CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-649

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-649

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

Dear Mr. Pollock:

We acknowledge receipt on December 18, 1996 of your December 17,1996, amendment to your new drug application (NDA) for Edex®, (alprostadil), injectable.

This amendment contains additional Pharmacokinetic, Chemistry, Manufacturing, and Controls, and Labeling information submitted in response to our November 8, 1996, approvable letter.

We consider this a major amendment under 21 CFR 314.60 of the regulations and it constitutes a full response to our letter. Therefore, the due date under the Prescription Drug User Fee Act of 1992 (PDUFA) is June 18, 1997.

If you have any questions, please contact Terri F. Rumble, B.S.N., Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,

Lana L. Pauls
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA N 20-649
HFD-580/Div. Files
HFD-580/CSO/T.Rumble
HFD-580/Jolson/Fourcroy/El-Hage/Jordan/Srinivasachar/Rhee/Dorantes
DISTRICT OFFICE

Drafted by: Rumble January 8, 1997 20649.ack
Final

ACKNOWLEDGMENT (AC)

NOV 27 1996

NDA 20-649

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 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Edex™ (alprostadil for injection).

We also refer to our approvable letter dated November 8, 1996.

We further refer to your amendment (telefacsimile) dated November 20, 1996, which addresses Item #1 of the Chemistry deficiencies noted in the aforementioned letter.

We have completed our review of your proposal in your submission and have identified the following deficiencies:

1. The amounts of alfadex per vial have been incorrectly listed in Table 1. For example, for the mcg strength, the amount of alprostadil - alfadex per vial should be mcg.

   The calculation of alfadex per vial is incorrect. For example, should equal mcg not Similarly, the amounts of alfadex per vial for the other strengths should be corrected.

2. The proposal to eliminate the % overage by decreasing the fill volume is acceptable. However, it should be noted that the vials still need to be reconstituted with mL of diluent.

3. Batch records and SOPs should be revised to reflect the change in fill volume.

4. A commitment should be made to provide Certificates of Analyses for drug products manufactured using the new fill volume.

5. The stability program should be revised as follows:

The number of mL lots proposed for stability monitoring should be:

mcg --- 2 lots
mcg-- 1 lots
mcg-- 2 lots
mcg -- 2 lots

The expiration dates cannot be extended until satisfactory full shelf-life stability data are provided for production scale lots of drug product manufactured using the new fill volume of mL. Until this time, the expiration dates should remain 12 months for the 5 mcg strength and 18 months for the 10 and 40 mcg strengths of the drug product.

For the 20 mcg strength, an expiration date of 18 months can only be considered after submission of satisfactory stability data for the mL fill volume lots (18 and 12 months CRT) and mL fill volume lots (3 month CRT and ACC) as outlined in the Amendment. Until that time, the expiration date for this strength should remain 12 months. Any further extension of the expiration date will depend on the generation of satisfactory full shelf-life data on lots manufactured using the new fill volume of mL.

The above comments should be considered when responding to the deficiencies specified in our letter of November 8, 1996. Any additional amendments 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.

If you have any questions, please contact:

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

Sincerely,

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-580/CSO/Rumble/Pauls
HFD-580/Srinivasachar/Rhee/Jolson/Rarick
HFD-820/Yuan Yuan Chiu (only for CMC related issues)

drafted: Rumble/November 25, 1996/20649.ir1
r/d Initials: Jolson, 11.26.96/Srinivasachar, 11.26.96/ Rhee, 11.26.96/ Pauls,11.26.96
final: Rumble, 11.26.96

ADVICE LETTER

NDA 20-649

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

Dear Mr. Pollock:

Please refer to your pending November 7, 1996, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Edex (alprostadil for injection).

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 request your commitment to address the following issues in Phase 4:

The purpose of this correspondence is to communicate these recommendations and to obtain your commitment to pursue these studies as Phase 4 investigations.

If you have any questions concerning these commitments, please contact Ms. Terri Rumble, Project Manager, at (301) 827-4260.

Terri F. Rumble, Project Manager

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic
Drug Products, HFD-580

NDA 20-649

JUL - 3 1996

Schwartz Pharma, Inc.
Attention: Mr. Steven R. Pollock
Director, Regulatory Affairs
5600 W. County Line Road
Mequon WI 53092

Dear Mr. Pollock:

Please refer to your pending December 13, 1995, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Viridal (alprostadil for injection).

We also refer to your amendment dated May 24, 1996.

We have completed our review of the amendment, and have the following questions regarding the container/closure integrity test:

1. What amount of dye must enter the syringe to result in a reading of florescence units?

2. What is the identity and volume of the fluid contained in the syringes?

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Ms. Christina Kish at (301) 443-3520.

Sincerely yours,

7-3-96

Lisa Rarick, M.D.
Acting Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Center for Drug Evaluation and Research

cc:
Original NDA
HFD-580
HFD-580/JFourcroy/KSrinivasachar
HFD-160/PStinavage/PCooney
HFD-580/CKish/6.20,7.1.96/n20649.ir
concurrence:KSrinivasachar 6.20.96/HDavies 6.20.96/LPauls 6.26.96

INFORMATION REQUEST (IR)

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention : Dan Boring, Chair, HFD-530, Corporate Building, Room N461

From: Division of Metabolism and Endocrine Drug Products. HFD-510
Attention: K. Srinivasachar, Ph.D. Phone: 443-3510

Date: 1 April 1996

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: 1) ADAM 2) ARTEX 3) EDEX 4) VANDEX NDA #: 20-649

Established name, including dosage form: alprostadil for injection: lyophilized powder in single dose vials containing 5,10,20 or 40 micrograms of alprostadil for intracavernosal injection

Other trademarks by the same firm for companion products: VASOPROST (alprostadil for injection) -- NDA

Indications for Use (may be a summary if proposed statement is lengthy):
For the diagnosis and treatment of erectile dysfunction of any origin.

Initial comments from the submitter (concerns, observations, etc.)
The dosage form is a sterile lyophilized powder for intracavernosal administration after reconstitution with sterile, isotonic saline. The drug (alprostadil or prostaglandin E_1) is contained in an alfadex (α-cyclodextrin) inclusion complex. The firm initially submitted the Tradename VIRIDAL which was deemed unacceptable by the L & N Committee. Two other tradenames, INSTAREX AND INVIGOR submitted by the firm were also judged unacceptable by the L & N Committee.. The proposed tradename ADAM is an acronym for Alprostadil Drug Administration for Men

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Consult #599 (HFD-510)

ADAM
ARTEX
EDEX
VANDEX alprostadil for injection

(1) ADAM - the manufacturer states that ADAM is an acronym for Alprostadil Drug Administration for Men. However, the Committee feels that this name will be used in a quasi-religious sense of the biblical progenitor of the human race. This seems like a misleading and fanciful application of the name and is unacceptable.

(2) ARTEX - The LNC found no look alike/sound alike conflicts nor misleading aspects in the proprietary name.

(3) EDEX - The LNC noted several potential look alike/sound alike conflicts with the proposed proprietary name: EURAX, EUPRAX, UREX, and EFUDEX. There are no obvious misleading aspects in the trademark.

(4) VANDEX - The LNC noted several potential look alike/sound alike conflicts with the proposed proprietary name: VAMATE, VANADRYX and VANTIN. There are no obvious misleading aspects in the trademark.

Overall, the Committee finds ARTEX to be the most acceptable proprietary name.

D Bowing 5/23/96, Chair
CDER Labeling and Nomenclature Committee

Cleared for Faxing: Marirus 6-20-96
Lisa Rarick, M.D.
Acting Director

NDA 20-649

NOV 21 1995

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

Dear Mr. Pollock:

We have received your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for the following:

Name of Drug Product:	alprostadil alphadex for injection 5 mcg, 10 mcg, 20 mcg, and 40 mcg
Therapeutic Classification:	Standard
Date of Application:	November 7, 1995
Date of Receipt:	November 8, 1995
Our Reference Number:	NDA 20-649

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 7, 1995, in accordance with 21 CFR 314.101(a).

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Should you have any questions concerning this NDA, please contact:

Mr. Stephen Trostle
Consumer Safety Officer
301-443-3520

Sincerely yours,

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Office of Review Management
Center for Drug Evaluation and Research

cc: Original NDA 20-649
HFD-510/Div. Files
HFD-80
HFD-510/STrostle/ft/stt/11/16,20/95 \N20649AK.000
ST 12/5/95

ACKNOWLEDGEMENT (AC)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-649

JUN 2 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 pending 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 also refer to your submission dated May 8, 1997, which addressed the CMC labeling recommendations and have found those changes acceptable.

We have completed our review of the proposed physician package insert submitted December 17, 1996, for your submission and have several comments. Revisions have been incorporated directly into the enclosed package insert. Additions have been noted in double underline, deletions have been noted in ~~strikeouts~~. Additional comments requiring response are in 14 pt bold face type.

Please submit your revised package insert as soon as available so that we can continue the evaluation of your NDA.

If you have any questions, please contact Terri F. Rumble, B.S.N.,Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,

5/30/97

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

Enclosure

cc:
Original NDA 20-649
HFD-580/Div. Files

drafted: Rumble/May 30, 1997/20649pi.ir1
concurrences: Jolson, 6.2.97
Final: Rumble,6.2.97

INFORMATION REQUEST (IR)

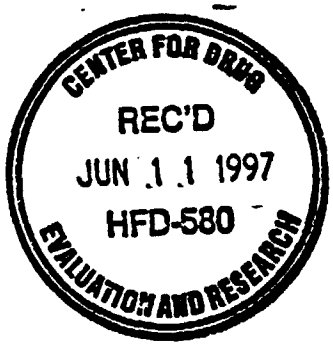
SCHWARZ
PHARMA

June 10, 1997

ORIGINAL

ORIG AMENDMENT

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and
Urologic Drug Products (HFD-580)
Attn: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857-1706



RE: NDA 20-649: EDEX™ (alprostadil for injection) for the Treatment of Erectile Dysfunction

AMENDMENT 030

Chemistry, Manufacturing and Control Data
Revised Professional Package Insert (6/10/97) and Patient Information Sheets (6/9/97)

Dear Sir/Madam:

Pursuant to 21 CFR § 314.60 and 314(a)(1), Schwarz Pharma, Inc. (SP) is submitting a single copy of an amendment for the above refereaced New Drug Application. Reference is made to the telephone conversation of June 10, 1997 between Terri Rumble, Regulatory Health Project Manager and Suzanne Bennett, Manager, Regulatory Affairs, SP, wherein additional changes to page 5 of the professional package insert (deletion of " ' in the first sentence under the heading Aspirin, Warfarin, Digoxin, Glyburide) and page 9 (typographical errors in the first paragraph under 7) Drug Interactions) were discussed.

This amendment contains revisions to the professional package insert (6/10/97) and Patient Information Sheets (6/9/97). All revisions are underlined.

If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs at (414) 238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett for

Steven Pollock, Director
Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

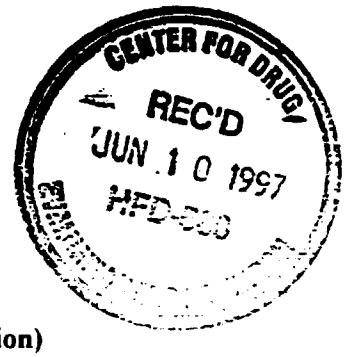
SCHWARZ
PHARMA

ORIGINAL

BC

June 9, 1997

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and
Urologic Drug Products (HFD-580)
Attn: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857-1706



RE: NDA 20-649: EDEX™ (alprostadil for injection) for the Treatment of Erectile Dysfunction

AMENDMENT 029

Chemistry, Manufacturing and Control Data
Revised Professional Package Insert (6/9/97) and Patient Information Sheets (6/9/97)

Dear Sir/Madam:

Pursuant to 21 CFR § 314.60 and 314(a)(1), Schwarz Pharma, Inc. (SP) is submitting duplicate copies of an amendment for the above referenced New Drug Application. An additional desk copy is enclosed. Reference is made to the telephone conversation of June 9, 1997 between Terri Rumble, Regulatory Health Project Manager and Suzanne Bennett, Manager, Regulatory Affairs, SP, wherein it was agreed that SP would fax the enclosed labeling changes in response to the Agency's facsimile dated June 9, 1997, followed by hard copy.

This amendment contains revisions to the professional package insert (6/9/97) and Patient Information Sheets (6/9/97). All revised text is underlined.

If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs at (414) 238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett for

Steven Pollock, Director
Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

SCHWARZ
PHARMA

June 4, 1997

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and
Urologic Drug Products (HFD-580)
Attn: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857-1706

RE: **NDA 20-649: EDEX™ (alprostadil for injection) for the Treatment of Erectile Dysfunction**

AMENDMENT 028

Chemistry, Manufacturing and Control Data
Revised Professional Package Insert (6/3/97) and Patient Information Sheets (6/4/97)

Dear Sir/Madam:

Pursuant to 21 CFR § 314.60 and 314(a)(1), Schwarz Pharma, Inc. (SP) is submitting duplicate copies of an amendment for the above referenced New Drug Application. An additional desk copy is enclosed. Reference is made to the telephone conversation of June 2, 1997 between Terri Rumble, Regulatory Health Project Manager and Suzanne Bennett, Manager, Regulatory Affairs, SP, wherein it was agreed that SP would forward the enclosed package insert changes, in response to the Agency's facsimile dated June 2, 1997, via facsimile followed by hard copy and diskette (WORD 6.0) versions. Reference is also made to the June 3, 1997 telephone conversation wherein it was agreed that any corresponding changes to the Patient Information Sheets would be forwarded as quickly as possible.

This amendment contains the above referenced revisions to the professional package insert (6/3/97) and Patient Information Sheets (6/4/97). SP has also incorporated the package insert revisions specified in Amendment 025, dated May 8, 1997, and Amendment 027, dated May 28, 1997. All revisions are underlined.

If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs at (414) 238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett for

Steven Pollock, Director
Regulatory Affairs

RIGINAL

SCHWARZ
PHARMA

ORIG AMENDMENT

May 28, 1997

ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and
Urologic Drug Products (HFD-580)
Attn: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857-1706

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

RE: NDA 20-649: EDEX™ (alprostadil for injection) for the Treatment of Erectile Dysfunction

AMENDMENT 027

Chemistry, Manufacturing and Control Data
Revised Trade Kit Information and Corresponding Labeling Changes

Noted 6/10/97

Dear Sir/Madam:

Pursuant to 21 CFR § 314.60 and 314(a)(1), Schwarz Pharma, Inc. (SP) is submitting duplicate copies of an amendment for the above referenced New Drug Application. An additional desk copy is enclosed. Reference is made to the telephone conversation of May 28, 1997 between Terri Rumble, Regulatory Health Project Manager and Suzanne Bennett, Manager, Regulatory Affairs, SP, wherein Ms. Bennett stated it was necessary to alter the EDEX trade kit to remove the locking mechanism as it appears to be patented according to recently received information. The locking mechanism has been deleted and replaced with a piece of tape to secure the kit after use. Accordingly, portions of the package insert and patient package insert have been revised and are enclosed. This amendment contains revised trade kit information.

If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs at (414) 238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett for

Steven Pollock, Director
Regulatory Affairs

SP:blb
Enclosures

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 2 9 1997
HFD-580

ORIGINAL

SCHWARZ
PHARMA

May 13, 1997

ORIG AMENDMENT
NV-516

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products (HFD-580)
Attn: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-649: EDEX™ (alprostadil for injection) for the Treatment of Erectile Dysfunction

AMENDMENT 026

CLINICAL DATA SECTION
Safety Update (11/1/96 - 3-31/97)

Dear Sir/Madam:

Pursuant to 21 CFR § 314.60, Schwarz Pharma, Inc. (SP) is submitting duplicate copies of an amendment for the above-referenced New Drug Application. An additional desk copy is enclosed. Reference is made to the agency's voice mail request of May 8, 1997, from Terri Rumble, Regulatory Health Project Manager, to Suzanne Bennett, Manager, Regulatory Affairs, SP, wherein Ms. Rumble requested a safety update. Reference is also made to the May 12, 1997 conversation between Ms. Rumble and Steven Pollock, Director, Regulatory Affairs, SP

This update contains safety information for the period November 1, 1996 through March 31, 1997. As reported in the May 12, 1997 conversation referenced above, the previous safety update (Amendment 023, December 20, 1996) reported a number of ongoing studies. These studies included open-label extensions, IIIb, and other European studies. A total of 137 new patients were enrolled across 4 studies (136 in the 3 IIIb studies and 1 in the European carpule study) during the referenced reporting period **(see Attachment 1)**. A summary of serious adverse experiences and study withdrawals due to adverse experiences from these trials is enclosed **(Attachment 2)**. The individual patient listings can be found in **Attachment 3**.

There were no serious adverse experiences from foreign marketing experience and no serious, unexpected adverse experiences associated with EDEX reported during this period. This safety update contains no new information that adversely affects the risk/benefit assessment of EDEX.

If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs at (414)238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett for

Steven Pollock, Director
Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

SCHWARZ
PHARMA

DUPLICATE

ORIG AMENDMENT

May 8, 1997

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products (HFD-580)
Attn: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-649: EDEX (alprostadil for injection)
for the Treatment of Erectile Dysfunction

AMENDMENT 025

CHEMISTRY, MANUFACTURING AND CONTROLS SECTION
Response to April 29, 1997 Facsimile

Dear Sir/Madam:

Pursuant to 21 CFR § 314.60 and 314.110(a)(1), Schwarz Pharma Inc. (SP) is submitting duplicate copies and a desk copy of an amendment to the above-referenced New Drug Application. Reference is made to the Agency's facsimile dated April 29, 1997.

This amendment contains SP's response to the aforementioned facsimile regarding the Chemistry, Manufacturing and Controls and Labeling comments presented by the Agency. This response was initially faxed to the Agency on April 30, 1997.

If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs at (414) 238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett for

Steven R. Pollock
Director, Regulatory Affairs

SRP:mmw

SCHWARZ
PHARMA

ORIGINAL

March 21, 1997

ORIG AMENDMENT

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products (HFD-580)
Attn: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-649: EDEX (alprostadil for injection)
for the Treatment of Erectile Dysfunction

AMENDMENT 024

CHEMISTRY, MANUFACTURING AND CONTROLS SECTION
Stability Data to Support 18-Month Expiry for 20 mcg Strength

Dear Sir/Madam:

Pursuant to 21 CFR § 314.60 and 314.110(a)(1), Schwarz Pharma is submitting duplicate copies of an amendment for the above-referenced New Drug Application. Additionally, one desk copy is enclosed. Reference is made to Item 5 of the Agency's facsimile dated November 27, 1996, wherein additional data was requested to support an 18-month expiry date for the 20 mcg strength.

This amendment contains the requested stability data on the 20 mcg strength to support an expiration date of 18 months, and Certificates of Analysis for the two 20 mcg lots manufactured with a 1.778 mL fill volume.

If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs at (414) 238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett for

Steven Pollock, Director
Regulatory Affairs Department

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

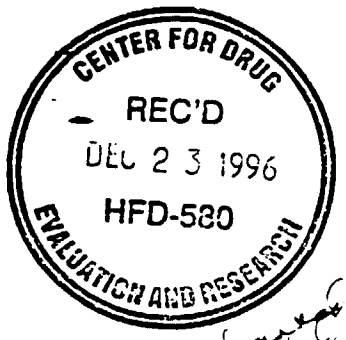
CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 2 4 1997
HFD-580

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

SCHWARZ

December 20, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products (HFD-580)
Attn: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857-1706



updated mailed & received 12/18/97

RE: NDA 20-649: EDEX (alprostadil for injection) for the Treatment of Erectile Dysfunction

AMENDMENT NO. 023

CLINICAL DATA SECTION
Safety Update

Dear Sir/Madam:

Pursuant to 21 CFR § 314.50 (d)(5)(vi)(b)(3) and 314.60, Schwarz Pharma, Inc. (SP) is submitting duplicate copies of an amendment to the above-referenced New Drug Application. Reference is made to the Agency's "action" letter, dated November 8, 1996, wherein the agency requested a safety update.

This safety update contains information on three recently completed studies on the short-term use of EDEX representing 217 patients treated with EDEX. Two of the studies are office studies for the diagnosis of erectile dysfunction and one study is a multicenter study with an office period and a short-term at-home treatment period. None of the established primary (long-term clinical use), secondary (uncontrolled older European long-term studies), or tertiary (clinical pharmacology) database criteria applied to these three studies. Therefore, the safety information obtained from these studies has not been integrated into the existing databases. However, for your convenience the rates for both local and clinical adverse experiences observed in the recently completed studies have been pooled manually with corresponding rates for the primary database (long-term therapy studies). As expected, the results from these short-term studies have no significant influence on the overall adverse experience rates reflecting long-term use of EDEX. Therefore, the numbers regarding the AE incidence rates presented in the draft professional package insert (Rev. 12/3/96) do not need revision. Brief summaries of the clinical trial reports for these three studies are enclosed. Requested safety information for other indications and routes of administration (Peripheral Arterial Occlusive Disease and renal dysfunction) is also included.

If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs, at 414/238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

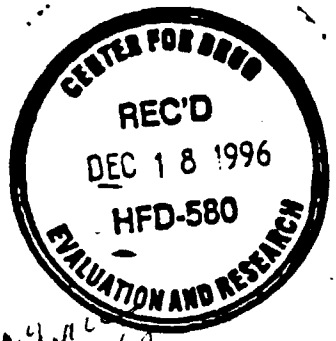
Suzanne Bennett for

Steven Pollock
Director, Regulatory Affairs

Enclosures

SCHWARZ
PHARMA

ORIGINAL



December 17, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products (HFD-580)
Attn: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-649: EDEX (alprostadil for injection) for the Treatment of Erectile Dysfunction

ORIG AMENDMENT

AMENDMENT 022

CHEMISTRY, MANUFACTURING AND CONTROLS SECTION
Response to November 8, 1996 Action Letter and November 27, 1996 Facsimile

Dear Sir/Madam:

Pursuant to 21 CFR § 314.60 and 314.110(a)(1), Schwarz Pharma (SP) is submitting duplicate copies of an amendment to the above-referenced New Drug Application. Additionally, five desk copies of Volume 1 are enclosed. Reference is made to the Agency's "action" letter dated November 8, 1996. Reference is also made to SP's facsimile dated November 20, 1996, containing a proposal to eliminate the % overage via a reduction in fill volume, and the Agency's response, via facsimile, dated November 27, 1996.

This amendment contains SP's response to the aforementioned "action" letter. The issues presented in the Agency's November 20, 1996 facsimile have been incorporated into this response. For ease of review, SP has boldfaced the Agency's "action" letter comments regarding Pharmacokinetic, Chemistry, Manufacturing, and Controls, and Labeling.

The requested safety update is targeted for submission on or before December 23, 1996.

A copy of the introductory promotional material proposed for this product is enclosed. Two copies of the promotional material and package insert are simultaneously being sent to the Division of Drug Marketing, Advertising and Communications.

If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs at (414) 238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett for

Steven Pollock, Director
Regulatory Affairs

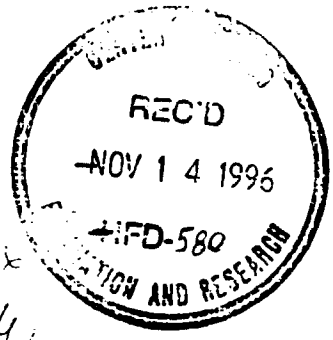
Enclosures

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Mail P.O. Box 2038 Milwaukee, WI 53201 5600 County Line Road Mequon, WI 53092
Telephone 414 354 4300 Telex 1[illegible] Fax 414 354 4309

SCHWARZ
PHARMA

ORIGINAL



NEW CORRESP

November 13, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products (HFD-580)
Attention Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-649: SPM 691/EDEX (alprostadil for injection) for the Treatment of Erectile Dysfunction

RESPONSE TO FDA CORRESPONDENCE

Dear Sir/Madam:

Reference is made to the agency's approvable letter dated November 8, 1996. Pursuant to 21 CFR § 314.110(a)(1), it is the intention of Schwarz Pharma, Inc. to amend the referenced New Drug Application.

If there are any questions regarding this correspondence, please contact Suzanne Bennett, Manager, Regulatory Affairs, at (414) 238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett for

Steven R. Pollock, Director
Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS DATE

:mmw

SCHWARZ
PHARMA

October 29, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products (HFD-580)
Attn: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-649: SPM 691/EDEX (alprostadil for injection) for the Treatment of Erectile Dysfunction

AMENDMENT 021

CHEMISTRY, MANUFACTURING AND CONTROLS SECTION
Response to Chemistry Reviewer's Comments

Dear Sir/Madam:

Pursuant to 21 CFR § 314.60, Schwarz Pharma (SP) is submitting duplicate copies of an amendment for the above-referenced New Drug Application. Two additional desk copies are enclosed. Reference is made to the Agency facsimile received on October 22, 1996, containing comments from the Chemistry Reviewer, and to the October 28, 1996 telephone conversation between Terri Rumble, Project Manager, Division of Reproductive and Urologic Drug Products, and Suzanne Bennett, Manager, Regulatory Affairs, SP., wherein a commitment was made to respond to the referenced Reviewer's comments by facsimile, October 29, 1996, with physical delivery of the entire amendment to occur Wednesday, morning, October 30, 1996.

This amendment contains SP's full response to the Chemistry Reviewer's comments contained in the referenced facsimile. For ease of review we have re-listed the Reviewer's questions in boldfaced type. SP proposes to schedule a conference call to discuss any outstanding issues, if deemed appropriate by the Agency.

If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs at (414) 238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett for

Steven Pollock, Director
Regulatory Affairs Department

SRP:blb
Enclosures

Mail P.O. Box 2038 · Milwaukee, WI 53201 · 5600 County Line Road · Mequon, WI 53092
Telephone 414 351 1200 · Telex 4711043 · Fax 414 351 1209

SCHWARZ

October 25, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products (HFD-580)
Attn Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-649: SPM 691/EDEX (alprostadil for injection) for the Treatment of Erectile Dysfunction

AMENDMENT 020

Revised Professional Package Insert (10/25/96)
Copy of 10/22/96 Facsimile - Response to Pharmtox Reviewer
Copy of 10/24/96 Facsimile - Response to Pharmacokinetic Reviewer

Dear Sir/Madam

Pursuant to 21 CFR § 314.60, Schwarz Pharma, Inc. (SPInc) is submitting duplicate copies of an amendment for the above-referenced New Drug Application. An additional desk copy is enclosed. Reference is made to the Agency facsimile received on October 22, 1996 (enclosed), and to the October 25, 1996 telephone conversation between Terri Rumble, Project Manager, Division of Reproductive and Urologic Drug Products, and Suzanne Bennett, Manager, Regulatory Affairs, SPInc., wherein a commitment was made to respond to the referenced facsimile by Monday, October 28, 1996.

This amendment contains the following: 1) revised labeling which incorporates the changes recommended in the referenced Agency facsimile; 2) a copy of our October 22, 1996 facsimile to Terri Rumble, responding to Dr. Jeri ElHage's concern over our stated exposure comparisons in the package insert, and 3) a copy of our October 24, 1996 facsimile to Dr. Albert Chen indicating requested revisions to the pharmacokinetic section of the package insert.

SPInc proposes to schedule a conference call to discuss any current or additional changes to the package insert, if deemed necessary by the Agency. If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs at (414) 238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett

Steven Pollock, Director
Regulatory Affairs Department

SRP:blb
Enclosures

SCHWARZ
PHARMA

October 16, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products(HFD-580)
Attn: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-649: SPM 691/EDEX (alprostadil for injection) for the Treatment of Erectile Dysfunction

GENERAL CORRESPONDENCE
Field Copy Certification

Dear Sir/Madam:

This statement certifies that a field copy of the Chemistry, Manufacturing and Control portions of NDA Amendments 011, 012, 014, 015, 017 and 019 have been sent to both the FDA Minneapolis and Chicago District Offices. The Minneapolis District has jurisdiction over Schwarz Pharma, Inc., Milwaukee, Wisconsin, who is responsible for the release testing of the active raw material, trade kit packaging operations and stability testing. The Chicago District has jurisdiction over the contract manufacturers: Abbott Laboratories, Abbott Park, Illinois, manufactures the drug product; and manufactures the prefilled diluent syringe.

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett

Suzanne Bennett, Manager
Regulatory Affairs

SB:blb
Enclosures

SCHWARZ
PHARMA

October 14, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products(HFD-580)
Attn: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-649: SPM 691/EDEX (alprostadil for injection) for the Treatment of Erectile Dysfunction

AMENDMENT 019

Revised Labeling
Copy of 10/4/96 Facsimile - Response to Chemistry Reviewer
Copy of 10/14/96 Facsimile - Response to Medical Reviewer

Dear Sir/Madam:

Pursuant to 21 CFR § 314.60, Schwarz Pharma, Inc. (SPInc) is submitting duplicate copies of an amendment for the above-referenced New Drug Application. An additional desk copy is enclosed. Reference is made to the two Agency facsimiles received on October 10, 1996, (enclosed) and to the telephone conversation between Dr. Jean Fourcroy, Medical Reviewer, Division of Reproductive and Urologic Drug Products, and Suzanne Bennett, Manager, Regulatory Affairs, SPInc., wherein Dr. Fourcroy requested that SPInc revise the product labeling to remove the diagnostic claim and withdraw Amendment 018 to avoid extending the review period. Reference is also made to the October 1, 1996, telephone conversation between Kasturi Srinivaschar, Chemistry Reviewer, Division of Reproductive and Urologic Drug Products, and Suzanne Bennett, wherein Mr. Srinivaschar requested additional information.

As a consequence of Dr. Fourcroy's referenced request to remove the diagnostic claim, SPInc hereby withdraws Amendment 018, dated 10/7/96, submitted in support of the diagnostic claim. SPInc will resubmit this information in a Supplement following NDA approval.

This amendment contains the following: 1) revised labeling which removes the diagnostic claim and incorporates a majority of the changes recommended in the referenced Agency facsimiles; 2) a copy of our October 4, 1996, facsimile to Mr. Srinivaschar, responding to his request for a revised specification for the NaCl diluent in the ml syringe; and 3) a copy of our October 14, 1996, facsimile to Dr. Fourcroy regarding erection quality parameters. Copies of the professional package insert and patient information sheets are also provided on diskette (Word 6.0). SPInc proposes to schedule a conference call with the appropriate reviewer to discuss any current or additional changes to the package insert or patient information sheets, if deemed necessary by the reviewer

If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs at (414) 238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett for

Steven Pollock, Director
Regulatory Affairs Department

SRP:blb
Enclosures

SCHWARZ
PHARMA

October 7, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products(HFD-580)
Attn: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-649: SPM 691/EDEX (alprostadil for injection) for the Treatment of Erectile Dysfunction and as an Adjunctive Diagnostic Tool

AMENDMENT 018

CTR: KU-620-007/F8958
Revised Professional Package Insert Pages with Modified Diagnostic Claim
Copy of 10/4/96 Facsimile - Response to Chemistry Reviewer

Dear Sir/Madam:

Pursuant to 21 CFR § 314.60, Schwarz Pharma, Inc. (SPInc) is submitting duplicate copies of an amendment for the above-referenced New Drug Application. Reference is made to the October 2, 1996, telephone conversation between Dr. Jean Fourcroy, Medical Reviewer, Division of Reproductive and Urologic Drug Products and Suzanne Bennett, Manager, Regulatory Affairs, Schwarz Pharma, Inc., wherein Dr. Fourcroy requested additional information to support our diagnostic claim. Reference is also made to the October 1, 1996, telephone conversation between Kasturi Srinivaschar, Chemistry Reviewer, Division of Reproductive and Urologic Drug Products, and Suzanne Bennett, wherein Mr. Srinivaschar requested additional information. Desk copies containing relevant sections are enclosed for the Statistical, Chemistry and Microbiology Reviewers.

This amendment contains the following: 1) CTR for KU-620-007/F8958 entitled "Single-Blind Study of Intracavernous Injections of Placebo Versus Alprostadil Alfadex for use in the Diagnosis of Erectile Dysfunction by Dynamic Pharmacocavernosometry", including a copy of the CTR on diskette; 2) revised professional package insert pages (both unannotated and annotated) in which the diagnostic claim has been modified from "is indicated for the diagnosis of erectile dysfunction regardless of origin (organic, psychogenic or mixed etiology)" to "may be a useful adjunct to other diagnostic tests in the diagnosis of erectile dysfunction", with revised text underlined; and 3) copy of the 10/4/96 facsimile to Mr. Srinivaschar, responding to his request for a revised specification for the NaCl diluent in the ml syringe.

If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs at (414) 238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett for
Steven Pollock, Director
Regulatory Affairs Department

SCHWARZ PHARMA

ORIGINAL

ORIG AMENDMENT

October 2, 1996

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products (HFD-580)
Attn: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-649: SPM 691/EDEX (alprostadil for injection) for the Diagnosis and Treatment of Erectile Dysfunction

AMENDMENT 017

Copy of 10/1/96 Facsimile - Response to Pharmacokinetic Reviewer
Supporting Pharmacokinetic Articles
Stability Data on Normal Saline Diluent

Dear Sir/Madam:

Pursuant to 21 CFR § 314.60, Schwarz Pharma, Inc. (SPInc) is submitting duplicate copies of an amendment for the above-referenced New Drug Application. Reference is made to the September 19th and 26th, 1996, telephone conversations between Dr. Albert Chen, Pharmacokinetic Reviewer, Division of Pharmaceutical Evaluation, FDA, and Suzanne Bennett, Manager, Regulatory Affairs, wherein Dr. Chen requested additional pharmacokinetic information. Reference is also made to the October 1, 1996, conversation with Kasturi Srinivaschar, the Reviewing Chemist, Division of Reproductive and Urologic Drug Products, wherein he requested additional stability data. Desk copies containing relevant sections are enclosed for the Chemistry, Microbiology and Pharmacokinetic Reviewers

This amendment contains the following: 1) A copy of the 10/1/96 facsimile to Dr. Chen, responding to his request for additional information; 2) supporting articles referenced in the above facsimile, and 3) three-month stability data on diluent Lot 51466, filled in a ml syringe.

If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs at (414) 238-5476

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett for

Steven Pollock, Director
Regulatory Affairs Department

SRP:blb

SCHWARZ

ORIGINAL

September 27, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products (HFD-580)
Attn: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-649: SPM 691/EDEX (alprostadil for injection) for the Diagnosis and Treatment of Erectile Dysfunction

AMENDMENT 016

Response to 9/18/96 Request for Information

Dear Sir/Madam:

Pursuant to 21 CFR § 314.60, Schwarz Pharma, Inc (SPInc) is submitting duplicate copies of an amendment for the above-referenced New Drug Application. Reference is made to the September 18, 1996 telephone conversation between Terri Rumble, Project Manager, Division of Reproductive and Urologic Drug Products, and Suzanne Bennett, Regulatory Affairs Manager, Schwarz Pharma, Inc. (SPInc), wherein additional information was requested by the Medical Reviewer, Dr. Jean Fourcroy.

This amendment contains SPInc's response to the Medical Reviewer's request.

If there are any questions regarding this submission, please contact Suzanne Bennett, Regulatory Affairs at (414) 238-5476

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett

Steven Pollock, Director
Regulatory Affairs Department

SP blb
Enclosures

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER
CSO INITIALS
DATE

SEP
8

SCHWARZ

ORIGINAL

ORIG AMENDMENT

September 20, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products (HFD-580)
Attn: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-649: SPM 691/EDEX (alprostadil for injection) for the Diagnosis and Treatment of Erectile Dysfunction

AMENDMENT 015

Response to 8/16/96 Chemistry Review

Dear Sir/Madam:

Pursuant to 21 CFR § 314.60, Schwarz Pharma, Inc. (SPInc) is submitting duplicate copies of an amendment for the above-referenced New Drug Application, and a desk copy for the Reviewing Chemist.

This amendment contains SPInc's response to the Chemistry Reviewer's questions faxed to us on August 16, 1996.

If there are any questions regarding this submission, please contact Suzanne Bennett, Regulatory Affairs at (414) 238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett for

Steven Pollock, Director
Regulatory Affairs Department

SP:blb
Enclosures

ORIGINAL

NDA ORIG AMENDMENT

SCHWARZ PHARMA

September 16, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products (HFD-580)
Attn: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857-1706

REC'D
SEP 1 3 1996
HFD-580

RE: NDA 20-649: SPM 691/EDEX (alprostadil for injection) for the Diagnosis and Treatment of Erectile Dysfunction

AMENDMENT NO. 014

Stability Data on Drug Product and Normal Saline Diluent
Copy of 8/8/96 Facsimile - Alternate Secondary Packager for Trade Kit
Copy of 8/19/96 Facsimile - Revision to Professional Package Insert (PPI)
Copy of 8/20/96 Facsimile - Revisions to PPI and Patient Information Sheets
Copy of 9/10/96 Facsimile - Response to Pharmacokinetic Reviewer and Revision to PPI
Case Report Form Pages for Study PHAKI 841
Additional Calculations for Study PHAKI 841
Revised Professional Package Insert and Patient Information Sheets (7/30//96)

mark 9-26-96
I have hard copy

Dear Sir/Madam:

Pursuant to 21 CFR § 314.60 and 314.50 (d)(5)(vi)(b)(3), Schwarz Pharma, Inc. (SPInc) is submitting duplicate copies of an amendment for the above-referenced New Drug Application. Reference is made to the, September 10, 1996 telephone conversation between Christina Kish, Consumer Safety Officer, Division of Reproductive and Urologic Drug Products, FDA, and Suzanne Bennett, Manager, Regulatory Affairs, wherein the contents of this amendment were discussed. Desk copies containing relevant sections are enclosed for the Chemistry, Microbiology, Medical, and Pharmacokinetic Reviewers.

This amendment contains the following: 1) 12-month stability data on 7 drug product lots (06-925-DH, 06-926-DH, 06-928-DH, 06-929-DH, 06-930-DH, 06-931-DH, 06-933-DH) submitted in the original NDA; 2) 12-month stability data on 3 diluent lots (31435, 41425, 41435) submitted in the original NDA; 3) 6-month accelerated stability data on 3 diluent lots (31435, 41425, 41435) submitted in the original NDA; 4) 2-month stability data on diluent Lot 51466 filled in a 2.25 ml syringe; 5) updated 3-month stability data for diluent Lot 21276, with an increase in fill volume, now includes micro testing results; 6) a copy of the 8/8/96 facsimile to Kasturi Srinivaschar, Chemistry Reviewer, regarding the alternate secondary packager for the Trade Kit, 7) a copy of the 8/19/96 facsimile to Dr. Albert Chen, Pharmacokinetic Reviewer, regarding a revision to the Professional Package Insert; 8) a copy of the 8/20/96 facsimile to Christina Kish, Consumer Safety Officer regarding revisions, requested by Dr. Jean Fourcroy, Medical Reviewer, to the Patient Package Insert and Patient Information Sheets; 9) a copy of the 9/10/96 facsimile to Dr. Chen responding to his request for additional information; 10) Case Report Form pages for PHAKI 841 as requested by Dr. Chen; 11) additional calculations for PHAKI 841; and 12) revised Professional Package Insert and Patient Information Sheets (July 30, 1996), including diskette

version (WORD 6.0). All revisions to these documents, as indicated in the referenced facsimiles, are underlined for ease of review.

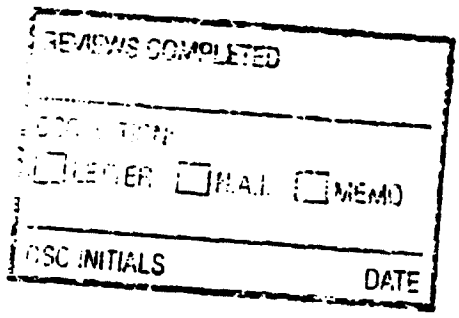
If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs, at 414/238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett

Steven Pollock
Director, Regulatory Affairs



SCHWARZ
PHARMA

ORIGINAL

3 September 1996

Christina Kish
FDA Consumer Safety Officer
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Endocrine and Metabolism Drug Products (HFD-580)
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-649: EDEX (alprostadil for injection)

Desk Copy of Package Insert on Diskette

Dear Ms. Kish:

Reference is made to the 30 August 1996, telephone conversation between Dr. Albert Chen, FDA Pharmacokinetic Reviewer, and Suzanne Bennett, Manager, Regulatory Affairs, Schwarz Pharma, Inc (SPInc). Pursuant to Dr. Chen's request, SPInc. is submitting two (2) diskettes each containing the package insert (rev. 6/14/96).

If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs, at (414) 238-5476.

Sincerely,
SCHWARZ PHARMA, INC.

Suzanne Bennett for

Steven R. Pollock
Director, Regulatory Affairs

mmw
Enclosure

noted 9-16-96

REC'D SEP 5 1996 HFD-510

REVIEWS COMPLETED
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

ORIGINAL

SCHWARZ
PHARMA

ORIG AMENDMENT

August 7, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products (HFD-580)
Attn: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-649: SPM 691/EDEX (alprostadil for injection) for the Diagnosis and Treatment of Erectile Dysfunction

AMENDMENT NO. 013

Second Safety Update

Dear Sir/Madam:

Pursuant to 21 CFR § 314.60 and 314.50 (d)(5)(vi)(b)(3), Schwarz Pharma, Inc. (SPInc) is submitting duplicate copies of an amendment for the above-referenced New Drug Application Reference is made to the June 10, 1996 telephone conversation between Christina Kish, Consumer Safety Officer, Division of Reproductive and Urologic Drug Products, FDA, and Suzanne Bennett, Manager, Regulatory Affairs, wherein the agency requested a safety update be submitted at least 90 days prior to the agency's anticipated goal date of November 7, 1996 for drafting an NDA action letter.

This amendment contains a non-cumulative safety update.

If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs, at 414/238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett for

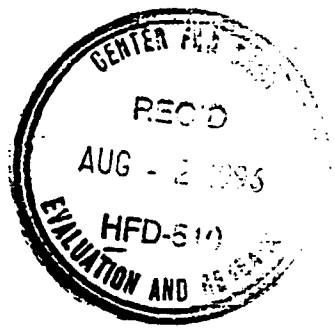
Steven Pollock
Director, Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ NLA ☐ MEMO
CSO INITIALS DATE

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 0 8 1996
HFD-580

Mail PO Box 2038 Milwaukee, WI 53201 5600 W County Line Road Mequon, WI 53092

SCHWARZ PHARMA



August 1, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products (HFD-580)
Attn: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-649: SPM 691/EDEX (alprostadil for injection) for the Diagnosis and Treatment of Erectile Dysfunction

AMENDMENT NO. 012

CHEMISTRY, MANUFACTURING AND CONTROL SECTION
Copy of 7/25/96 Facsimile Containing Update on NDA Issues
Copy of 7/26/96 Facsimile Containing Response to July 3, 1996 FDA Letter
3-month Stability Data on Drug Product Lots #15-948-DH, 15-949-DH, 15-950-DH
3-month Stability Data on Normal Saline Diluent Lot #21276
1-month Stability Data on Normal Saline Diluent Lot # 51466
Executed Batch Record on Normal Saline Diluent Lot #51466
Revised Trade Kit Information: Alternate Secondary Packagers of Trade Kit ; 30-gauge Needle

8-7-96

Dear Sir/Madam:

Pursuant to 21 CFR § 314.60, Schwarz Pharma, Inc. (SPInc) is submitting triplicate copies of an amendment for the above-referenced New Drug Application: an archival copy, and two review copies, one for the Reviewing Chemist (red copy) and one for the Reviewing Microbiologist (white copy).

This amendment contains the following: 1) SPInc's facsimile to the agency, dated July 25, 1996, containing an update on various NDA issues; 2) SPInc's facsimile to the agency, dated July 26, 1996, responding to the Agency's letter of July 3, 1996, regarding the container/closure integrity test protocol for the prefilled diluent syringe; 3) 3-month stability data on three lots (# 15-948-DH, 15-949-DH, 15-950-DH) of the drug product with increased fill volumes; 4) 3-month stability data on normal saline diluent lot #21276, filled in a 1 ml syringe with a 1.2 ml fill volume; 5) 1-month stability data on normal saline diluent lot #51466, filled in a ml syringe with a 1.2 ml fill volume; 6) an executed batch record for lot #51466; and 7) revised trade kit information providing for the addition of alternate secondary packagers of the trade kit, and a drawing of the 30-gauge needle.

The 3-month stability data for the drug product and normal saline diluent is submitted in support of the increased fill volumes (Amendment 006, dated March 28, 1996), and the 1-month stability data for the diluent is in support of the larger ml syringe (Amendment 009, dated May 24, 1996).

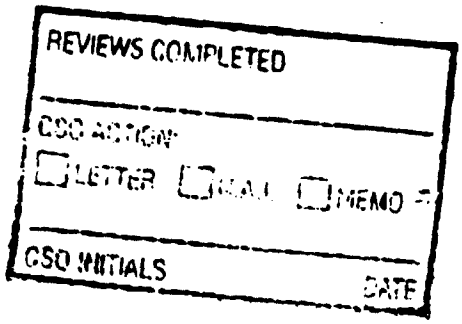
If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs, at 414/238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett

Steven Pollock
Director, Regulatory Affairs



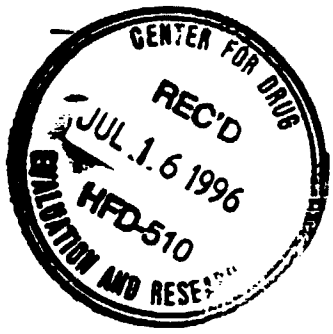
Mail P.O. Box 2038 Milwaukee, WI 53201 5600 County Line Road Mequon, WI 53092

ORIGINAL

SCHWARZ
PHARMA

July 12, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine Drug Products (HFD-510)
Attn: Document Control Room 14B-19
5600 Fishers Lane, Rockville, MD 20857-1706



RE: NDA 20-649: SPM 691 (alprostadil for injection)
for the Diagnosis and Treatment of Erectile Dysfunction

AMENDMENT NO. 011

CHEMISTRY, MANUFACTURING AND CONTROL SECTION

Copy of 7/8/96 Response to Pharmacokinetic Reviewer
Response to Microbiology Review #2

Dear Sir/Madam:

Pursuant to 21 CFR § 314.60, Schwarz Pharma, Inc. (SPInc) is submitting duplicate copies of an amendment for the above referenced New Drug Application. Reference is made to the June 26, 1996 request for information from Dr. Albert Chen, the Pharmacokinetic Reviewer; and also the May 30, 1996 facsimile recieved from the agency containing Microbiology Review #2. This amendment contains a copy of SPInc's July 8, 1996 facsimile to the agency, responding to the pharmacokinetic reviewer's request for information; and SPInc's response to Microbiology Review #2.

If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs, at 414/238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett for

Steven Pollock
Director, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Mail PO Box 2038 Milwaukee, WI 53201 5600 W. County Line Road Mequon, WI 53092

ORIGINAL

BZ

SCHWARZ
PHARMA

June 19, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine Drug Products (HFD-510)
Attn: Document Control Room 14B-19
5600 Fishers Lane, Rockville, MD 20857-1706

RE: NDA 20-649: SPM 691 (alprostadil for injection)
for the Diagnosis and Treatment of Erectile Dysfunction

AMENDMENT NO. 010

CHEMISTRY, MANUFACTURING AND CONTROL SECTION
Copy of 5/30/96 Request for Guidance
Copy of 5/30/96 Response to Pharmacokinetic Reviewer
Copy of 6/5/96 Request to Review Protocol for Microbiological Testing
Copy of 6/18/96 Request for Guidance
2-month Stability Data on the Normal Saline Diluent Lot with Increased Fill Volume
2-month Stability Data on the Drug Product Lots with Increased Fill Volume
New Draft Labeling

Dear Sir/Madam:

Pursuant to 21 CFR § 314.60, Schwarz Pharma, Inc. (SPInc) is submitting triplicate copies of an amendment for the above referenced New Drug Application: an archival copy and two review copies, one for the Reviewing Chemist (red copy) and one for the Reviewing Microbiologist (white copy). Two desk copies of the new draft labeling are also enclosed. Reference is made to the telephone conversation between Christina Kish, FDA Consumer Safety Officer, and Suzanne Bennett, Manager, Regulatory Affairs, SPInc, on June 10, 1996.

This amendment contains a copy of SPInc's facsimile to the agency, dated May 30, 1996, requesting guidance regarding the proposed use of a 30 gauge needle for injection of the drug solution; a copy of SPInc's facsimile to the agency, dated May 30, 1996, responding to the pharmacokinetic reviewer's questions of May 20, 1996; a copy of SPInc's facsimile to the agency requesting review of a protocol for microbiologic testing; a copy of SPInc's facsimile to the agency, dated June 18, 1996, requesting guidance regarding the proposed use of a 30 gauge needle for injection of the drug solution, and the date of the next safety update; 2-month stability data on one lot (# 21276) of prefilled diluent syringes with increased fill volume; 2-month stability data on three lots (# 15-948-DH, 15-949-DH, 15-950-DH) of drug product with increased fill volume; and new draft labeling as discussed in the referenced telephone conversation. The stability data is being submitted in support of the increased fill volume, as committed to in Amendment 006.

SPInc certifies that true and complete copies of this amendment are being forwarded to the Chicago and Minneapolis District Offices of the FDA. If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs, at 414/238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett for
Steven Pollock
Director, Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION:	
☐ LETTER ☒ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Mail PO 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

May 24, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine Drug Products (HFD-510)
Attn: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-649: SPM 691 (alprostadil for injection)
for the Diagnosis and Treatment of Erectile Dysfunction

AMENDMENT NO. 009

CHEMISTRY, MANUFACTURING AND CONTROL SECTION
Copy of 5/13/96 Request for Guidance
Revised Information on Trade Kit Components
Copy of 5/16/96 Request to Review Container/Closure Integrity Test Protocol
9-month Stability Data on the Drug Product Lots Submitted to the Original NDA
1-month Stability Data on the Normal Saline Diluent Lot with Increased Fill Volume
1-month Stability Data on the Drug Product Lots with Increased Fill Volume
Executed Batch Records for the Drug Product Lots with Increased Fill Volume

Dear Sir/Madam:

Pursuant to 21 CFR § 314.60, Schwarz Pharma, Inc. (SPInc) is submitting triplicate copies of an amendment for the above referenced New Drug Application: an archival copy and two review copies, one for the Reviewing Chemist (red copy) and one for the Reviewing Microbiologist (white copy). Reference is made to SPInc's facsimile to the agency, dated May 13, 1996; the telephone conversation between Stephen Trostle, FDA Consumer Safety Officer, and Suzanne Bennett, Manager, Regulatory Affairs, SPInc, on May 15, 1996; SPInc's facsimile to the agency, dated May 16, 1996; and NDA Amendment 006, dated March 28, 1996.

This amendment contains a copy of SPInc's facsimile to the agency, dated May 13, 1996, requesting guidance; revised information on trade kit components as committed to in Item 3 of the May, 13, 1996 facsimile and discussed in the referenced telephone call; a copy of SPInc's facsimile to the agency, dated May 16, 1996, requesting review of a container/closure test protocol; 9-month stability data on the drug product lots (# 06-925-DH, 06-929-DH, 06-928-DH, 06-931-DH, 06-933-DH, 06-926-DH, 06-930-DH) submitted to the original NDA; 1-month stability data on three lots (# 15-948-DH, 15-949-DH, 15-950-DH) of drug product with increased fill volume; 1-month stability data on one lot (# 21276) of prefilled diluent syringes with increased fill volume; and executed batch records for three lots (# 15-948-DH, 15-949-DH, 15-950-DH) of drug product with increased fill volume. The stability data and executed batch records are being submitted, in support of the increased fill volume, as committed to in Amendment 006.

If here are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs, at 414/238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett for

Steven Pollock
Director, Regulatory Affairs

ORIGINAL

SCHWARZ
PHARMA

May 13, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Attn: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-649: SPM 691 (alprostadil for injection)
for the Diagnosis and Treatment of Male Erectile Dysfunction

AMENDMENT NO. 008

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY SECTION
Response to Pharmacokinetic Reviewer's Request for Information -
Clinical Trial Report (CTR) Amendments: DA 229, PHAKI 829
CTRs: PHAKI 830, PHAKI 841, PHAKI 941, PHAKI 942, and PHAKI 943

Dear Sir/Madam:

Pursuant to 21 CFR § 314.60, Schwarz Pharma, Inc. (SPInc) is submitting duplicate copies of an amendment for the above-referenced New Drug Application. **A desk copy for the Pharmacokinetic Reviewer is enclosed.** Reference is made to the April 30, 1996, telephone conversation between Dr. Albert Chen, FDA Pharmacokinetic Reviewer, and Suzanne Bennett, Manager, Regulatory Affairs, SPInc wherein he requested corrected report pages for studies DA 229 and PHAKI 829; the Agency's December 13, 1995 facsimile from Dr. Chen; and the May 25, 1995 pre-NDA meeting.

This amendment contains CTR amendments for studies DA 229 and PHAKI 829, providing the corrected information requested by Dr. Chen; CTRs for studies PHAKI 830 and PHAKI 841, as requested in the referenced facsimile; and CTRs for the ADME studies, PHAKI 941, PHAKI 942, and PHAKI 943, SPInc committed to providing at the referenced pre-NDA meeting.

If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs, at (414) 238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett for
Steven Pollock
Director, Regulatory Affairs

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

ORIGINAL

SCHWARZ
PHARMA

April 29, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Attn: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-649: SPM 691 (alprostadil for injection)
for the Diagnosis and Treatment of Male Erectile Dysfunction

AMENDMENT NO. 007

CHEMISTRY, MANUFACTURING AND CONTROL SECTION
Response to Microbiology Reviewer's Request for Information

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY SECTION
Response to Pharmacokinetic Reviewer's Request for Information

GENERAL CORRESPONDENCE
Request to Consider Trade Names

Dear Sir/Madam:

Pursuant to 21 CFR § 314.60, Schwarz Pharma, Inc. (SPInc) is submitting duplicate copies of an amendment for the above-referenced New Drug Application. **Desk copies of the relevant portions for the Microbiology and Pharmacokinetic Reviewers are enclosed.** Reference is made to the April 2, 1996, telephone conversation between Stephen Trostle, Consumer Safety Officer (CSO), Division of Metabolism and Endocrine Drug Products, and Suzanne Bennett, Manager, Regulatory Affairs, SPInc, and subsequent agency facsimile requesting additional microbiological information. Reference is also made to the December 4, 1995, April 10, 1996, and April 15, 1996, telephone conversations between Dr. Albert Chen, Pharmacokinetic Reviewer, and Suzanne Bennett, wherein he requested clarification of several items in the referenced NDA.

This amendment contains responses to the referenced April 2, 1996, telephone call and agency facsimile; copies of the December 6, 1995, April 15, 1996, and April 22, 1996, facsimiles sent to the Pharmacokinetic Reviewer, in response to his referenced requests for additional information; and a copy of SPInc's April 19, 1996, facsimile requesting the Labeling and Nomenclature Committee to review and comment on the proposed trade name "FORTIS", as a back-up trade name to "EDEX", at their next regularly scheduled meeting.

SPInc certifies that true and complete copies of the CMC portion of this amendment are being forwarded to the Chicago and Minneapolis District Offices of the FDA.

If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs, at (414) 238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett for

Steven Pollock
Director, Regulatory Affairs

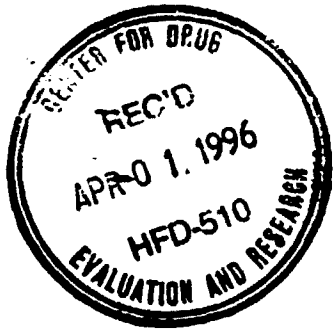
REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

SCHWARZ
PHARMA

March 28, 1996



Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Attn: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-649: SPM 691 (alprostadil for injection)
for the Diagnosis and Treatment of Male Erectile Dysfunction

AMENDMENT NO. 006

CHEMISTRY, MANUFACTURING AND CONTROL SECTION
Increased Fill Volume: Drug Product and Prefilled Diluent Syringe
Blank Batch Record for the Drug Product
Blank and Executed Batch Record for the Prefilled Diluent Syringe
Updated Drug Product Specifications, Methods, Stability Protocols, Labeling
New Test Method (Container Integrity - Visual Evaluation)
Updated Test Methods (Water Determination, Bacterial Endotoxins, Content Uniformity)
Alternate Test Method for Dosage Uniformity (Weight Variation)

Dear Sir/Madam:

Pursuant to 21 CFR § 314.60, Schwarz Pharma, Inc. (SPInc) is submitting duplicate copies of an amendment for the above-referenced New Drug Application. **A desk copy for the Reviewing Microbiologist is being sent under separate cover**. Reference is made to the March 5, 1996 telephone conversation between Stephen Trostle, Consumer Safety Officer (CSO), Division of Metabolism and Endocrine Drug Products, and Suzanne Bennett, Manager, Regulatory Affairs, SPInc, and a subsequent facsimile forwarded to the agency on the same date.

This submission contains documentation reflecting the increase in fill volume for the drug product and prefilled diluent syringes; a new test method for Container Integrity (Visual Evaluation); updated test methods for Water Determination, Bacterial Endotoxins, and Content Uniformity; and an alternate test method for Dosage Uniformity (Weight Variation).

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

INCREASED FILL VOLUME: DRUG PRODUCT AND PREFILLED DILUENT SYRINGE

As discussed in the referenced telephone conversation and facsimile, the maximum dose from the existing NDA product can be effectively withdrawn; however, a certain amount of practice and expertise is required because the stopper limits accessibility to the product when the vial is inverted. SPInc has therefore increased the fill volume of the reconstituted drug product to make it easier to withdraw the maximum dose. More specifically, the target fill volume of the drug product prior to lyophilization has been increased from ml, and the prefilled diluent syringe from ml. SPInc is effectively changing only the mcg/vial, not the mcg/ml. To accommodate the larger fill volume, a change in batch size from L is needed to maintain full lyophilizer loads. The lyophilization cycle remains unchanged.

In support of the referenced fill volume increases, Abbott Laboratories is manufacturing three 24 L lots of drug product (5, 10, and 40 mcg), and has manufactured one lot of prefilled diluent syringes, all of which will be placed on stability. For ease of review, SPInc has included a complete blank batch record for the 5 mcg strength, which incorporates revised pages for the 10, 20, and 40 mcg strengths. Changes to the blank batch record contained in the NDA are denoted by colored pages (5 mcg-lavender; 10 mcg-pink; 20 mcg-green; 40 mcg-yellow). The changes to the batch record are minimal and are located as follows:

	SECTION OF BATCH RECORD	# of pages revised
1.	Commodity Preparation	1 page
2.	Solution Manufacturing	10 pages
3.	Filling Operation	5 pages
4.	Lyophilization	No change
5.	Capping and Inspection	4 pages
6.	Finishing	3 pages
7.	Quality Assurance	4 pages

Blank and executed batch records for the one lot of prefilled diluent syringes are enclosed. Additionally, specifications, test methods, stability protocols, and labeling for the drug product have been updated to reflect the change in fill volume.

One month of accelerated stability data for the drug product will be submitted in mid-May, 2-month accelerated stability data and executed batch records for the 5, 10, and 40 mcg strengths will be submitted in mid-June 1996, and 3-month controlled room temperature and accelerated stability data in mid-July 1996. Stability data for the prefilled diluent syringe will be submitted with the referenced drug product stability data.

NEW TEST METHOD
A new test method for Container Integrity - Visual Evaluation is enclosed.

UPDATED TEST METHODS
Updated test methods for Water Determination, Bacterial Endotoxins, and Content Uniformity are enclosed.

ALTERNATE TEST METHOD
An alternate test method for Dosage Uniformity (Weight Variation) is enclosed.

SPInc certifies that a true and complete copy of this amendment is being forwarded to the Minneapolis District Office of the FDA.

If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs, at (414) 238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

Steven Pollock
Director, Regulatory Affairs

SCHWARZ
PHARMA

March 20, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Attn: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-649: SPM 691 (alprostadil for injection)
for the Diagnosis and Treatment of Male Erectile Dysfunction

AMENDMENT NO. 005
Clinical Information
Non-IND ICCAI Study

Dear Sir/Madam:

Pursuant to CFR § 314.60, Schwarz Pharma, Inc. is submitting duplicate copies of an amendment for the above-referenced New Drug Application. This submission contains clinical information pertaining to the Safety Reporting for the non-IND ICCAI Study conducted by the , using the referenced NDA drug product for a separate indication (IND

If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs, at (414) 238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett for

Steven Pollock
Director, Regulatory Affairs

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

March 15, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Endocrine and
Metabolism Drug Products (HFD-510)
Attn: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-649; SPM 691 (alprostadil for injection)
for Diagnosis and Treatment of Male Erectile Dysfunction

AMENDMENT NO. 004

120-day Safety Report

Dear Sir/Madam:

Pursuant to 21 CFR §314.50(5)(vi)(b), Schwarz Pharma, Inc. (SPInc) is submitting, in duplicate, a 120-day update for the above-referenced New Drug Application (NDA). This submission consists of 33 volumes. For ease of review, a detailed table of contents follows this letter.

This safety update provides cumulative, integrated safety information for all clinical studies completed as of September 30, 1995. Since the submission of the original NDA on November 7, 1995, 2 additional clinical studies have been completed and 10 clinical studies are ongoing. Information for deaths, serious adverse experiences, and adverse experiences resulting in discontinuation is provided for the ongoing studies.

The updated integrated safety report concludes there is no new information learned about SPM 691 that affects the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling submitted in the original NDA.

If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs, at (414) 238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

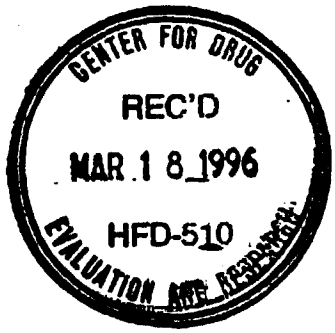
Suzanne Bennett for

Steven R. Pollock
Director, Regulatory Affairs

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

March 14, 1996



Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Attn: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-649: SPM 691 (alprostadil for injection)
for the Diagnosis and Treatment of Male Erectile Dysfunction

AMENDMENT NO. 003

CHEMISTRY, MANUFACTURING AND CONTROL SECTION
Response to Relevant Items Contained in the **Chemistry Information Request for NDA 20-546**
(Alprostadil for Injection indicated for severe Peripheral Arterial Occlusive Disease)

Dear Sir/Madam:

Pursuant to CFR § 312.60, Schwarz Pharma Inc. (SPInc) is submitting duplicate copies and an additional desk copy of an amendment for the above referenced New Drug Application. Reference is made to the **Chemistry Information Request for NDA** dated December 6, 1995, from the Division of Gastrointestinal and Coagulation Drug Products; and to the March 5, 1996 conversation between Stephen Trostle, Consumer Safety Officer (CSO), Division of Metabolism and Endocrine Drug Products, and Suzanne Bennett, Manager, Regulatory Affairs, SPInc, and subsequent facsimile forwarded to the agency on that same date. Finally, reference is made to our commitment contained in NDA 20-649 (Volume 1.18, page 146), to forward additional stability data when it became available.

As indicated in the referenced facsimile, SPInc is enclosing an amendment addressing the agency's request for additional Chemistry, Manufacturing, and Control information. Accordingly, this submission contains a point by point response to those questions contained in the referenced **Chemistry Information Request for NDA** which are germane to the NDA 20-649 (SPM 691). The additional stability data referred to in the above paragraph has been included under our response to item 11C.

SPInc certifies that a true and complete copy of this amendment is being forwarded to the Minneapolis District Office of the FDA.

If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs, at (414) 238-5476.

REVIEWS COMPLETED

Sincerely,

CSO ACTION:

SCHWARZ PHARMA, INC.

Suzanne Bennett for ☐ LETTER ☐ N.A.I.

Steven Pollock
Director, Regulatory Affairs

CSO INITIALS DATE

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

March 1, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Attn: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

RE: NDA 20-649: SPM 691 (alprostadil for injection) for Male Erectile Dysfunction

AMENDMENT NO. 002

GENERAL CORRESPONDENCE
Request to Consider Trade Names

Dear Sir/Madam:

Reference is made to the telephone conversation on February 28, 1996, between Stephen Trostle, CSO, Division of Metabolism and Endocrine Drug Products, and Suzanne Bennett, Manager, Regulatory Affairs, Schwarz Pharma, Inc. (SPInc), wherein Ms. Bennett indicated that SPInc would like to submit additional proposed trade names for the referenced NDA product to the Labeling and Nomenclature Committee for their consideration. SPInc hereby requests that the trade names listed below be presented to the Labeling and Nomenclature Committee for their review and comment at the next regularly scheduled meeting.

ADAM (Alprostadil Drug Administration for Men)
ARTEX
CONFIDAN
EDEX
PROCIRC
FORTIS
VANDEX
VASOPRO

If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs, at (414) 238-5476.

Sincerely,

Schwarz Pharma, Inc.

Suzanne Bennett for

Steven Pollock
Director, Regulatory Affairs

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

ORIG

SCHWARZ
PHARMA

February 13, 1996

Dr. Harold G. Turner
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Scientific Investigations (HFD-344)
7520 Standish Place
Rockville, MD 20855

Noted 2-96 GG
Noted 3-19-96
Noted Telecon 3-20-96

RE: NDA 20-649: SPM 691 (alprostadil for injection)
for the Diagnosis and Treatment of Male Erectile Dysfunction

Response to Request for Information

Dear Dr. Turner:

Reference is made to NDA 20-649, and the telephone call between yourself and Suzanne Bennett, Manager, Regulatory Affairs, Schwarz Pharma, Inc., on February 2, 1996, wherein you requested additional information to prepare for the clinical site inspections.

1. Copies of Case Report Forms (CRFs) were requested as follows:

Study KU-620-001: Dr. Auerbach (every 5th patient)
Dr. Goldstein (every 4th patient)

Study KU-620-002: Dr. Castellanos (every 6th patient)
Dr. Gittleman (every 6th patient)
Dr. Rajfer (every 7th patient)

Enclosed are copies of the following Case Report Forms:

Study KU-620-001 (orange binders)

CRFs for 7 of Dr. Auerbach's patients:

CRFs for 6 of Dr. Goldstein's patients:

Mail P.O. Box 2038 · Milwaukee, WI 53201 · 5600 W. County Line Road · Mequon, WI 53092
Phone 414 354 4300 · Telex 4311042 · Fax 414 354 4309

Study KU-620-002 (yellow binders)

CRFs for 6 of Dr. Castellanos' patients:

CRFs for 7 of Dr. Gittleman's patients:

CRFs for 9 of Dr. Rajfer's patients:

2. Line listings of all AE reports submitted to the NDA were also requested.

Enclosed, following the referenced patient CFRs for each site, are AE listings for both the controlled and uncontrolled phases as reported in the original NDA.

If you have any questions or additional requests, please contact Suzanne Bennett, Manager, Regulatory Affairs, at (414) 238-5476.

Sincerely,

SCHWARZ PHARMA, INC.

Suzanne Bennett for

Steven Pollock
Director, Regulatory Affairs

cc: Stephen Trostle, CSO, Division of Metabolism and Endocrine Drug Products (HFD-510)

SCHWARZ
P H A R M A

February 12, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Attn: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
FEB 13 1996
HFD-510

RE: NDA 20-649: SPM 691 (alprostadil for injection) for the diagnosis and treatment of Male Erectile Dysfunction

<u>AMENDMENT NO. 001</u>

CHEMISTRY, MANUFACTURING AND CONTROL SECTION
Batch Records for the Prefilled Diluent Syringe

Dear Sir/Madam:

Reference is made to the February 9, 1996 conversation between Steven Trostle, Consumer Safety Officer (CSO), Division of Metabolism and Endocrine Drug Products, and Suzanne Bennett, Manager, Regulatory Affairs, Schwarz Pharma, Inc. (SPInc), wherein the batch records for the prefilled diluent syringe were requested by the Reviewing Microbiologist. Reference is also made to correspondence to SPInc, dated December 14, 1995, and previously forwarded to the agency. The referenced correspondence refers to the relevant pages of Drug Master File covering the aseptic filling of sterile syringes with Sodium Chloride for Injection, USP. Additional information specific to the manufacture of the diluent syringes is contained in the enclosed batch records.

SPInc certifies that a true and complete copy of this amendment is being forwarded to the Minneapolis District Office of the FDA. If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs, at (414) 238-5476.

Sincerely,

SCHWARZ PHARMA INC.

Suzanne Bennett for

Steven Pollock
Director, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

Mail PO Box 2038 Milwaukee, WI 53201 5600 W County Line Road Mequon, WI 53092

SCHWARZ
PHARMA

January 29, 1996

Dr. Harold G. Turner
Food and Drug Administration,
Center for Drug Evaluation and Research
Division of Scientific Investigations (HFD-344)
7520 Standish Place
Rockville, MD 20855

noted 2-1-96 JE

noted 2-5-96

RE: NDA 20-649: SPM 691 (alprostadil for injection) for the Diagnosis and Treatment of Male Erectile Dysfunction

Response to Request for Information

noted 2-7-96

Dear Dr. Turner:

Reference is made to NDA 20-649, and the telephone call between yourself and Suzanne Bennett, Manager, Regulatory Affairs, Schwarz Pharma Inc. on January 23, 1996, wherein you requested the following information to prepare for clinical site inspections:

1. A Desk copy of the **Application Summary** (NDA 20-649, Volume 1.1) is enclosed as two volumes for ease of use.

2. A copy of **Protocol KU-620-001**/GHBA 712 (NDA 20-649, Volume 1.63, Pages 2 - 127) is enclosed.

3. A copy of **Protocol KU-20-002**/GHBA 713 (NDA 20-649, Volume 1.68, Pages 2 - 124) is enclosed.

4. A list of the **clinical investigators** for each of the referenced protocols, including the number of patients per site, is enclosed.

Please contact Suzanne Bennett, Manager, Regulatory Affairs, at (414) 238-5476 if you have any additional needs.

Sincerely,

SCHWARZ PHARMA INC.

Suzanne Bennett for

Steven Pollock
Director, Regulatory Affairs

cc: Stephen Trostle, CSO, Division of Metabolism and Endocrine Drug Products (HFD-510)

Mail P.O. Box 2038 · Milwaukee, WI 53201 · 5600 W. County Line Road · Mequon, WI 53092
Phone 414-354-4300 · Telex 4911043 · Fax 414-354-4338

SCHWARZ
PHARMA

November 7, 1995

Solomon Sobel, M.D.
Director, Division of Metabolism and Endocrine
Drug Products (HFD-510)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852

RE: NDA 20-649
SPM 691 (alprostadil for injection)
for the diagnosis and treatment of
male erectile dysfunction

Dear Dr. Sobel:

Pursuant to 21 CFR § 314.50, Schwarz Pharma, Inc. (SPInc) is submitting duplicate copies of the above-referenced New Drug Application (NDA). This submission consists of 178 volumes numbered 1.1 through 1.178.

Reference is made to the May 18, 1995 pre-NDA meeting between the Division of Metabolism and Endocrine Drug Products and SPInc. The essential components of the clinical development program, on which this NDA is based, were presented at this pre-NDA meeting. The clinical data section of the NDA consists of 13 intracavernous studies: 3 U.S. studies and 10 European studies. A total of 1,580 subjects were enrolled in the clinical development program for SPM 691, with 1,505 subjects exposed to alprostadil. The focus of this NDA is the intracavernous administration of SPM 691 for the treatment of erectile dysfunction as supported by four pivotal trials: KU-620-001, KU-620-002, KU-620-003, and F8653; and the diagnosis of erectile dysfunction as supported by Study F8598 and literature. In addition, the results of two ongoing diagnostic studies, KU-620-006 and KU-620-007, will be submitted to the agency early next year. Based on the above referenced studies, it has been concluded that SPM 691 is safe and effective for the treatment and diagnosis of erectile dysfunction as described in the proposed Package Insert.

We consider this application to be complete and in agreement with agency requirements as discussed at the referenced pre-NDA meeting, and as such, is suitable for filing as described in 21 CFR § 314.101. Diskettes containing SAS stability data are enclosed in both the archive and review copies of Volume 1.18 of this application. SAS data sets for Studies KU-620-001, KU-620-002, KU-620-003, and F8653, and for both the medical reviewer and the statistical reviewer, will be delivered to the agency within 60 days of agency receipt of this application.

Mail PO Box 2038 · Milwaukee, WI 53201 · 5600 W. County Line Road · Mequon, WI 53092

We are cognizant of our obligations regarding submission of a 120-day Safety Update Report according to 21 CFR § 314.50(d)(5)(vi)(b). We also reference 21 CFR § 314.102, which provides for an informal meeting with the reviewer of the NDA, and express our interest in such a meeting if deemed appropriate by the agency. We certify that a true and complete copy of the Chemistry, Manufacturing, and Controls section, Volumes 1.2 through 1.20, of this application is being forwarded to the Minneapolis District Office of the FDA. In accordance with the Prescription Drug User Fee Act of 1992, a check in the amount of was sent on October 10, 1995, by courier to Mellon Bank, check

Reference is made to the September 6, 1995, phone conversation between Steven Trostle, CSO, Division of Metabolism and Endocrine Drug Products, and Suzanne Bennett, Manager, Regulatory Affairs, wherein SPInc was notified of the Labeling and Nomenclature Committee's decision to disallow the use of the trade name "Viridal". The drug product is currently referred to as "SPM 691" pending a suitable trade name. Due to SPInc.'s recent notification of the status of the trade name both names appear throughout the NDA document.

Please note that effective August 29, 1995, SCHWARZ PHARMA Kremers Urban Company changed corporate names and is now registered as SCHWARZ PHARMA, INC. For future correspondence regarding this application, please refer to the new corporate name.

For your convenience, the location of the various sections of the NDA are listed in **Attachment I** to this letter. Also provided, as **Attachment II**, is the location of documents for the clinical studies reported in this NDA. If there are any questions regarding this submission, please contact Suzanne Bennett, Manager, Regulatory Affairs, at (414) 238-5476.

Sincerely,

Schwarz Pharma, Inc.

Suzanne Bennett for

Ron Stratton, Ph.D.
Vice President
Research and Development

Enclosures