# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 20-649

# ENVIRONMENTAL ASSESSMENT AND/OR FONSI

# ENVIRONMENTAL ASSESSMENT
# AND
# FINDING OF NO SIGNIFICANT IMPACT
# FOR

## ALPROSTADIL FOR INJECTION
## 5, 10, 20 AND 40 MCG
## NDA 20-649


**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**
**DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS**
**HFD-580**

# FINDING OF NO SIGNIFICANT IMPACT

NDA 20-649
Alprostadil for Injection, 5, 10, 20 and 40 mcg

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Alprostadil for Injection, 5, 10 , 20 and 40 mcg, Schwarz Pharma, Inc. has conducted a number of studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(b)(5)(attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Alprostadil is a chemically synthesized drug, which is administered as an inclusion complex with alfa-cyclodextrin, a glucose oligomer, via intracavernosal injection, for the treatment of erectile dysfunction of any origin. The active ingredient, alprostadil, and its complex with alfa-cyclodextrin are manufactured at two sites in Japan. The drug substance-complex (alprostadil-alfadex) is shipped to the United States to Schwarz Pharma, Inc., Mequon, WI, where the compound is tested and released for shipment to the contract manufacturer of the drug product. The finished dosage form, manufactured by Abbott Laboratories, North Chicago, Illinois, will be used by patients throughout the United States and its territories.

Alprostadil, or prostaglandin $E_1$ ($PGE_1$), is an endogenous substance which is rapidly metabolized in vivo. Any excreted metabolites will enter public water and sewage treatment facilities. The manufacture of the drug substance takes place in Japan and the manufacturer operates in accordance with all environmental regulations imposed by local and federal authorities. The substances that may be emitted during the manufacture of the drug product have been identified. The manufacturer has certified that they are in compliance with local, state and US environemtal laws and regulations. Calculations show that approval of this NDA would result in only a very small increase in the amount of the drug substance already present in the environment which would not be expected to have any discernible effects on the environment.

Disposal of the drug may result from out of the specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of by a licensed waste disposal company by incineration. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

# NDA 20-649
## *SPM 691 for Injection*
**(alprostadil)**

# FREEDOM OF INFORMATION ENVIRONMENTAL ASSESSMENT

I. **Date:** October 31, 1995

II. **Applicant:** SCHWARZ PHARMA, INC.

III. **Address:** 5600 W. County Line Road
Mequon, Wisconsin 53092

IV. **Description of the Proposed Action:**

### A. Description of the Requested Approval

This Environmental Assessment (EA) Report for NDA 20-649 provides the consumer with documentation that Schwarz Pharma, Inc. (SPInc) is in compliance with the United States Food and Drug Administration's regulations governing the manufacture and distribution of SPM 691 (alprostadil) for injection.

### B. Need for the Action

SPM 691 is indicated for the diagnosis of erectile dysfunction regardless of origin (organic or psychogenic) and for the treatment of erectile dysfunction of any origin including vasculogenic, neurogenic, or mixed etiology. Diabetic and non-diabetic patients, men with low circulating levels of serum testosterone, and the elderly have been effectively treated with SPM 691.

## C. Locations of Production and Disposal

### Drug Substance Manufacturing

As described in the SPM 691 New Drug Application, (NDA 20-649), Schwarz Pharma, Inc. (SPInc) proposes to have the drug substance manufactured by a contract facility in Japan. Several processes are involved in the manufacture of the drug substance. These processes are performed at two different facilities and sites in Japan. Both facilities are located in industrial areas. One site has an average annual temperature of 16° C with an annual precipitation of 1300 mm. Employees at this facility number approximately 150. The second facility is located in an area with an average annual temperature of 14° C and annual precipitation of 2400 mm. Approximately 100 employees work at this facility.

The drug substance-complex (alprostadil-alfadex) is shipped to the United States to SPInc, Mequon, WI, where the compound is tested and released for shipment to the contract manufacturer for the drug product. SPInc's facility in Mequon is located approximately five (5) miles from the western shore of Lake Michigan. Mixed residential, farming, commercial and industrial areas surround this facility on predominantly flat terrain in a suburban area. The average annual temperature of the area is 55.4° F maximum and 40.3° F minimum, with an average annual precipitation of 30.94 inches. Approximately 100 employees work at this facility.

### Formulation and Packaging

The final drug product will be formulated by Abbott Laboratories, 1401 Sheridan Road, N. Chicago, Illinois. This facility is located on the western shore of Lake Michigan, in an area of mixed residential, commercial and industrial properties. The average annual temperature is 49° F and annual precipitation is 33 in. Approximately 3700 people work at this facility.

### Sites of Product Use

After product release, the drug product will be distributed by SPInc located in Mequon, WI. The drug will be prescribed to patients throughout the United States and its territories.

### Site of Disposal

SPInc has contracted with to dispose of all pharmaceutical waste in accordance with US EPA, DEA, state, and local regulations (Governmental Permit #2820005643). A description of is included in the confidential version of the EA.

## V. Identification of Chemical Substances:

**Drug substance**

SPM 691 contains alprostadil (prostaglandin $E_1$; $PGE_1$) as an inclusion complex with α-cyclodextrin, a cyclic glucose oligomer.

**Generic Name:** Alprostadil

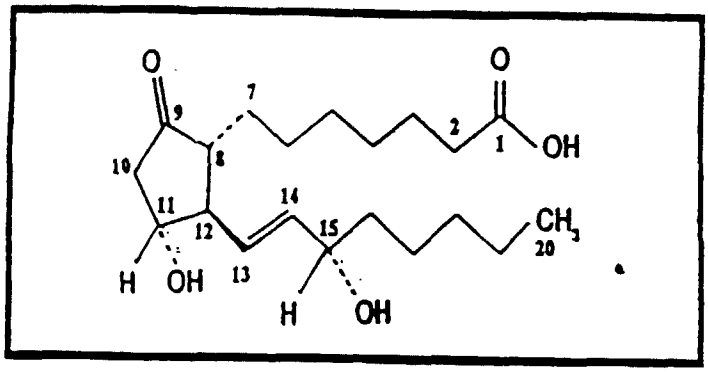
**CAS Number:** 745-65-3

**Nomenclature:** Prost-13-en-1-oic acid, 11,15-dihydroxy-9-oxo, (11α,-13E,15S)-(USP,USAN)

**Molecular Formula:** $C_{20}H_{34}O_5$

**Physical Description:** A white to off-white, crystalline powder

**Structural Formula:**



V. Identification of Chemical Substances (cont.):

**Drug Product**

SPM 691 (alprostadil for injection) contains alprostadil-alfadex complex as the active ingredient and lactose as a bulking agent. Inactive ingredients are listed below:

Lactose Anhydrous, NF
Nitrogen, NF
Water for Injection, USP

VI. Introduction of Substances into the Environment:

**A. Introductions from the Production Sites**

**Introduction From Site of Production of the Drug Substance (Alprostadil)**

The manufacture of the drug substance takes place in Japan. The drug substance manufacturer operates in accordance with all environmental regulations imposed by local and federal authorities. A copy of the General Compliance Statement verifying compliance with all applicable governmental environmental regulations has been provided in the confidential version of the Environmental Assessment.

Material Safety Data Sheets for alprostadil, alpha-cyclodextrin, and alprostadil-alfadex are included in **Appendix 5**.

**Introduction From Site of Production of the Drug Product (SPM 691, alprostadil for injection)**

The manufacture and packaging of the final drug product takes place at Abbott Laboratories in N. Chicago, Illinois. The substances that may be emitted during the manufacture of the drug product have been identified. Abbott certifies compliance with local, State of Illinois and United States environmental laws and regulations. A Compliance Statement can be found in **Appendix 4**.

**B. Introductions from Product Use**

$PGE_1$ is an endogenous substance with an extremely short half life due to rapid and extensive biotransformation. Enzymatic oxidation of C15-hydroxy-group followed by reduction of the C13, 14-double-bond produces the metabolites 15-keto-$PGE_1$, $PGE_0$ and 15-keto-$PGE_0$. After further degradation by β-oxidation and omega-oxidation, the metabolites are eliminated via urine (88%) and the feces (12%).

## VI. Introduction of Substances into the Environment (cont.):

### C. Introductions from Product Disposal

Disposal of returned or rejected goods will be performed by a contract waste disposal company. The method of disposal is incineration at a facility which specifically allows the acceptance of pharmaceutical waste (permit #2820005643). A description of is included in the confidential version of the EA.

### Statement of Compliance from Applicant

Schwarz Pharma, Inc. verifies compliance with all applicable environmental laws and regulations. A Statement of Compliance is located in Appendix 4.

## VII. Fate of the Substances Emitted to the Environment:

$PGE_1$ is recognized as a naturally occurring substance. As such, it has been demonstrated to be readily metabolized by a variety of organisms. Detailed information regarding patient metabolism is included in Section IV, Description of the Proposed Action, of the confidential version of the EA. As an endogenous substance, $PGE_1$ is already found in the environment. Humans naturally produce approximately 50 - 100 mcg of $PGE_1$ per day. In the U.S., with a population of 260,000,000, approximately 26,000 grams of $PGE_1$ are produced daily (260,000,000 x 100 mcg/day x 0.000001 g/mcg). This corresponds to 9,490,000 grams per year. Approval of this NDA will result in an additional 80 grams in the fifth year after approval, an increase of 0.0008%. This will have no discernible impact on the environment and will not alter the concentration and distribution of $PGE_1$ in the environment.

## VIII. Environmental Effects of the Released Substances

A summary of the toxicology reports included in the NDA representing the results of studies conducted over a 20-year period is included in the confidential version of the EA. Prostaglandin $E_1$ is a naturally occuring hormone in humans, and the drug substance, alprostadil, has been previously approved in the United States by the FDA for use as Prostin VR Pediatric® sterile solution (Upjohn) in the palliative treatment of neonates who are dependent upon a patent ductus arteriosus for survival, and more recently, as Caverject® sterile powder (Upjohn) for treatment of male erectile dysfunction.

There are no literature citations on the effects of $PGE_1$ on organisms such as invertebrates, plants, fungi and bacteria. However, there have been studies on the effects of

VIII. Environmental Effects of the Released Substances (cont.)

prostaglandins on the spawning behavior of goldfish. In two reports, (Effects of indomethacin and prostaglandins on ovulation of goldfish, Stacey, N.E. and Pandey, S., in *Prostaglandins*, (1975), Vol. 9, No. 4, pp. 597-607, and Effects of indomethacin and prostaglandins on the spawning behavior of female goldfish, Stacey, N.E., in *Prostaglandins*, (1976), Vol. 12, No. 1, pp. 113-26), goldfish were injected with indomethacin after which spawning behavior was inhibited. Subsequent injection of the fish with $PGF_{2\alpha}$ restored spawning behavior. $PGE_2$ was significantly less effective, and $PGE_1$ had no effect. There is no data to suggest any effect of $PGE_1$ when injected into fish, or when it might be introduced in an aqueous environment.

IX. Use of Resources and Energy:

No impact will occur to endangered or threatened species. Since this activity does not involve the alteration, demolition, or construction of building or earth projects, approval will have no impact on property listed in the National Register of Historic Places.

X. Mitigation Measures:

No potential adverse environmental impacts are foreseen with the production, use, and disposal of the product. The manufacture of the drug product takes place under highly regulated and controlled conditions which further mitigate against negative environmental consequences.

XI. Alternatives to the Proposed Action:

No potential adverse environmental impacts are foreseen with the production, use, and disposal of the product. The use of SPM 691 will directly benefit patients with erectile dysfunction. Approval of SPM 691 is justified from an environmental perspective and is preferable to non-approval.

One alternative to the proposed action is non-approval. This will deprive humankind of the benefit of this therapeutic treatment.

## XII. List of Preparers

### Formulation, Production and Packaging

Dennis W. Hanify,
Senior Engineer,
Abbott Laboratories
Abbott Park, Illinois
BS, Mech. Engineering
M. B. A.

John H. Robbins, PE., CHMM
Manager, HPD Environmental Engineering
Abbott Laboratories
Abbott Park, Illinois
BS, Chem. Engineering
MS, Env. Engineering.

### Use and Disposal

Steven R. Pollock
Director of Regulatory Affairs
Schwarz Pharma, Inc.
Mequon, Wisconsin
BS, Pharmacy/M.B.A. - Finance

### SCHWARZ PHARMA Environmental Officer

Dr. rer.nat. Klaus Sandrock, Dipl. Chem.
Director Safety and Environmental Department
Schwarz Pharma AG
Diplom-Chemist/Doctorate

## XIII. Certification:

The undersigned preparers and officials certify that the information presented is true, accurate and complete to the best of the knowledge of the firm or agency responsible for preparation of this environmental assessment.

Date October 10, 1995

Steven R. Pollock
Director of Regulatory Affairs
SCHWARZ PHARMA, INC.

Date October 19, 1995

John H. Robbins, PE., CHMM,
Manager, HPD Environmental Engineering
Abbott Laboratories

Date October 12, 1995

Klaus Sandrock, Ph.D.
Director Safety and Environmental Department
SCHWARZ PHARMA AG

## XIV. References

1. Altiere FJ, BR Piti, CN Gillis. Separation of prostaglandin $E_1$ from its major metabolites: Application of the technique to measure first-pass clearance of $PGE_1$ in the pulmonary and cerebral circulations of the anesthetized dog. *Biochem Pharm 1981; 30:2953-61.*

2. Costa P., et al. Moxisylyte plasma kinetics in humans after intracavernous administration. *Biopharm & Drug Disposition 1992; 13: 671-679.*

3. Cox JW; Andreadis NA; Bone RC; Maunder RJ; Pullen RH; Usprung MJ. Pulmonary extraction and pharmacokinetics of prostaglandin $E_1$ during continuous intravenous infusion in patients with adult respiratory distress syndrome. *Am Rev Respir Dis 1988; 137: 5-12.*

4. Rosenkranz B; Fischer CH; Boeynaems JM; Frölich JC. Metabolic disposition of prostaglandin $E_1$ in man. *Biochem Biophys Acta 1983; 750:231-6.*

## XV. Appendices

Appendix 1 - *Confidential* - DMF Letters of Authorization

Appendix 2 - *Confidential* - Letter from BFI Pharmaceutical Services/ Hempstead Resource Recovery Facility History and Initial Operating Results

Appendix 3 - *Confidential* - Impurities and Degradation Report

Appendix 4 - Compliance Statements
*Confidential* - Drug Substance Manufacturer
*Nonconfidential* - Abbott Laboratories
*Nonconfidential* - SCHWARZ PHARMA, INC.

Appendix 5 - *Nonconfidential* - Material Safety Data Sheets

## XV. Appendices (con't)

Appendix 6 - *Confidential* - Formulation and Packaging exhibits

Exhibit A - North Shore Sanitary District (POTW) Sewer Ordinance
Exhibit B - Abbott Laboratories Spill Control Plan
Exhibit C - Waste Management of Wisconsin Nonhazardous Waste Disposal Agreement

Appendix 7 - *Confidential* - Detailed Calculations of MEEC

Appendix 8 - *Confidential* - Toxicology Summary

## Appendix 4 - Compliance Statements

*Nonconfidential* - Abbott Laboratories

*Nonconfidential* - SCHWARZ PHARMA, INC.

ABBOTT

ABBOTT LABORATORIES

HOSPITAL PRODUCTS DIVISION

MANUFACTURING FACILITY IN NORTH CHICAGO, ILLINOIS

## CERTIFICATE OF COMPLIANCE: EMISSION REQUIREMENTS

## VASOPROST FOR INJECTION

Abbott Laboratories certifies that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees, and administrative orders applicable to solution preparation and filling of this drug product at its facility in North Chicago, Illinois, as well as emission requirements set forth in applicable federal, state, and local environmental statues and regulations applicable to this product at its facility in North Chicago, Illinois.

Signature: John H. Robbins

Title: Manager, Environmental Engineering, Hospital Products Division

Date: June 5, 1995

SCHWARZ PHARMA, INC
Milwaukee, WI 53201



# SCHWARZ PHARMA, INC.

## CERTIFICATE OF COMPLIANCE

SCHWARZ PHARMA, INC. certifies that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees, and administrative orders applicable to the production of this drug product at its facility in Mequon, Wisconsin, as well as emission requirements set forth in applicable federal, state, and local environmental statutes and regulations applicable to this product at its facility in Mequon, Wisconsin.

Signature Barry A. Berkley

Title V.P. Operations

Date October 10, 1995

## Appendix 5 - *Nonconfidential* - Material Safety Data Sheets

Alprostadil
Common Name
Cat # 01600
Unit package size: 25 mg

**MATERIAL SAFETY DATA SHEET**
**UNITED STATES PHARMACOPEIAL CONVENTION, INC.**

address:
12601 Twinbrook Parkway
Rockville, MD 20852 USA

emergency and information telephone calls:
(301) 881-0666

Jerome A. Halperin
Responsible Party

04-22-92
date prepared

**WARNING STATEMENT**
**WARNING! REFERENCE STANDARD; NOT FOR HUMAN CONSUMPTION; AVOID INGESTION, INHALATION, SKIN CONTACT. FOR CHEMICAL TEST AND ASSAY USE ONLY.**

## SECTION 1 - IDENTITY

| | |
|---|---|
| COMMON NAME | Alprostadil |
| SYNONYMS | Prostin VR Pediatric |
| CAS NUMBER | 745-65-3 |
| RTECS NUMBER | GY4569800 |
| CHEMICAL NAME | Prost-13-en-1-oic acid, 11,15-dihydroxy-9-oxo-, (11alpha, 13E, 15S)- |
| CHEMICAL FAMILY | A Prostaglandin |
| THERAPEUTIC CATEGORY | Vasodilator |
| FORMULA | $C_{20}H_{34}O_5$ |

## SECTION 2 - HAZARDOUS INGREDIENTS

| | NAME | PERCENT | THRESHOLD LIMIT VALUE (UNITS) |
|---|---|---|---|
| PRINCIPAL HAZARDOUS COMPONENT(S) / [Chemical & Common name(s)] | Alprostadil | Pure Material | Not Established |

## SECTION 3 - PHYSICAL AND CHEMICAL CHARACTERISTICS (Fire & Explosion Data)

| | |
|---|---|
| MELTING POINT | 115 - 116°C |
| BOILING POINT | n/a |
| SPECIFIC GRAVITY ($H_2O$ = 1) | n/a |
| VAPOR PRESSURE (mm Hg) | n/a |
| PERCENT VOLATILE BY VOLUME (%) | n/a |
| VAPOR DENSITY (AIR = 1) | n/a |
| EVAPORATION RATE | n/a |

n/a not applicable

MATERIAL SAFETY DATA SHEET
UNITED STATES PHARMACOPEIAL CONVENTION, INC.

| | |
|---|---|
| SOLUBILITY IN WATER | Slightly soluble |
| REACTIVITY IN WATER | n/a |
| APPEARANCE AND ODOR | White to off-white crystalline powder; odorless |
| FLASH POINT | n/a |
| FLAMMABLE LIMITS IN AIR % BY VOLUME | LOWER n/a UPPER n/a |
| EXTINGUISHER MEDIA | Water spray, dry chemical, carbon dioxide or foam as appropriate for surrounding fire and materials. |
| AUTO-IGNITION TEMPERATURE | n/a |
| SPECIAL FIRE FIGHTING PROCEDURES | As with all fires, evacuate personnel to safe area. Firefighters should use self-contained breathing equipment and protective clothing. |
| UNUSUAL FIRE AND EXPLOSION HAZARDS | This material is assumed to be combustible. As with all dry powders it is advisable to ground mechanical equipment in contact with dry material to dissipate the potential buildup of static electricity. When heated to decomposition material emits toxic fumes. Emits toxic fumes under fire conditions. |

## SECTION 4 - PHYSICAL HAZARDS

| | |
|---|---|
| STABILITY | ( ) Unstable ( X ) Stable |
| CONDITIONS TO AVOID | Material is stable from a safety point of view. |
| INCOMPATIBILITY (MATERIALS TO AVOID) | n/a |
| HAZARDOUS DECOMPOSITION PRODUCTS | When heated to decomposition material emits acrid smoke and irritating fumes. Emits toxic fumes under fire conditions. |
| HAZARDOUS POLYMERIZATION | ( ) May Occur ( X ) Will Not Occur |

## SECTION 5 - HEALTH HAZARDS

| | |
|---|---|
| THRESHOLD LIMIT VALUE | None established |
| SIGNS AND SYMPTOMS OF OVEREXPOSURE | [Alprostadil CAS RN: 745-65-3<br>$LD_{50}$: 228 mg/Kg oral-rat;<br>$LD_{50}$: 24900 micrograms/Kg intraperitoneal-rat;<br>$LD_{50}$: 18600 micrograms/Kg subcutaneous-rat;<br>$LD_{50}$: 19200 micrograms/Kg intravenous-rat |

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not applicable

Alprostadil
Common Name
Cat # 01600

**MATERIAL SAFETY DATA SHEET**
**UNITED STATES PHARMACOPEIAL CONVENTION, INC.**

$LD_{50}$: 21 mg/Kg intraarterial-rat;
$LD_{50}$: 186 mg/Kg oral-mouse;
$LD_{50}$: 19800 micrograms/Kg intraperitoneal-mouse;
$LD_{50}$: 26400 micrograms/Kg subcutaneous-mouse;
$LD_{50}$: 21 mg/Kg intravenous-mouse;
Mutagenicity Data [RTECS]
Reproductive Effects Data [RTECS]]
The usual child dose (intravenous) of alprostadil is 0.1 microgram/Kg/minute initially, not to exceed a maximum of 0.4 microgram/Kg/min. Adverse effects include shortness or absence of breath, fever, headache, flushing, nausea, diarrhea, hypotension, irregular heartbeat, and seizures. Possible allergic reaction to dust if inhaled, ingested or in contact with skin.

ACUTE — Eye, skin and/or respiratory tract irritation
CHRONIC — Possible hypersensitization, increased bone formation

PRECAUTIONS TO CONSIDER — Persons developing hypersensitivity (anaphylactic) reactions must receive immediate medical attention. Material may be irritating to mucous membranes and respiratory tract. Pregnant individuals should avoid exposure to this compound. Great care should be taken to avoid all contact and inhalation of dust, fumes, mist, and/or vapors associated with the material. Keep container tightly closed and use with adequate ventilation; wash thoroughly after handling. Individuals working with chemicals should consider all chemicals to be potentially hazardous even if their individual hazards may be uncharacterized or unknown.

MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE — Hypersensitivity to material, respiratory distress syndrome, and bleeding disorders.

| CHEMICAL LISTED AS CARCINOGEN OR POTENTIAL CARCINOGEN | | | |
|---|---|---|---|
| | NATIONAL TOXICOLOGY PROGRAM | ( ) Yes | ( X ) No |
| | I.A.R.C. Monographs | ( ) Yes | ( X ) No |
| | OSHA | ( ) Yes | ( X ) No |
| | OTHER | n/a | |

ACGIH TLV: n/a

OTHER EXPOSURE LIMIT(S) USED: n/a

not applicable

Alprostadil
Common Name
Cat # 01600

MATERIAL SAFETY DATA SHEET
UNITED STATES PHARMACOPEIAL CONVENTION, INC.

| | |
|---|---|
| OSHA PERMISSIBLE EXPOSURE LIMIT: | Not established |
| OTHER EXPOSURE LIMIT USED | Not established |
| EMERGENCY AND FIRST AID PROCEDURES | Remove from exposure. Remove contaminated clothing. Persons developing serious hypersensitivity reactions must receive immediate medical attention. If not breathing give artificial respiration. If breathing is difficult give oxygen. Obtain medical attention. |
| 1. INHALATION | May cause irritation of respiratory tract. Remove to fresh air. |
| 2. EYES | May cause irritation. Flush with copious quantities of water. |
| 3. SKIN | May cause irritation. Flush with copious quantities of water. |
| 4. INGESTION | May cause irritation. Flush out mouth with water. |

## SECTION 6 - SPECIAL PROTECTION INFORMATION

| | |
|---|---|
| RESPIRATORY PROTECTION (SPECIFY TYPE) | NIOSH approved respirator |
| VENTILATION | Adequate |
| LOCAL EXHAUST | Recommended |
| MECHANICAL (GENERAL) | Recommended |
| OTHER | n/a |
| PROTECTIVE GLOVES | Rubber |
| EYE PROTECTION | Safety goggles |
| OTHER PROTECTIVE CLOTHING OR EQUIPMENT | Appropriate laboratory apparel; protect exposed skin. |

## SECTION 7 - SPECIAL PRECAUTIONS AND SPILL/LEAK PROCEDURES

| | |
|---|---|
| PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE | Store in tight container as defined in the United States Pharmacopeia.. Keep refrigerated but protect from freezing. This material should be handled and stored per label and other instructions to ensure product integrity. |

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not applicable

Alprostadil
Common Name
Cat # 01600

MATERIAL SAFETY DATA SHEET
UNITED STATES PHARMACOPEIAL CONVENTION, INC.

OTHER PRECAUTIONS

Avoid contact with eyes, skin or clothing. Avoid breathing dust or mist. Use with adequate dust control. Wash thoroughly after handling. Wear fresh clothing daily. Wash contaminated clothing before reuse. Do not permit eating, drinking or smoking near material. Pregnant females should avoid exposure to this compound.

STEPS TO BE TAKEN IN CASE MATERIAL IS SPILLED OR RELEASED

Wear approved respirator and chemically compatible gloves. Vacuum or sweep up spillage. Avoid dust. Place spillage in appropriate container for waste disposal. Wash contaminated clothing before reuse. Neutralize area with a 1:1 bleach and water solution.

WASTE DISPOSAL METHODS

Dispose of waste in accordance with all applicable Federal, State and local laws.

NOTICE: The information contained herein is applicable solely to the chemical substance when used as a USP Reference Standard and does not relate to any other use of the substance described. Its use is intended by persons having technical skill and at their own discretion and risk. The information has been developed by USP staff from sources considered reliable but has not been independently verified by the USP. Therefore, the USP Convention cannot guarantee the accuracy of the information in these sources nor should the statements contained herein be considered an official expression. NO REPRESENTATION OR WARRANTY, EXPRESS OR IMPLIED, INCLUDING THE WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE is made with respect to the information contained herein.

ATTENTION:

This Product is Sold as a Reference Standard for Use In Chemical Analysis Not For Human Consumption.

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na = not applicable

Alpha Cyclodextrin
Common Name
Cat # 15455
Unit package size: 50 mg

# MATERIAL SAFETY DATA SHEET
## UNITED STATES PHARMACOPEIAL CONVENTION, INC.

address:
12601 Twinbrook Parkway
Rockville, MD 20852 USA

emergency and information
telephone calls:
(301) 881-0666

Jerome A. Halperin
Responsible Party

10-10-90
date prepared

**WARNING STATEMENT**

**WARNING! REFERENCE STANDARD; NOT FOR HUMAN CONSUMPTION; AVOID INGESTION, INHALATION, SKIN CONTACT. FOR CHEMICAL TEST AND ASSAY USE ONLY.**

## SECTION 1 - IDENTITY

| | |
|---|---|
| COMMON NAME | Alpha Cyclodextrin |
| SYNONYMS | n/a |
| CAS NUMBER | 10016-20-3 |
| RTECS NUMBER | GU2292000 |
| CHEMICAL NAME | alpha-Cyclodextrin |
| CHEMICAL FAMILY | n/a |
| THERAPEUTIC CATEGORY | Carrier molecule for drug delivery systems |
| FORMULA | $C_{36}H_{60}O_{30}$ |

## SECTION 2 - HAZARDOUS INGREDIENTS

| | NAME | PERCENT | THRESHOLD LIMIT VALUE (UNITS) |
|---|---|---|---|
| PRINCIPAL HAZARDOUS COMPONENT(S) / [Chemical & Common name(s)] | Alpha Cyclodextrin | Pure Material | Not Established |

## SECTION 3 - PHYSICAL AND CHEMICAL CHARACTERISTICS (Fire & Explosion Data)

| | |
|---|---|
| BOILING POINT | n/a |
| SPECIFIC GRAVITY ($H_2O$ = 1) | n/a |
| VAPOR PRESSURE (mm Hg) | n/a |
| PERCENT VOLATILE BY VOLUME (%) | n/a |
| VAPOR DENSITY (AIR = 1) | n/a |
| EVAPORATION RATE | n/a |
| SOLUBILITY IN WATER | n/a |
| REACTIVITY IN WATER | n/a |
| APPEARANCE AND ODOR | Hexagonal plates or blade shaped needles |

n/a = not applicable

Alpha Cyclodextrin
Common Name
Cat # 15455

**MATERIAL SAFETY DATA SHEET**
**UNITED STATES PHARMACOPEIAL CONVENTION, INC.**

n/a
LOWER n/a UPPER n/a

Water spray, dry chemical, carbon dioxide or foam as appropriate for surrounding fire and materials.

:RATURE n/a
:NG

As with all fires, evacuate personnel to safe area. Firefighters should use self-contained breathing equipment and protective clothing.

:PLOSION

This material is assumed to be combustible. As with all dry powders it is advisable to ground mechanical equipment in contact with dry material to dissipate the potential buildup of static electricity. When heated to decomposition material emits toxic fumes. Emits toxic fumes under fire conditions.

**SECTION 4 - PHYSICAL HAZARDS**

( ) Unstable ( X ) Stable
Material is stable from a safety point of view.

n/a

When heated to decomposition material emits toxic fumes. Emits toxic fumes under fire conditions.

( ) May Occur ( X ) Will Not Occur

**SECTION 5 - HEALTH HAZARDS**

Not Established

[Alpha Cyclodextrin CAS RN: 10016-20-3
$LD_{50}$: 1000 mg/Kg intraperitoneal-rat:
$LD_{50}$: 788 mg/Kg intravenous-rat [RTECS]]

Possible allergic reaction to dust if inhaled, ingested or in contact with skin.

Eye, skin and/or respiratory tract irritation
Possible hypersensitization

Alpha Cyclodextrin
Common Name
Cat # 15455

**MATERIAL SAFETY DATA SHEET**
**UNITED STATES PHARMACOPEIAL CONVENTION, INC.**

| | |
|---|---|
| PRECAUTIONS TO CONSIDER | Persons developing hypersensitivity (anaphylactic) reactions must receive immediate medical attention. Material may be irritating to mucous membranes and respiratory tract. As a general rule, when handling USP Reference Standards avoid all contact and inhalation of dust, fumes, mists, and/or vapors associated with the material. Keep container tightly closed and use with adequate ventilation; wash thoroughly after handling. Individuals working with chemicals should consider all chemicals to be potentially hazardous, even if their individual hazards may be uncharacterized or unknown. |
| MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE | Hypersensitivity to the material |
| CHEMICAL LISTED AS CARCINOGEN OR POTENTIAL CARCINOGEN | NATIONAL TOXICOLOGY PROGRAM ( ) Yes ( X ) No<br>I.A.R.C. Monographs ( ) Yes ( X ) No<br>OSHA ( ) Yes ( X ) No<br>OTHER: n/a |
| | ACGIH TLV: n/a — OTHER EXPOSURE LIMIT(S) USED: n/a |
| OSHA PERMISSIBLE EXPOSURE LIMIT: | Not Established |
| OTHER EXPOSURE LIMIT USED | Not Established |
| EMERGENCY AND FIRST AID PROCEDURES | Remove from exposure. Remove contaminated clothing. Persons developing hypersensitivity reactions must receive immediate medical attention. If not breathing give artificial respiration. If breathing is difficult give oxygen. Obtain medical attention. |
| INHALATION | May cause irritation of respiratory tract. Remove to fresh air. |
| EYES | May cause irritation. Flush with copious quantities of water. |
| SKIN | May cause irritation. Flush with copious quantities of water. |
| INGESTION | May cause irritation. Flush out mouth with water. |

Not applicable

Alpha Cyclodextrin
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Cat # 15455

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**SECTION 6 - SPECIAL PROTECTION INFORMATION**

| | |
|---|---|
| RESPIRATORY PROTECTION (SPECIFY TYPE) | NIOSH approved respirator |
| VENTILATION | Adequate |
| LOCAL EXHAUST | Recommended |
| MECHANICAL (GENERAL) | Recommended |
| OTHER | n/a |
| PROTECTIVE GLOVES | Rubber |
| EYE PROTECTION | Safety goggles |
| OTHER PROTECTIVE CLOTHING OR EQUIPMENT | Appropriate laboratory apparel; protect exposed skin. |

**SECTION 7 - SPECIAL PRECAUTIONS AND SPILL/LEAK PROCEDURES**

| | |
|---|---|
| PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE | Store in tight container as defined in the United States Pharmacopeia. This material should be handled and stored per label and other instructions to ensure product integrity. |
| OTHER PRECAUTIONS | Avoid contact with eyes, skin or clothing. Avoid breathing dust or mist. Use with adequate dust control. Wash thoroughly after handling. Wear fresh clothing daily. Wash contaminated clothing before reuse. Do not permit eating, drinking or smoking near material. |
| STEPS TO BE TAKEN IN CASE MATERIAL IS SPILLED OR RELEASED | Wear approved respirator and chemically compatible gloves. Vacuum or sweep up spillage. Avoid dust. Place spillage in appropriate container for waste disposal. Wash contaminated clothing before reuse. Ventilate area and wash spill site. |
| WASTE DISPOSAL METHODS | Dispose of waste in accordance with all applicable Federal, State and local laws. |

not applicable

Alpha Cyclodextrin
Common Name
Cat # 15455

**MATERIAL SAFETY DATA SHEET**
**UNITED STATES PHARMACOPEIAL CONVENTION, INC.**

NOTICE: The information contained herein is applicable solely to the chemical substance when used as a USP Reference Standard and does not relate to any other use of the substance described. Its use is intended by persons having technical skill and at their own discretion and risk. The information has been developed by USP staff from sources considered reliable but has not been independently verified by the USP. Therefore, the USP Convention cannot guarantee the accuracy of the information in these sources nor should the statements contained herein be considered an official expression. NO REPRESENTATION OR WARRANTY, EXPRESS OR IMPLIED, INCLUDING THE WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE is made with respect to the information contained herein.

**ATTENTION:**

**This Product is Sold as a Reference Standard for Use In Chemical Analysis Not For Human Consumption.**

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not applicable

## MATERIAL SAFETY DATA SHEET

| | | |
|---|---|---|
| | Product name | : PGE1-ALPHA-CD-3/97 |
| | Status | : 15.04.94 |
| 1.1 | Chem.characterization | : (1R,2R,3R)-3-hydroxy-2-[(e)-(3S)-3-hydroxy-1-Octenyl]-5-oxo-cyclopentane heptanoic acid<br>C20 H34 O5 MW-354,49 (Alprostadil)<br>PGE1-αCD contains 2,7 -3,3 % Alprostadil |
| 1.2 | Form | : powder |
| 1.3 | Colour | : white to off-white |
| 1.4 | Odour | : odorless |
| 1.5 | Hazardous constituents: | |

| | | | | Tested according to: |
|---|---|---|---|---|
| 2. | Physical data and safety data | | | |
| 2.1 | Change in physical state | | | |
| | Melting point | : | n.a. °C | |
| | Boiling point | : | n.a. °C | |
| | Decomposition temp. | : | n.a. °C | |
| 2.2 | Density | : | ( °C) | n.a. g/cm3 |
| 2.3 | Vapour pressure | : | ( °C) | n. a. mbar |
| 2.4 | Viscosity dynam. | : | ( °C) | n. a. |
| 2.5 | Solubility in water | : | ( °C) | insoluble |
| 2.6 | pH value | : | ( 20 °C) | 3,5 -5,5 |
| | | | at g/l $H_2O$ = | 5 |
| 2.7 | Flash point | : | n.a.°C | |
| 2.8 | Ignition temperature | : | n. a.°C | |
| 2.9 | Explosion limits -top: | | n.a. | |
| 2.10 | Thermal decomposition | : | When heated to decomposition, material emits acrid smoke and irritating fumes. | |
| 2.11 | Hazardous decomposition products | : | Emits toxic fumes under fire exposure. | |

| | | | |
|---|---|---|---|
| 3. | Transport | | Packaging group |
| | Other information | : | |
| | Not applicable. | | |
| | Store cool in tight container. | | |

| | | | |
|---|---|---|---|
| 4. | Regulations | | |
| | S-phrases | : | 03/07/09-20/21-24/25 Keep container tightly closed in a cool, well-ventilated place. When using do not eat, drink or smoke. Avoid contact with skin and eyes. |
| | Other points | : | |

## 5. Protective measures, storage and handling

5.1 Technical protective meassure : Avoid inhalation of dust. Minimize direct contact with skin and eyes.

5.2 Personal protective equipment

- Respiration : NIOSH approved respirator
- Eye protective : Safety goggles
- Hand protective : Rubber gloves
- Other : Appropiate laboratory equipment, protect exposed skin.

5.3 Industrial hygiene : Don't eat, drink or smoke during work; wash thoroughly after handling. Remove contaminated clothing.

5.4 Protection against fire and explosion : This material is assumed to be combustible. As with all dry powders it is advisable to ground mechanical equipment in contact with dry material to dissipate the potential buildup of static electrcity. When heated to decomposition material emits toxic fumes.

5.5 Disposal : Dispose of in accordens with all local, state and federal regulations.

Waste code (D) : 53502

## 6. Measures in case of accidents and fires

6.1 After spillage/leakage/gas leakage : Avoid dust. Sweep up and place in closed containers for disposal. Wash contaminated clothing before reuse.

6.2 Extinguishing media

Suitable : Water spray, dry chemicals, carbon dioxide or foam.

6.3 Firstaid

Body : Remove from exposure. Remove contaminated clothing. Wash skin with water and soap.

Eyes : In case of contact, immediately flush eyes with copius amounts of water for at least 15 minutes.

Respiratory : Remove to fresh air. Call a physician.

Devour : Call a physician.

6.4 Further information

6.5 Other information : Persons developing serious hypersensitivity reactions must receive immediate medical attention. If not breathing give artificial respiration. If breathing is difficult give oxygen.

## 7. Information on toxicity

Results from animal experiments

LD50 oral : ( )

LD50 dermal : ( )

LC50 inhal : ( )

Risk for health : Possible allergic reaction to dust if inhaled, ingested or in contact with skin, stimulates smooth muscle contraction, may cause skin or eye irritation, may cause intense bronchospasm particularly in asthmatic patients, gastrointestinal disturbances increased bone formation and adverse reproductive effects.

Other characteristics :

LD 50-Mouse orl-5667-7667 mg/kg (complex)
and 170 - 230 mg/kg (pure PGE 1)
LD 50-Rat orl - 6667-8667 mg/kg (complex)
and 200 - 260 mg/kg (pure PGE 1)
Harmful if swallowed, inhaled, or absorbed through skin. May cause eye irritation. May cause skin irritation.

Exposure can cause: nausea, headache and vomiting.
Other effects include diarrhea, flushing, shivering and dizziness.
May be fetotoxic. Appropriate protective equipment should be worn by women during pregnancy.

8. Information on ecological effects

8.1 Acute toxicity

8.2 Other information : PGE1-alpha-CD-3/97 is a pharmaceutical substance with applications to humans, so any ecological problems appear unlikely. We have no information about any problems in a sewage plant.

9. For further information and for emergency contact:

Schwarz Pharma AG
Environmental Protection and Safety Dept.
Alfred-Nobel-Str. 10
40789 Monheim
Tel. 02173 - 481185

All the above-mentioned details correspond to our current level of knowledge. These details describe the product with regard to safety data; they do not guarantee the product properties in the sense of the technical specifications.