# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 20-755

## CORRESPONDENCE

Rumble

OCT 16 1997

NDA 20-755

Pharmacia & Upjohn, Inc.
Attention: Mr. Greg Shawaryn
Senior Regulatory Manager
7000 Portage Road
Kalamazoo, MI 49001-0199

Dear Mr. Shawaryn:

Please refer to your pending July 26, 1996, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Caverject® Injection (alprostadil aqueous injection).

We also refer to your amendments dated July 23 and October 6, 1997.

In addition, we reference your September 4 teleconference with Drs. Rhee and Srinivasachar and Ms. Rumble of this division, in which the storage conditions of the drug product were discussed.

We have completed our review of the Chemistry and Labeling sections of your submission and have identified the following deficiencies:

Chemistry

Regarding the drug product:

1. Certificates of Analysis should be provided for inactive ingredients used in the formulation.

2. A tentative expiration date of 18 months can be granted for the 5 mcg/mL strength when stored at freezer temperature. For the 10 and 20 mcg/mL and 40mcg/2 mL strengths, a tentative expiration data of 24 months may be allowed, again for storage at freezer temperature. The stability protocol on page 3/3/38 should be revised to include sterility testing at initial and shelf-life time points for all lots, and not just the first three lots. This is necessary because Caverject Injection does not have a preservative in the formulation.

3. No drug product samples are listed in the tabular listing of all samples to be supplied. Samples of the finished dosage form will be needed for methods validation and the missing information should be provided.

Labeling

Package Insert

Redacted 3 pgs

pages of trade

secret and/or

confidential

commercial

information

**BLISTER LABEL AND CARTON LABEL**

We would appreciate your prompt written response so we can continue our 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,

10/15/97

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 20-755
HFD-580/Div. Files
HFD-580/PM/Rumble/Pauls
HFD-580/Rarick/Jolson/Hirsch/Srinivasachar/Rhee/Dorantes

drafted: Rumble/October 7, 1997/October 14, 1997/20755.ir2
concurrence: Rarick,10.10.97/ Jolson,10.10.97,10.15.97/Hirsch,10.8.97/
Srinivasachar,10.8.97,10.14.97/Rhee,10.8.97,10.14.97/Dorantes,10.9.97 / Pauls,10.8.97
final: Rumble,10.15.97

INFORMATION REQUEST (IR)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-755

AUG - 8 1997

Pharmacia & Upjohn
Attention: Mr. Gregory G. Shawaryn
Regulatory Manager, Regulatory Affairs
Unit 0635-298-113
7000 Portage Road
Kalamazoo, MI 49001-0199

Dear Mr. Shawaryn:

We acknowledge receipt on July 24, 1997, of your July 23, 1997, amendment to your new drug application for Caverject® Injection(alprostadil aquesous injection).

We consider this a major amendment received by the agency within three months of the user fee due date. Therefore, the user fee clock is extended three months. The new due date is November 2, 1997.

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

Sincerely,

8/6/97

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

cc:
Original NDA 20-755
HFD-580/Div. Files
HFD-580/T.Rumble
DISTRICT OFFICE

Drafted by:
Rumble/August 4, 1997/20755ext.90d
Initialed by:Rarick, Jolson, Pauls
final: Rumble,

REVIEW EXTENSION

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-755

June 20, 1997

Pharmacia & Upjohn, Inc.
Attention: Mr. Greg Shawaryn
Regulatory Manager
7000 Portage Road
Kalamazoo, MI 49001-0199

The non-confidential Environmental Assessment submitted in Appendix A, pages 3.6/16-3.6/44, vol. 1.7, is a copy of the Environmental Assessment submitted to NDA 20-379 (Caverject Sterile Powder). Many sections of this are not relevant to alprostadil aqueous injection since this is a different formulation manufactured at another location. A revised non-confidential Environmental Assessment should be submitted with information pertinent to the formulation for which marketing approval is being sought.

An estimate of the maximum possible environmental concentration should be provided in the confidential Environmental Assessment. This information is missing on page 3.6/10, vol. 1.7, where only the equation used in arriving at this number is given.

**Conclusions and Recommendations**: The Applicant should be requested to resubmit an Environmental Assessment section with the revisions detailed above. It is recommended that this information be submitted as soon as possible to facilitate the review of this NDA.

Kumble

DEC 2 7 1996

NDA 20-755

Pharmacia & Upjohn, Inc.
Attention: Ms. Julianna Stewart
Senior Regulatory Manager
7000 Portage Road
Kalamazoo, MI 49001-0199

Dear Ms. Stewart:

Please refer to your pending July 26, 1996, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Caverject® Injection (alprostadil aqueous injection).

We have completed our review of the Microbiology section of your submission and have identified the following deficiencies:

1. Incomplete sterilization validation of the filler and the product transfer piping was submitted. Please provide the following:

   a. a schedule for requalification of the cycle for the filler and associated transfer pipework; and

   b. a schematic representation of the filler and associated transfer piping indicating the positioning of temperature probes and biological indicators.

2. The environmental monitoring program was inadequate. Please provide the following:

   a. the actions taken when environmental monitoring limits are exceeded; and

   b. the procedures for periodic anaerobic and fungal monitoring of the environment, including the frequency of monitoring, limits, and procedures (incubation parameters, microbiological media, etc.).

3. The stability testing program for the product was inadequate. Please provide the following specifications:

   the testing periods for sterility (preferably container/closure integrity tests) and endotoxin levels as part of the stability testing protocol.

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

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 20-755
HFD-580/Div. Files
HFD-580/CSO/Rumble/Pauls
HFD-580/Jolson/Fourcroy/Srinivasachar/Rhee/Dorantes
HFD-160/Stinavage/Cooney

drafted: Rumble/December 19, 1996/20755.ir1
concurrence: Rarick/Joslon,12.20.96/Pauls, 12.19.96/Stinavage,12.20.96/Cooney,12.20.96
final:

INFORMATION REQUEST (IR)

NDA 20-755

OCT 9 1996

Pharmacia and UpJohn Company
Attention: Ms. Julianna C. Stewart
Sr. Regulatory Manager, Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001

Dear Ms. Stewart:

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

Name of Drug Product: Caverject Injection (alprostadil aqueous injection)

Therapeutic Classification: Standard

Date of Application: July 26, 1996

Date of Receipt: August 2, 1996

Our Reference Number: 20-755

Your application has been filed under section 505(b) of the Act as of October 2, 1996, in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations and in accordance with the policy described in the Center for Drug Evaluation and Research Staff Manual Guide CDER 4820.6, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Please request the meeting at least 15 days in advance. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact:

Terri Rumble
Consumer Safety Officer
Telephone: (301) 827-4260

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Lana L. Pauls, M.P.H.
Chief, Project Management Staff
Division of Reproductive and Urologic
Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-755
HFD-580/Div. Files
HFD-80
HFD-580/CKish/10.8.96/n20755.ak
concurrence: LPauls 10.8.96

ACKNOWLEDGEMENT (AC)

Kumble

# Memorandum

**Date:** 2 June 1997

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

**Subject:** NDA 20-755 Stability Information

**To:** NDA 20-755

During the review of the original NDA submission, it was found that the stability section pertaining to drug product (vol. 1.4) was full of errors, typographical as well as incorrect statements. These errors have made it difficult to review the stability data coherently and consequently, it is recommended that this whole section be revised and re-submitted. The major problems encountered are listed below. These are not meant to be a list of deficiencies--they are just an identification of sections where major misstatements and errors were found. Clarification of these points will help in the review process:

1) page 3/3/175: at assay and values are outside of the specifications well before the month time point for the mcg strength contrary to the statement on pages 3/3/34 and 3/3/35. Although the other strengths show greater stability, some of them also fail the specifications before months at this temperature.

2) No data has been submitted for the long term accelerated stability of the mcg mL strength contrary to the statement on page 3/3/34. The tables on pages 3/3/189 and 3/3/190 are just repetitions (up to the month time point) of the long term freezer ( °C) data on pages 3/3/125 and 3/3/126.

3) Pages 3/3/157-3/3/160: short term °C) accelerated data for the mcg/ mL strength: the footnotes at the bottom of all these tables state that samples were moved tc °C controlled temperature after storage in · °C controlled temperature room for months whereas, on page 3/3/3 it is mentioned that samples were pulled after months and months' storage in the freezer. There are 3 tables pertaining to batch A088 and only one for batch A089-- this needs to be clarified. It is not clear if the Cycle # in the table heading and the Cycle # in the column under "Months" are supposed to have the same meaning--the numbers are the same in the table on page 3/3/157 but different on pages 3/3/158-160.

4) The statement on page 3/3/36 that all results were within the limits for the mcg/ml, mcg/mL and mcg/ mL strengths for months is incorrect in that results from regression analysis and real time data have been combined. While regression anlysis can be useful in the extapolation of data to predict probable outcomes, it should not treated on an equal footing with

real time data. Real time stability data have been provided for months and it is only for this time period that test results are within the limits.

5) Typographical errors are numerous--the following is just a representative sample, not an exhaustive compilation:
page 3/3/126: Container/Closure: mL
Page 3/3/148: The data is for the mcg/mL strength, yet, the second column refers to a mcg/mL strength.
Page 3/3/160: Container/Closure: mL....
Page 3/3/191: The target specification for in the table at the bottom of the page is nmt % wrt alprostadil whereas on page 3/3/193 the target specification for is stated to be nmt % wrt alprostadil.

**Conclusions and Recommendations**: The Applicant should be informed of the errors and inconsistencies in the presentation of the stability data for the drug product. It is recommended that parts of this section be re-submitted after revision to facilitate review.

cc: Orig. NDA 20-755
HFD 580/ Div. Files
HFD 580/ K. Srinivasachar/Rhee/CSO
R/D initialed by: 6/2/97

Filename: nda20755.mem

# TELECONFERENCE MINUTES

**Meeting Date:** October 20, 1997
**Time:** 10:00-10:15 am
**Location:** T. Rumble's office

**Application:** NDA 20-755 / Caverject® Injection (alprostadil aqueous injection)

**Type of Meeting:** Guidance (established name)

**Meeting Chair and Recorder:** Terri Rumble, Project Manager, Division of Reproductive and Urologic Drug Products, (DRUDP, HFD-580)

**External Participant:** Greg Shawaryn, Regulatory Affairs, Pharmacia and Upjohn

**Background:**
- on October 14, 1997, the sponsor was asked to clarify with USP the acceptability of their proposed established name, "alprostadil aqueous injection" vs. the USP recommendation of "alprostadil injection"; that responce is pending
- the sponsor wants to differentiate this product and name from their Prostin VR product
- Dr. Rhee requested input/feedback on the established name from ONDC; that recommendation was conveyed to the sponsor in this Tcon

**Meeting Objectives:**
- to clarify the established name for this pending product

**Discussion Points:**
- the sponsor was notified of the DRUDP recommendation for the established name based on consultation with ONDC
- the established name should be "(alprostadil injection) aqueous"
- this name will be consistent with the Prostin VR labeling format

**Action Items:**

- the sponsor will take the recommendation under consideration when revising the current label

Chair and Minutes Preparer: _____

cc: Original NDA 20-755
HFD-580/Div. Files
HFD-580/Rarick/Jolson/Hirsch/Srinivasachar/Rhee/El-Hage/Dorantes/Rumble
HFD-160/Stinavage/Cooney

drafted and final: Rumble,10.24.97

TELECONFERENCE MINUTES

Rumble

# MEMORANDUM OF MEETING MINUTES

**Meeting Date:** September 22, 1997
**Time:** 10:45-11:45 am
**Location:** Parklawn 17B43

**Application:** NDA 20-755 / Caverject Injection (alprostadil aqueous injection)

**Type of Meeting:** Labeling Meeting

**Meeting Chair:** Heidi Jolson, M.D., M.P.H., Deputy Director, Division of Reproductive and Urologic Drug Products, (DRUDP, HFD-580)

**Meeting Recorder:** Terri Rumble, Project Manager, DRUDP; (HFD-580)

**FDA Attendees:**
Heidi Jolson, M.D., M.P.H., Deputy Director, DRUDP; (HFD-580)
Mark Hirsch, M.D., Medical Officer, DRUDP; (HFD-580)
Kasturi Srinivasachar, Ph.D., Chemist, Division of New Drug Chemistry II @ DRUDP; (HFD-580)
Terri Rumble, Project Manager, DRUDP; (HFD-580)

**Background:**
- Caverject Sterile Powder was approved on July 6, 1995
- this NDA is for an aqueous alprostadil injection that requires no reconstitution
- the labeling changes are based on the approved labeling for EDEX and Caverject Sterile Powder with changes as appropriate for the aqueous product
- extended PDUFA goal date: November 2, 1997

**Meeting Objectives:**
- to identify recommendations for the sponsor regarding the proposed label

**Discussion Points:**

**Clinical Pharmacology**
- review comments will be communicated to the sponsor

**Chemistry**
- the ampule should indicate that the product should be used immediately as soon as opened
- the product can be stored for hours at room temperature; there are stability issues related to the storage conditions which could pose confusion for the patient
- the sponsor has not had a final rule from USP regarding the use of the term "aqueous injection"
- the spelling of the term "ampule" should be change from "ampoule"
- due to the lack of a preservative for this product, the sponsor should include a statement similar to that used in the EDEX label, for using the product immediately

**Clinical (See MOR dated 10/7/97)**
- the sponsor should propose a **Clinical Studies** section, which is a subsection of the **CLINICAL PHARMACOLOGY** section
- the **WARNINGS** section should include information about priapism rather than in the **PRECAUTIONS** section; this should include the rates of prolonged erection, the number of patients requiring intervention, and methods to minimize the occurrence of priapism (See EDEX label); also,

the **Clinical Studies** section should include the frequency of priapism

- the first paragraph in the proposed **DOSAGE AND ADMINISTRATION** section, should be deleted and moved to the **Clinical Studies** section
- the term "as soon as possible" related to storage conditions, in the **PRECAUTIONS** section, **Information for Patients** subsection, and **Storage** section, should be more specific in regard to the time requirements
- **Patient Instructions** recommendations:
  - page 4/2/21, Prepare the Dose, item #6, the first sentence should be struck as this is not necessary when using an ampule
  - page 4/2/22, item #9, propose an earlier step for opening the needle package; this procedure is too difficult to do with one hand
  - page 4/2/24, illustration D, the patient instructions should include a picture demonstrating attaching a needle to the syringe
- **INDICATIONS AND USAGE** section, the second indication should be revised to read as the following:
- **PRECAUTIONS** section should enumerate the effects of increased peripheral levels of and its metabolites; the list of **General Precautions** should be enumerated
- **ADVERSE REACTIONS** section should begin with an introductory paragraph, this also applies to the Systemic ADEs Table; propose a statement indicating that the clinical data was derived from controlled and uncontrolled clinical studies using Caverject sterile powder for injection
- **Pregnancy, Nursing Mothers, and Pediatric Use** section should read

- page 4/2/8, **ADVERSE REACTIONS** section, **Prolonged Erection/Priapism**, the first two sentences with the priapism information can remain with the following statements moved to the **WARNINGS** section; this section should also reference this information in the **WARNINGS** section, i.e., "See **WARNINGS**"
- **ADVERSE REACTIONS** section should also include a statement such as,
  **(See MOR dated 10/7/97)**

**Pharmacology (communicated in E-Mail from reviewer)**

- no new changes or recommendation from previously approved labeling for the Caverject sterile powder for injection

**Action Items:**

- provide these recommendations to the sponsor in a letter

Minutes Preparer: _____

Chair Concurrence: 10/10/97

cc: Original NDA 20-755
HFD-580/Div. Files
HFD-580/Meeting Minutes files
HFD-580/PM/Rumble
HFD-580/reviewers & attendees

drafted by: Rumble/10.6.97/20755lab.002
concurrences: Jolson,10.6.97/Hirsch,10.7.97/Srinivasachar,10.7.97/Pauls,10.6.97
final: Rumble,10.10.97

MEETING MINUTES

# MEMORANDUM OF TELECONFERENCE MINUTES

**Meeting Date:** September 4, 1997
**Time:** 5:00-5:40 PM
**Location:** Parklawn 17B43

**Application:** NDA 20-755 Caverject® (alprostadil, aqueous)

**Type of Meeting:** guidance

**Meeting Chair:** Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

**External Chair:** Gregory Shawaryn, Regulatory Affairs, Pharmacia & Upjohn

**Meeting Recorder:** Terri Rumble, Project Manager, DRUDP (HFD-580)

**FDA Participants:**
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, DNDC II @ DRUDP (HFD-580)
Kasturi Srinivasachar, Ph.D., Chemist, DNDC II @ DRUDP (HFD-580)
Terri F. Rumble, Project Manager, DRUDP (HFD-580)

**External Participants:**
Gregory Shawaryn, Regulatory Affairs, Pharmacia & Upjohn
David Baker, Pharmacia & Upjohn
Dirk Teagarden, Senior Scientist, Pharmaceutical Development, Pharmacia & Upjohn
Paul Allen, Chemist, Pharmaceutical Development, Pharmacia & Upjohn

**Background:**

- NDA original due date was August 2, 1997; IR letter sent for Microbiology deficiencies and a fax sent with Chemistry deficiencies
- Major Chemistry amendment sent in extending the PDUFA Goal Date; goal date of NDA extended to November 2, 1997

**Meeting Objectives:** Inform the sponsor of stability issues related to the proposed storage conditions.

**Discussion Points:**

- the data provided to support the stability of the product at ° C marginally demonstrates the ability of the product to meet specifications for ·month as proposed by the sponsor; thus, DRUDP has reservations about the proposed storage conditions of refrigeration for month
- the sponsor intended to cover the event that the small ampules may thaw on the way home from the pharmacy by allowing storage at refrigerated temperature for month for the convenience of the consumer; the Marketing department of the sponsor is focusing on patient convenience; the product is available in a 5-pack carton
- the sponsor claims that the product would not readily re-freeze once thawed, but would instead possibly take several days to re-freeze or would remain only very cold due to the nature of the product

- due to the large variation in temperatures of the average consumers refrigerators and the data provided in the NDA demonstrating that the product meets specifications for only the month period at ' C, DRUDP recommends that the sponsor amend the NDA to change the storage conditions to in freezer storage up to month following dispensing from the pharmacy and at refrigerated temperatures for 1 week of that month not to exceed the 1 month expiration and remaining within the shelf-life expiration of the product
- the sponsor was reminded to submit a request for a categorical exclusion for the Environmental Assessment (EA) for this product

**Decisions (agreements) reached:**

- the sponsor agreed to the above proposal to change the storage conditions of the product
- additional data can be submitted at a later time to support proposed changes in storage conditions in a Supplemental NDA

**Action Items:**

- the sponsor will submit an amendment to NDA 20-755 as recommended in this Teleconference and will include revisions to the carton and container labels as well as the Package Insert as applicable to this change
- the sponsor will submit a request for a categorical exclusion for the EA for this NDA

Minutes Preparer: _____

Chair Concurrence: _____

cc: Original NDA 20-755
HFD-580/Div. Files
HFD-580/Meeting Minutes files
HFD-580/PM/Rumble/Pauls
HFD-580/Rarick/Jolson/Hirsch/Srinivasachar/Rhee

Drafted by: Rumble/9.04.97/20755chm.stb
Concurrences: Rhee,9.5.97/Srinivasachar/Pauls,9.5.97
Final: Rumble,9.5.97

TELECONFERENCE MEETING MINUTES

# MEMORANDUM OF MEETING MINUTES

**Meeting Date:** June 4, 1997
**Time:** 9:00-9:30 am
**Location:** Parklawn 17B43

**Application:** NDA 20-755 / Caverject Injection (alprostadil aqueous injection)

**Type of Meeting:** Labeling Meeting

**Meeting Chair:** Heidi Jolson, M.D., M.P.H., Deputy Director, Division of Reproductive and Urologic Drug Products, (DRUDP, HFD-580)

**Meeting Recorder:** Terri Rumble, Project Manager, DRUDP; (HFD-580)

**FDA Attendees:**
Heidi Jolson, M.D., M.P.H., Deputy Director, DRUDP; (HFD-580)
Jean Fourcroy, M.D., Ph.D., Medical Officer, DRUDP; (HFD-580)
Kasturi Srinivasachar, Ph.D., Chemist, Division of New Drug Chemistry II @ DRUDP; (HFD-580)
Angelica Dorantes, Ph.D., Pharmacokinetic Team Leader, Division of Pharmaceutical Evaluation II (DPE II) @ DRUDP (HFD-580)
Terri Rumble, Project Manager, DRUDP; (HFD-580)

**Background:**
- Caverject Sterile Powder was approved on July 6, 1995
- the sponsor is now submitting an NDA for an aqueous alprostadil injection that requires no reconstitution
- the labeling changes are based on the approved labeling for Caverject Sterile Powder with changes as appropriate for the aqueous product

**Meeting Objectives:**
- to identify recommendations for the sponsor regarding the proposed label

**Discussion Points:**

**Chemistry**
- the sponsor needs to clearly state in the label the total amount of the drug in the vial and the deliverable amount of the drug product; some of the drug is lost in the syringe, i.e.. mcg dose has mcg in vial with mcg being lost in the syringe
- the sponsor needs to further clarify or provide a rationale for the storage issue regarding their recommendation to not keep the product longer than hours following removal from the foil wrapper
- the active excipients need to be listed on the vial or foil wrapper
- the term "aqueous injection" was objected to by USP, but P&UJ wanted to differentiate this product from the Prostin VR injection for children and infants; will check with the sponsor

**Clinical**
- this product could be focused for in-office, diagnostic, multi-dose usage or for home-use for easier management due to no reconstitution
- this could be a problem for ease of identification in the PDR; unknown whether sponsor will replace their other product; only difference is that this product has no preservative

- precautionary language will be needed because of the lack of preservative (like the EDEX label; for example, "Caution: Do not use remaining drug due to possible bacterial contamination")
- the spelling of ampule vs. ampoule needs to be clarified
- will review this label as comparison to the EDEX label; the sponsor needs to include a "Clinical Studies" subsection, a Warning about priapism, a Precaution regarding the systemic levels of PGE1, Drug-Drug Interaction information in the Precautions section vs. the Information for Patient section, and a pediatric use statement
- will also request sponsor to incorporate the most recent labeling changes for Caverject, NDA 20-379/S-007, approved May 7, 1997, into these label recommendations

**Pharmacology (communicated in E-Mail from reviewer)**

- no labeling changes to the carcinogenicity, mutagenicity, fertility or chronic toxicity testing sections from the currently approved labeling
- the sponsor conducted a bridging pharmacology/toxicology study comparing the lyophilized formulation with the new aqueous formulation; there were no significant differences in penile toxicity between the two formulations

**Action Items:**

1. check with sponsor regarding the name "aqueous injection" for acceptance by USP
2. verify spelling of "ampule" vs. "ampoule" for label
3. provide these labeling comments to the sponsor for amendment of proposed labeling

Minutes Prepared: _____

Chair Concurrence: _____ 9/11/97

cc: Original NDA 20-755
HFD-580/Div. Files
HFD-580/Meeting Minutes files
HFD-580/PM/Rumble
HFD-580/reviewers & attendees

Drafted by: Rumble/6.13.97/20755lab.001
Concurrences: Jolson,6.19.97/Fourcroy,6.24.97/Dorantes,6.19.97/Pauls,6.18.97
No response: Srinivasachar
final: Rumble,9.11.97

MEETING MINUTES

# Meeting Minutes

**Date:** May 7, 1997 **Time:** 10:00-10:30 am **Location:** 17B43

**NDA 20-755** **Drug:** Caverject aqueous (alprostadil) **Indication:** erectile dysfunct.

**Sponsor:** Pharmacia & Upjohn

**Type Of Meeting:** Status Meeting

**Meeting Chair:** Heidi Jolson, M.D., M.P.H., Deputy Director, Division of Reproductive and Urologic Drug Products; (DRUDP, HFD-580)

**Meeting Recorder:** Terri Rumble, Project Manager, DRUDP; HFD-580

**FDA Attendees:**
Heidi Jolson, M.D., M.P.H., Deputy Director, DRUDP; HFD-580
Jean Fourcroy, M.D., Ph.D., Medical Officer, DRUDP; HFD-580
Kasturi Srinivasachar, Ph.D., Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Jeri El-Hage, Ph.D., Pharmacologist, DRUDP; HFD-580
Paul Stinavage, Ph.D., Microbiologist, Office of New Drug Chemistry (HFD-805)
Terri Rumble, B.S.N., Project Manager, DRUDP; HFD-580

**Meeting Objectives:** To provide a status update of the NDA reviews by discipline; provide Division goal dates with feedback from reviewers; and identify issues of note regarding the review process and discuss among team members as needed.

**Background:**

- NDA received August 2, 1996; Action date August 2, 1997 (Division sign-off)
- division goal date: July 2, 1997; completion of primary and secondary reviews: June 13, 1997
- this is an aqueous product vs. the approved lyophilized product that is frozen and then can be stored at refrigerated temperature for one month

**Discussion Points:**

Labeling
- labeling meeting scheduled for June 4, 1997; identify labeling issues for PM prior to meeting

Clinical
- no issues identified; no clinical data
- chemist confirmed that the vial could be used for the "trimix" of alprostadil, papaverine and phentolamine

Pharmacology/Toxicology
- sponsor has provided bridging toxicity studies between this product and the originally approved product showing no differences in intrapenile irritation

- no labeling changes apply from the P/T perspective

Chemistry
- sponsor is making change in product to market to patients for home use
- product comes frozen and can be stored at refrigerated temperature for 1 month
- there is no preservative in the aqueous product
- stability issues are under review; see if expiry date is supported by data provided: months for the mcg dose (with one month refrigeration) and months for the mcg strengths (with one month refrigeration)

Microbiology
- IR letter sent to sponsor in December 1996; amendment recently received, addressing issues
- most likely issues will be adequately addressed and answered

Biopharmaceutics
- review complete; acceptable PK/Biopharm section of the NDA
- labeling recommendations for sponsor

**Action Items:**

- PM will check on Microbiology amendment recently submitted for review (completed 5/7/97)
- PM will distribute label with EDEX label for comparison prior to labeling meeting (completed 5/7/97)
- will send sponsor letter requesting a Labeling Supplement to include information based on forthcoming recommendations

Minutes Preparer

Concurrence, Chair

CC:
Original NDA 20-755
HFD-580/DivFile
HFD-580/Rarick/Jolson/Fourcroy/El-Hage/Jordan/Srinivasachar/Rhee/Dorantes/Rumble/Pauls

drafted: Rumble/May 20, 1997/wpfiles/minutes/nda/20755sta.mtg
concurrences: Jolson,6.1.97/Fourcroy,5.22.97/Srinivasachar,5.27.97/El-Hage,5.27.97
/Stinavage,5.27.97/Pauls,5.22.97
final: Rumble, 6.2.97

MEETING MINUTES

DUPLICATE COPY

Pharmacia & Upjohn

Office of:
Julianna C. Stewart
Senior Regulatory Manager
Regulatory Affairs

Phone: 616/833-8063
Fax: 616/833-0409



ORIG AMENDMENT

November 22, 1996



Division of Reproductive and Urological Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 17B-30
5600 Fishers Lane
Rockville, MD 20857

**AMENDMENT NO. 001**

**RE: NDA 20-755**
**CAVERJECT® Injection**
**(alprostadil aqueous injection)**

Dear Sir/Madam:

The following information is provided in response to questions related by telephone on November 20, 1996 from Dr. Albert Chen (Biopharmaceutics Reviewer) to Pharmacia & Upjohn (Julianna C. Stewart). FDA questions appear in bold type, followed by P&U responses.

1. **NDA Vol 1.1, p 1/1/113 , Table of Information on Formulations Used in Upjohn Sponsored Clinical Studies. This table cites drug lot numbers for CAVERJECT Injection 5/10/20 mcg used in Protocol M/5650/0077. Which specific clinical formulation was used in this study?**

   RESPONSE: The formulations of alprostadil aqueous injection used in Protocol M/5650/0077 are as follows:

| Strength | Drug Lot | Formula | NDA (page) |
|---|---|---|---|
| Placebo | A9310 | 9 | 1/1/122 |
| 2.5 mcg | A9344 | 10 | 1/1/122 |
| 5 mcg | A9345 | 11 | 1/1/123 |
| 10 mcg | A9347 | 12 | 1/1/123 |
| 20 mcg | A9349 | 13 | 1/1/124 |

2. **NDA Vol 1.3, p 3/2/9, Table IIE.1 Comparison of Early Clinical Formulations and Alprostadil Aqueous Injection 20 mcg/mL Strength. In which clinical protocol was this early formulation used?**

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo MI 49001-0199
USA

Telephone (616) 833-4000

RESPONSE: This early formulation was used in Protocol M/5650/0077 (lot ZE112; Formulation #7). It is prepared extemporaneously by diluting 1 part of PROSTIN VR PEDIATRIC® Sterile Solution (500 mcg/mL) with 24 parts of saline solution (0.9%). This is described in NDA 20-755 Part IIE.1.3 (Vol. 1.3, pg 3/2/8). We wish to point out that Table IIE.1 contains an error in that the amount of in each mL after dilution is mcL ng), rather than mcL mg) as listed in the table.

The alprostadil aqueous injection, which is also presented in Table IIE.1, is referenced to Formulation #13. Please note that a nominal quantity of alprostadil is cited in this table, which does not account for the manufacturing overage needed in the formulation, as presented in the full description of Formulation #13.

3. **NDA Vol 1.3, p 3/2/14, Table IIE.3 Alprostadil Levels Observed During the Manufacture of Alprostadil Aqueous Injection Stability Lots. In which clinical protocol was Batch No. A9436 used?**

RESPONSE: Batch No. A9436 was used in ongoing clinical Protocol M/5660/005, "Evaluation of the Usability, Efficacy, and Safety of Intracavernosal CAVERJECT Injection Using the in Patients with Erectile Dysfunction (ED)."

If you should have any questions regarding this information, please contact Julianna C. Stewart at (616) 833-8063. Please address correspondence to Unit 0636-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Julianna C. Stewart
Sr. Regulatory Manager

cc: Terri Rumble (CSO)

ORIGINAL

Pharmacia & Upjohn

Office of:
Gregory G. Shawaryn
Regulatory Manager
U.S. Regulatory Affairs

Telephone No. (616) 833-8239
Facsimile No. (616) 833-8237

ORIG AMENDMENT

October 6, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
OCT - 7 1997
HFD-580

Dr. Lisa Rarick
Division of Reproductive & Urological Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 17B-30
5600 Fishers Lane
Rockville, MD 20857

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

**Re: NDA 20-755**
**Caverject® Injection**
**(alprostadil aqueous injection)**

**Amendment to Application**

Dear Dr. Rarick:

Reference is made to the September 4, 1997 teleconference in which representatives from the Division and Pharmacia & Upjohn discussed stability data as they pertained to storage conditions upon dispensing the product.

Pursuant to these discussions we are submitting excerpted labeling indicating changes to the text which are reflective of agreements made during the teleconference. In Attachment 1, original and revised draft label text is included for the following:

--Physician Insert--How Supplied section only
--Patient Instructions--Storage section only
--Blister copy -- shown in its entirety
--Carton copy -- shown in its entirety

Please note that the blister and carton copy show an "X" for the strength and are intended as representative of the various concentrations of product/mL. The copy for the 40 mcg strength will indicate a 2 mL fill.

In addition, pursuant to 21 CFR 25.15 (d), we have included "Environmental Assessment Claim for Categorical Exclusion" as Attachment 2.

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

Telephone (616) 833-4000

If you should have any questions regarding this information, please contact Gregory G. Shawaryn at (616) 833-8239. Please address correspondence to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Gregory Shawaryn

Gregory G. Shawaryn
Regulatory Manager
U.S. Regulatory Affairs

GGS:crdt
Attachments

Attachment 2

# ENVIRONMENTAL ASSESSMENT
# CLAIM FOR CATEGORICAL EXCLUSION

As cited at 21 CFR 25.15(d), an environmental assessment (EA) is not required if it is stated that the action requested qualifies for a categorical exclusion and, to the applicant's knowledge, no extraordinary circumstances exist.

Pharmacia & Upjohn Company's NDA for Alprostadil Aqueous Injection [active ingredient, alprostadil (prostaglandin $E_1$ or $PGE_1$ )] qualifies for a categorical exclusion based on Sec. 25.31(b) wherein the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb). A calculation of the expected introduction concentration (EIC) is provided below:

## EXPECTED INTRODUCTION CONCENTRATION (EIC)

The maximum marketing forecast at the fifth year of production is projected to 500 grams.

Based on the equation for the theoretical maximum expected introduction concentration (EIC), the fifth-year production scenario is projected in the following equation:

EIC-aquatic (ppm) = A x B x C x D

where:

| | | |
|---|---|---|
| A | = | kg/year production |
| B | = | 1/liter per day entering POTWs* |
| C | = | year/365 days |
| D | = | $10E^6$ mg/kg (conversion factor) |

= kg/year x 1/1.115 x $10E^{11}$ x year/365 days x [$10E^6$] mg/kg

*1.115 x $10^{11}$ liters per day entering publicly owned treatment works (POTWs) (1992 Needs Survey, Report to Congress, September 1993, EPA 832-R-93-002.)

Utilizing the fifth-year production forecast for the drug substance of 500 grams, the maximum environmental concentration of alprostadil that could be achieved is 1.2 x $10^{-8}$. This concentration assumes complete and instantaneous release of the entire year's production, with no degradation.

## EXTRAORDINARY CIRCUMSTANCES

To P&U's knowledge, no extraordinary circumstances, as specified in 21 CFR 25.21, exist in connection with action on this filing.

## CERTIFICATION

The undersigned officials certify that the information presented is true, accurate, and complete to the best of their knowledge.

Randal S. Senger

Sept 15, 1997
Date

Randal S. Senger, Associate Director
Environment, Safety & Loss Control
Environmental Quality
(telephone 616/833-5341)

Jeffrey Mehring

15 SEPT 97
Date

Jeffrey S. Mehring, Manager
Environment, Safety & Loss Control
Science & Data Management
(telephone 616/833-4746)

ORIGINAL

Pharmacia & Upjohn

Office of:
Gregory G. Shawaryn
Regulatory Manager
Regulatory Affairs

Telephone No. (616) 833-8239
Facsimile No. (616) 833-8237

April 25, 1997

ORIG AMENDMENT

Dr. Lisa Rarick
Division of Reproductive & Urological Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 17B-30
5600 Fishers Lane
Rockville, MD 20857

**Re: NDA 20-755**
**Caverject® Injection**
**(alprostadil aqueous injection)**

**Amendment to Application**

Dear Dr. Rarick:

We are amending the above referenced NDA to revise the Product Box section of the Final Product Packaging. The product box containing 5 ampoules is the unit dispensed to one patient, therefore, one patient insert rather than five is adequate.

**Original Text:**

Each ampoule of Alprostadil Aqueous Injection will be packaged in individual foil blister packs. Each box will contain five (5) individual blister packs, five (5) patients inserts, and one (1) physician insert.

**Revised Text:**

Each ampoule of Alprostadil Aqueous Injection will be packaged in individual foil blister packs. Each box will contain five (5) individual blister packs, **one (1)** patient insert, and one (1) physician insert.

A replacement to page 57 (3/2/57) of Volume 1.3 is included in Attachment 1.

If you have any questions regarding the contents of this submission, please contact Gregory G. Shawaryn at (616) 833-8239. Please send correspondence addressed to Unit 0635-298-113.

NCD 5-1-97

Sincerely,

PHARMACIA & UPJOHN COMPANY

Gregory Shawaryn

Gregory G. Shawaryn
Regulatory Manager
Regulatory Affairs

GGS:crdt
Attachment

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 2 8 1997
HFD-580

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo MI 49001-0199
USA

Telephone (616) 833-4000

ORIGINAL

Pharmacia & Upjohn

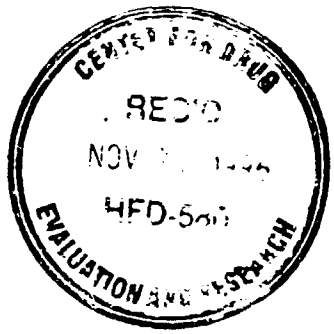
Office of:
Julianna C. Stewart
Senior Regulatory Manager
Regulatory Affairs

Phone: 616/833-8063
Fax: 616/833-0409

NEW CORRESP

November 19, 1996

Division of Reproductive and Urological Drug Products, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 17B-30
5600 Fishers Lane
Rockville, MD 20857
Attention: Ms. Terri Rumble, Project Manager




**RE: NDA 20-755**
**CAVERJECT® Injection**
**(alprostadil aqueous injection)**

**GENERAL CORRESPONDENCE DESK COPIES**

Dear Ms. Rumble:

Pursuant to your telephone request on November 19, 1996, enclosed for your reference and use as needed is the draft package insert and patient instructions for CAVERJECT Injection, which were included in the original submission of NDA 20-755, dated July 26, 1996.

These texts are provided both in hard copy and in WP 5.2 diskette.

If you should have any questions regarding this information, please contact Julianna C. Stewart at (616) 833-8063. Please address correspondence to Unit 0636-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Julianna C. Stewart
Sr. Regulatory Manager

JCS:SEH
Attachments

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

Telephone (616) 833-4000