion complex, for the treatment of erectile dysfunction by intracavernosal injection. In support of this indication, the sponsor has submitted the results of four studies conducted in 1065 men with erectile dysfunction of varying etiologies. The results of these studies, which are described in Dr. Fourcroy's memorandum, suggest that the efficacy and adverse event profile of Edex are comparable to that of a previously approved alprostadil-containing drug (Caverject®). I concur with the recommendation that this application is approvable.

Outstanding issues at the time of this regulatory action include the following:

1) The diluent for reconstitution of alprostadil (sodium chloride injection) lacks a preservative. Caverject®, which is also packaged in single use vials for reconstitution, contains a bacteriostatic diluent. In several communications, Schwarz Pharma has asserted that a bacteriostatic diluent is not necessary for the safe use of this product because patients are instructed by their clinician to use the drug immediately after reconstitution and because the vials are intended for single use only. Further, they assert that infection was not experienced during the conduct of clinical trials.

However, the microbiologist's review of the submitted data raises concerns about the potential for bacterial contamination of the reconstituted drug if the labeled instructions are not followed. As noted in the review dated September 11, 1996, after the reconstituted solution was spiked with microbes, counts of *E. coli* were in excess of acceptance limits following 6 hours of incubation at room temperature. *C. albicans and P. aeruginosa* counts were in excess of acceptance limits after 24 hours and 48 hours of incubation, respectively. In contrast, during refrigeration, the acceptance criteria for microbe counts were met at all time points (2, 4, 6, 24, 48, and 72 hours) for the tested organisms.

To address this concern, the sponsor has been requested to:

1. Strengthen and highlight the professional and patient labeling regarding the need to use the product immediately after reconstitution, and to discard any remaining drug after use.

2. Perform the following investigations as Phase 4 commitments: (a) to monitor patient compliance with the labeled instruction to use the product immediately after reconstitution and to discard any residual drug; and (b) to develop an appropriate preservative system for the diluent and subsequently the reconstituted product.

2) Several chemistry deficiencies were communicated to the sponsor on October 22, 1996. Most notable of the deficiencies that are still outstanding include: (a) the need to correct the % overage for alprostadil, and (b) limitations on allowable shelf life (12 months for the 5 and 20 mcg strengths, and 18 months for the 10 and 40 mcg strengths) based on available stability data.

3) The clinical portions of the professional and patient package inserts require substantial revision. Clinical labeling comments on the October 25, 1996 revised label are appended to this memorandum. Additional comments on the readability of the patient package insert from the Division of Drug Advertising, Communications and Marketing will additionally be conveyed.

Heidi Jolson M.D

Heidi M. Jolson, M.D., M.P.H.
Acting Deputy Division Director, HFD-580

cc:
NDA20-649
HFD-580/LRarick/JFourcroy/HJolson

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Attachment 1
Clinical Comments on Alprostadil Draft Package Insert
November 5, 1996

Clinical Pharmacology
Mode of action

Results of Clinical Trials

Warnings

Precautions

Adverse Reactions

Overdosage

Dosage and Administration

Stability

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-649 Trade (generic) names Alprostadil for injection

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ b. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

Signature of Preparer

10/21/96
Date

Orig NDA
HFD-580/Div File
NDA Action Package

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine Drug Products

Memorandum

Date: 2 June 1997

From: Kasturi Srinivasachar, Ph.D., Review Chemist, HFD-580

Subject: NDA Amendment dated 28 May 1997 for revised trade kit information and corresponding labeling changes

To: NDA 20-649

The locking mechanism for the trade kit proposed in the original NDA submission is a patented device and so cannot be used by the Applicant. Accordingly, the Applicant has proposed the use of a tape for securing the kit after use. The tape, provided by

is to be wrapped around the kit after used needles, syringe and vial are placed inside. The kit can then be discarded. Revised trade kit information, providing for the use of this tape, has been submitted in this Amendment. Portions of the package insert and patient package insert have been revised.

CONCLUSIONS AND RECOMMENDATIONS: The revised trade kit information submitted in this Amendment is satisfactory.

cc: Orig. NDA 20-649
HFD 580/ Div. Files
HFD 580/ K. Srinivasachar/Rhee/CSO
R/D initialed by:

Filename: nda20649.me3

MEMORANDUM

Date: 27 June 1996

From: K. Srinivasachar, Ph.D., Review Chemist, HFD-580

To: NDA 20-649, alprostadil for injection, Schwartz Pharma, Inc.

Subject: Tradename

The firm submitted several tradenames for the drug product which is the subject of this NDA: ADAM, ARTEX, EDEX and VANDEX. These were forwarded to the Labeling and Nomenclature Committee for review. The Committee found ARTEX to be the most acceptable proprietary name. ADAM was deemed misleading and fanciful and consequently unacceptable. EDEX and VANDEX were not considered misleading but several potential look alike/ sound alike conflicts with these names were identified. When informed of these conclusions, the firm indicated that their preference was for the proprietary name EDEX.
The Medical Officer reviewing this Application, Dr. Fourcroy, was consulted regarding this tradename and she had no objections to it. The Acting Division Director, Dr. Rarick, concurred that the name EDEX was acceptable. The potential conflicts identified (EURAX, EUPRAX, UREX, EFUDEX) were not considered serious because of different dosage forms, routes of administration etc.

Conclusions and Recommendations: Schwartz Pharma was informed, by telephone, on 27 June 1996, of the acceptability of the proprietary name EDEX for the Alprostadil for Inj. formulation submitted to NDA 20-649.

CC:
Orig. NDA 20-649
HFD-580/ Div. Files
HFD-580/ K. Srinivasachar
HFD-580/Davies/Fourcroy/Rarick
R/D initialed by
H Davies 6/27/96