

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-649

CHEMISTRY REVIEW(S)

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS - HFD-580
Review of Chemistry, Manufacturing and Controls

NDA: 20-649

CHEMISTRY REVIEW # 5

DATE REVIEWED: 14 May 1997

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	7 Nov. 1995	9 Nov. 1995	17 Nov. 1995
AMENDMENTS	8 May 1997	9 May 1997	-

NAME & ADDRESS OF APPLICANT: Schwarz Pharma, Inc.
5600 W. County Line Rd.
Mequon, WI 53092

DRUG PRODUCT NAME

Proprietary:	Edex
Nonproprietary/Established/USAN:	Alprostadil - α -cyclodextrin
Code Name/#:	SPM 691
Chem. Type/Ther. Class:	3S

PHARMACOLOGICAL CATEGORY/INDICATION: Prostaglandin for the treatment and diagnosis of male erectile dysfunction

DOSAGE FORM:	Lyophilized Powder for Injection
STRENGTHS:	5, 10, 20 and 40 mcg
ROUTE OF ADMINISTRATION:	Intracavernosal
DISPENSED:	<input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

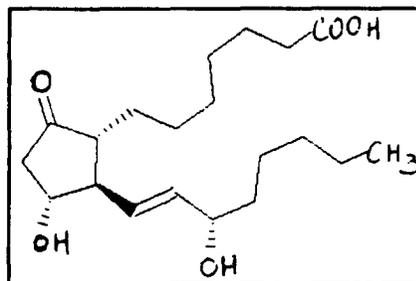
Two Parts:

a. Alprostadil: (1R, 2R, 3R)-3-Hydroxy-2[(E)-(3S)-3-hydroxy-1-octenyl]-5-oxo-cyclopentane heptanoic acid

Prostaglandin E₁

C₂₀H₃₄O₅

M.Wt. 354.49



b. Alfadex

Chemical Names: α -cyclodextrin, cyclohexaamylose, cyclo (hexa (α [1-4 linked] glucopyranose))

CAS Number: 10016-20-3

Mol. Wt. : 972.85

Mol. Formula: $C_{36}H_{60}O_{30}$

SUPPORTING DOCUMENTS:

DMES:

RELATED DOCUMENTS:

IND

CONSULTS:

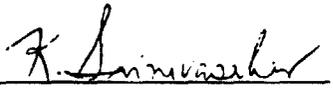
Microbiology--Review complete with the recommendation that bacteriostatic sodium chloride injection or other appropriate bacteriostatic diluent be used in place of sodium chloride injection.

Environmental Assessment--complete; FONSI signed off by Nancy Sager on 30 Sep. 1996.

REMARKS/COMMENTS:

This amendment is a response to the deficiencies identified in the Agency's facsimile dated 29 Apr. 1997. The response is satisfactory and there are no pending CMC issues.

CONCLUSIONS AND RECOMMENDATIONS: The NDA may be approved from a Chemistry, Manufacturing and Controls perspective.


K. Srinivasachar, Ph.D.
Review Chemist

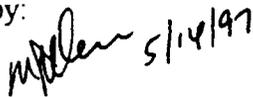
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Org. NDA 20-649

HFD-580/Division File

HFD-580/ K. Srinivasachar/Rhee/CSO

R/D Initialed by:


5/14/97

Filename: nda20649.8

APR 17 1997

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS - HFD-580
Review of Chemistry, Manufacturing and Controls

NDA: 20-649
CHEMISTRY REVIEW # 4

DATE REVIEWED: 17 Apr. 1997

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	7 Nov. 1995	9 Nov. 1995	17 Nov. 1995
AMENDMENTS	21 Mar. 1997		

NAME & ADDRESS OF APPLICANT: Schwarz Pharma, Inc.
5600 W. County Line Rd.
Mequon, WI 53092

DRUG PRODUCT NAME

Proprietary:	Edex
Nonproprietary/Established/USAN:	Alprostadil - α -cyclodextrin
Code Name/#:	SPM 691
Chem. Type/Ther. Class:	3S

PHARMACOLOGICAL CATEGORY/INDICATION: Prostaglandin for the treatment and diagnosis of male erectile dysfunction

DOSAGE FORM:	Lyophilized Powder for Injection
STRENGTHS:	5, 10, 20 and 40 mcg
ROUTE OF ADMINISTRATION:	Intracavernosal
DISPENSED:	<input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

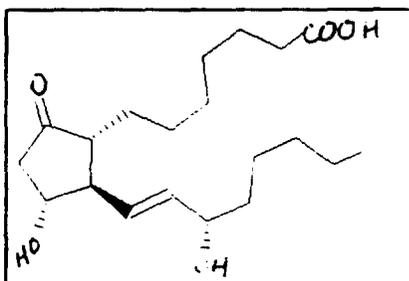
Two Parts:

a. Alprostadil: (1R, 2R, 3R)-3-Hydroxy-2[(E)-(3S)-3-hydroxy-1-octenyl]-5-oxo-cyclopentane heptanoic acid

Prostaglandin E₁

C₂₀H₃₄O₅

M.Wt. 354.49



b. Alfadex

Chemical Names: α -cyclodextrin, cyclohexaamylose, cyclo (hexa (α [1-4 linked] glucopyranosè))

CAS Number: 10016-20-3

Mol. Wt. : 972.85

Mol. Formula: $C_{36}H_{60}O_{30}$

SUPPORTING DOCUMENTS:

DMES:

RELATED DOCUMENTS:

IND

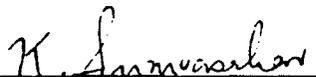
CONSULTS:

Microbiology--Review complete with the recommendation that bacteriostatic sodium chloride injection or other appropriate bacteriostatic diluent be used in place of sodium chloride injection.

Environmental Assessment--complete; FONSI signed off by Nancy Sager on 30 Sep. 1996.

REMARKS/COMMENTS: This Amendment provides the additional stability data requested by the Agency in order to grant an expiration date of 18 months for the 20 mcg strength of Edex.

CONCLUSIONS AND RECOMMENDATIONS: A tentative expiration date of 18 months can be granted for the 20 mcg strength of Edex. The firm should be requested to closely monitor the stability of the 2 lots with a 1.778 mL fill volume and inform the Agency if any of the test parameters are out of specifications before 18 months at CRT or 6 months under accelerated conditions.


K. Srinivasachar, Ph.D.
Review Chemist

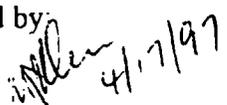
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Org. NDA 20-649

HFD-580/Division File

HFD-580/ K. Srinivasachar/Rhee/CSO

R/D Initialed by:



Filename: nda20649.7

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS - HFD-580
Review of Chemistry, Manufacturing and Controls

NDA: 20-649

CHEMISTRY REVIEW # 3

DATE REVIEWED: 10 Mar. 1997

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	7 Nov. 1995	9 Nov. 1995	17 Nov. 1995
AMENDMENTS	17 Dec. 1996		

NAME & ADDRESS OF APPLICANT: Schwarz Pharma, Inc.
5600 W. County Line Rd.
Mequon, WI 53092

DRUG PRODUCT NAME

Proprietary:	Edex
Nonproprietary/Established/USAN:	Alprostadil - α -cyclodextrin
Code Name/#:	SPM 691
Chem. Type/Ther. Class:	3S

PHARMACOLOGICAL CATEGORY/INDICATION: Prostaglandin for the treatment and diagnosis of male erectile dysfunction

DOSAGE FORM:	Lyophilized Powder for Injection
STRENGTHS:	5, 10, 20 and 40 mcg
ROUTE OF ADMINISTRATION:	Intracavernosal
DISPENSED:	<input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC

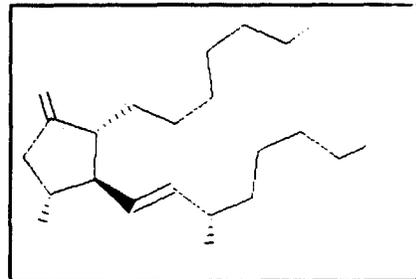
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Two Parts:

a. Alprostadil: (1R, 2R, 3R)-3-Hydroxy-2[(E)-(3S)-3-hydroxy-1-octenyl]-5-oxo-cyclopentane heptanoic acid

Prostaglandin E₁C₂₇H₄₄O₃

M.Wt. 352.49



b. Alfadex

Chemical Names: α -cyclodextrin, cyclohexaamylose, cyclo (hexa (α [1-4 linked] glucopyranose))

CAS Number: 10016-20-3

Mol. Wt. : 972.85

Mol. Formula: $C_{36}H_{60}O_{30}$

SUPPORTING DOCUMENTS:

DMFS:

RELATED DOCUMENTS:

IND

CONSULTS:

Microbiology--Review complete with the recommendation that bacteriostatic sodium chloride injection or other appropriate bacteriostatic diluent be used in place of sodium chloride injection.

Environmental Assessment--complete; FONSI signed off by Nancy Sager on 30 Sep. 1996.

REMARKS/COMMENTS:

This amendment is a complete response to the deficiencies identified in the Agency's Approvable letter dated 8 Nov. 1996 and to the comments sent to the firm, via facsimile, on 27 Nov. 1996. A few pending issues remain which are identified in the draft letter.

CONCLUSIONS AND RECOMMENDATIONS: The deficiencies listed in the draft letter should be conveyed to the Sponsor via fax. The NDA may be approved only after a satisfactory response to these deficiencies, in the form of an Amendment, is received.

cc:

Org. NDA 20-649

HFD-580/Division File

HFD-580/ K. Srinivasachar/Rhee/CSO

R/D Initialed by:

[Handwritten signature] 3/12/97

[Handwritten signature]
K. Srinivasachar, Ph.D.
Review Chemist

Filename: nda20649.6

NOV 1 1996

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS - HFD-580
Review of Chemistry, Manufacturing and Controls

NDA: 20-649

CHEMISTRY REVIEW # 2

DATE REVIEWED: 31 Oct. 1996

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	7 Nov. 1995	9 Nov. 1995	17 Nov. 1995
AMENDMENTS	29 Oct. 1996		

NAME & ADDRESS OF APPLICANT: Schwarz Pharma, Inc.
5600 W. County Line Rd.
Mequon, WI 53092

DRUG PRODUCT NAME

Proprietary:	Edex
Nonproprietary/Established/USAN:	Alprostadil - α -cyclodextrin
Code Name/#:	SPM 691
Chem. Type/Ther. Class:	3S

PHARMACOLOGICAL CATEGORY/INDICATION: Prostaglandin for the treatment and diagnosis of male erectile dysfunction

DOSAGE FORM:	Lyophilized Powder for Injection
STRENGTHS:	5, 10, 20 and 40 mcg
ROUTE OF ADMINISTRATION:	Intracavernosal
DISPENSED:	<input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

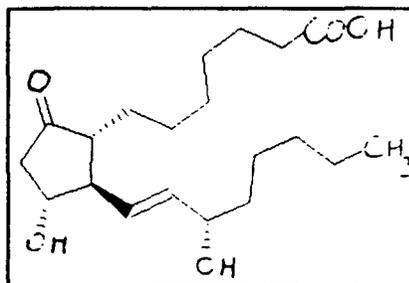
Two Parts:

a. Alprostadil: (1R, 2R, 3R)-3-Hydroxy-2[(E)-(3S)-3-hydroxy-1-octenyl]-5-oxo-cyclopentane heptanoic acid =

Prostaglandin E₁

C₂₀H₃₄O₅

M Wt 354.49



b. Alfadex

Chemical Names: α -cyclodextrin, cyclohexaamylose, cyclo (hexa (α [1-4 linked] glucopyranose))

CAS Number: 10016-20-3

Mol. Wt. : 972.85

Mol. Formula: $C_{36}H_{60}O_{30}$

SUPPORTING DOCUMENTS:

DMS

RELATED DOCUMENTS:

IND

CONSULTS:

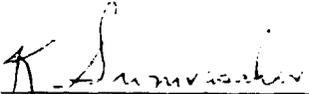
Micrbiology--Review complete with the recommendation that bacteriostatic sodium chloride injection or other appropriate bacteriostatic diluent be used in place of sodium chloride injection.

Environmental Assessment--complete; FONSI signed off by Nancy Sager on 30 Sep. 1996.

REMARKS/COMMENTS:

This amendment is a complete response to the deficiencies identified in Chemistry Review # 1.

CONCLUSIONS AND RECOMMENDATIONS: The Application is APPROVABLE from a chemistry, manufacturing and controls perspective provided satisfactory responses are received to the deficiencies identified in the draft deficiency letter and an acceptable cGMP compliance status is received for the secondary packaging site,


K. Srinivasachar, Ph.D.
Review Chemist

cc:

Org. NDA 20-649

HFD-580/Division File

HFD-580/ K. Srinivasachar/Rhee/CSO

R/D Initialed by:


11/1/96

Filename: nda20649.4

OCT 22 1996

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS - HFD-580
Review of Chemistry, Manufacturing and Controls

NDA: 20-649

CHEMISTRY REVIEW # 1

DATE REVIEWED: 17 Oct. 1996

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	7 Nov. 1995	9 Nov. 1995	17 Nov. 1995
AMENDMENTS	12 Feb. 1996, 14 Mar. 1996, 28 Mar. 1996, 29 Apr. 1996, 24 May 1996 19 Jun. 1996, 12 Jul. 1996, 1 Aug. 1996, 16 Sep. 1996, 20 Sep. 1996 2 Oct. 1996, 7 Oct. 1996, 14 Oct. 1996.		

NAME & ADDRESS OF APPLICANT: Schwarz Pharma, Inc.
5600 W. County Line Rd.
Mequon, WI 53092

DRUG PRODUCT NAME

Proprietary:	Edex
Nonproprietary/Established/USAN:	Alprostadil - α -cyclodextrin
Code Name/#:	SPM 691
Chem. Type/Ther. Class:	3S

PHARMACOLOGICAL CATEGORY/INDICATION: Prostaglandin for the treatment and diagnosis of male erectile dysfunction

DOSAGE FORM:	Lyophilized Powder for Injection
STRENGTHS:	5, 10, 20 and 40 mcg
ROUTE OF ADMINISTRATION:	Intracavernosal
DISPENSED:	<input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

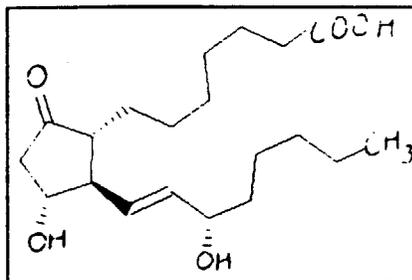
Two Parts:

a. Alprostadil: (1R, 2R, 3R)-3-Hydroxy-2[(E)-(3S)-3-hydroxy-1-octenyl]-5-oxo-cyclopentane heptanoic acid

Prostaglandin E₁

C₂₀H₃₄O₅

M Wt. 354.49



b Alfadex

Chemical Names: α -cyclodextrin, cyclohexaamylose, cyclo (hexa (α [1-4 linked] glucopyranose))

CAS Number: 10016-20-3

Mol. Wt. : 972.85

Mol. Formula: $C_{36}H_{60}O_{30}$

SUPPORTING DOCUMENTS:

DMES: -

RELATED DOCUMENTS:

IND

CONSULTS:

Micrbiology--Review complete with the recommendation that bacteriostatic sodium chloride injection or other appropriate bacteriostatic diluent be used in place of sodium chloride injection.

Environmental Assessment--complete; FONSI signed off by Nancy Sager on 30 Sep. 1996.

REMARKS/COMMENTS:

The main issue with alprostadil is its instability and insolubility in aqueous media. In this Application, an attempt has been made to improve these properties by forming an inclusion complex of alprostadil with alpha cyclodextrin. This is not a tightly bound complex and readily dissociates into free alprostadil in solution, especially upon dilution. While the complexation seems to improve aqueous solubility, the data presented does not conclusively establish increased stability. The major problem seems to be the substantial amount of water (release specification--NMT %) in the dosage form (lyophilized powder) probably because of the presence of a large excess of cyclodextrin. Alprostadil is known to be degraded by moisture which makes it necessary to rigidly control water content during storage.

CONCLUSIONS AND RECOMMENDATIONS: The Application is APPROVABLE from a chemistry, manufacturing and controls perspective provided satisfactory responses are received to the deficiencies identified in the draft deficiency letter and an acceptable cGMP compliance status is received for the secondary packaging site, It has been decided at the Division level that the Microbiologist's recommendation to replace sodium chloride injection with a suitable bacteriostatic diluent will not be a requirement for approvability of this Application in view of the fact that the drug is dispensed in single dose vials and is to be used immediately after reconstitution.

cc:

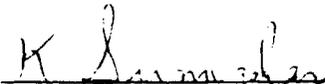
Org. NDA 20-649

HFD-580/Division File

HFD-580/ K. Srinivasachar/Rhee/CSO

R/D Initialed by:

K. Srinivasachar
10/22/96


K. Srinivasachar, Ph.D.
Review Chemist

Filename: nda20649 2