CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-212

ADMINISTRATIVE DOCUMENTS

ITEMS 13 AND 14. PATENT INFORMATION AND CERTIFICATION

A. Patent Information & Certification

1.	Active Ingredient(s)	Alprostadil (Prostaglandin E_1, PGE_1)
2.	Strength(s)	10 mcg in 0.5 ml and 20 mcg in 0.5 ml
3.	Trade Name	CAVERJECT® DC (alprostadil for injection)
4.	a. Dosage Form	Powder for reconstitution for injection
	b. Route of Administration	Intracavernosal injection
5.	Applicant Firm Name	Pharmacia & Upjohn Company
6.	NDA Number	21-212
7.	NDA Approval Date	To be determined
8.	Exclusivity – Date first ANDA could be approved and length of exclusivity period	Three (3) years after date of NDA approval.
9.	Applicable patent numbers and expiration date of each	N/A

In the opinion and to the best knowledge of Pharmacia & Upjohn Company, there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

EXCLUSIVITY SUMMARY for NDA # 21-212

Trade Name Caverject Generic Name Alprostadil for injection

Applicant Name Pharmacia & Upjohn HFD-580

Approval Date June 11, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_x__/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_x__/

      If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_x__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /_x__/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Three years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_x__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /_x__/ NO /___/

If yes, NDA # NDA 20-379 and NDA 20,755
Drug Name: Caverject

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there ~~are~~ published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain:
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

Eufrecina DeGuia
Signature of Preparer Date June 11, 2002
Title: Regulatory Project Manager

(See appended electronic page)
Daniel Shames, M.D.
Signature of Division Director Date June 11, 2002

cc:
Archival NDA
HFD- /Division File
HFD- /DeGuia
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Daniel A. Shames
6/11/02 02:11:18 PM

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number:	021212	**Trade Name:**	CAVERJECT DC (ALPROSTADIL) 10/20MCG INJ
Supplement Number:	000	**Generic Name:**	ALPROSTADIL
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	FOR THE TREATMENT/DIAGNOSIS OF ERECTILE DYSFUNCTION/ED/VIA INTRACAVERNOSAL INJECTION.
Action Date:	1/21/00		

Indication # 1 treatment of erectile dysfunction
Label Adequacy: Adequate for ALL pediatric age groups
Forumulation Needed: NO NEW FORMULATION is needed
Comments (if any): 11/07/00 Full waiver requested and granted

Lower Range	Upper Range	Status	Date
0 years	16 years	Waived	11/21/00

Comments: Erectile dysfunction is not an indication for which treatment represents a clinically meaningful benefit in the pediatric population.

This page was last edited on 11/7/00

Signature - Sreya. G\

Date 11/7/00

DEBARMENT CERTIFICATION FOR CAVERJECT
Dual Chamber Syringe (NDA #21-212)

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that, the applicant did not and will not use in any capacity the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act in connection with this application.

12/15/99

Ed L. Patt
Associate Director
Global Regulatory Affairs, CMC

Date

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: March 10, 2000 LLP 3/10/00

From: Lana L. Pauls, M.P.H.
Associate Director, Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Review of Financial Disclosure documents

To: The file (NDA 21-212)

I have reviewed the financial disclosure information submitted by Pharmacia & Upjohn in support of NDA 21-212.

One large study was conducted to support the safety and efficacy for Caverject DC (alprostadil), a liquid formulation of the originally-approved lyophilized powder. The study number and its respective outcome with regard financial disclosure obligations is summarized below:

Study No.	Study Status	Financial Disclosure Documentation
98-DUAL-001	Study completed August 10, 1999	Appropriate documentation; no financial arrangements/proprietary interest

Conclusion:

Adequate documentation has been provided to ensure that the sponsor is in compliance with 21 CFR 54.

cc:
Orig NDA 21-212
HFD-580/KColangelo

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. XXXX-XXXX
Expiration Date: xx/xx/xxxx

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Re: NDA supplement for Caverject Dual Chamber

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further clarify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See Attached List	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

Name Gunilla Casserstedt	Title Vice President, R&D Finance
Firm/Organization Pharmacia & Upjohn	
Signature	Date 11/30/97

Please DO NOT RETURN this application to this address

FORM FDA 3454 (7/97)

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

Electronic Mail Message

Date: 1/21/00 11:09:07 AM
From: RCV_SIMMS (RCV_SIMMS@OCOFM.FDA.GOV)
Subject: USER FEE PAYMENT & ARREARS LIST

IMPORTANT ** NEW** USER FEE NOTICE:

Effective January 1, 2000, applicants must send the full Fiscal Year 2000 application fee at the time of submission for fee liable applications and supplements. The fees for Fiscal Year 2000, as announced in the Federal Register on December 28, 1999 (Vol. 64 page 72669) are:

Application/Clinical Data Required..... $ 285,740
Supplement/Clinical Data Required..... $ 142,870
Application/No Clinical Data Required... $ 142,870

An application should be accepted for filing if a fee is submitted even if the amount of the fee is incorrect. The firm should be contacted and told to promptly remit the balance (same user fee ID number). As before, applications for which NO FEE has been received by FDA within 5 days of the receipt date of the application should not be accepted for filling.

NOTE: * denotes entries since last report

APPLICATION PAYMENTS

The following application payments have been received:

Date	Firm	Userfee ID	Application #	Payment

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

ICANT'S NAME AND ADDRESS

PHARMACIA & UPJOHN COMPANY
7000 Portage Road
Kalamazoo, MI 49001

Robert A. Paarlberg
Director, External Affairs

TELEPHONE NUMBER *(Include Area Code)*
(616) 833-0646

3. PRODUCT NAME
CAVERJECT® — (alprostdil for injection)

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

USER FEE I.D. NUMBER
3848

6. LICENSE NUMBER / NDA NUMBER
NDA 21-212

IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Gregory A. Brew /for	Terry Reinstein, Regulatory Manager	January 20, 2000

FORM FDA 3397 (8/98)

Robert A. Paarlberg, Senior Director
Global Regulatory Affairs
Mailstop 0636-298-112

TELEPHONE (616) 833-0646
Facsimile No. (616) 833-8237

January 19, 2000

Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15251-6909

Re: NDA 21-212
CAVERJECT®
(alprostadil for injection)

User Fee Payment
User Fee ID # 3848

Dear Sir or Madam:

In accord with the "Prescription Drug User Fee Act", we are enclosing a check in the amount of $285,740.00 regarding the original submission of NDA 21-212, CAVERJECT DC (alprostadil for injection). This submission contains clinical data. The indication is for the treatment and diagnosis of erectile dysfunction by intracavernosal injection.

If you have any questions, please feel free to contact me at (616) 833-0646.

Sincerely,

Robert A. Paarlberg
Senior Director, Global Regulatory Affairs
Pharmacia & Upjohn

RAP/llp

enclosure

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

Telephone (616) 833-4000

10003

PHARMACIA & UPJOHN CO.
8320-243-74
KALAMAZOO MI 49001-0199

No. 10184821

DETAIL OF PAYMENT

LINDA PORLIER
0636-298-112
PLEASE CALL 3-1249 FOR LINDA
TO PICK UP CHECK

USER FEE ID#3848 NDA 21-212
CAVERJECT (ALPROSTADIL FOR
INJECTION)

REF. DOC. #	DOC. DATE	DOC. NO.	GROSS AMOUNT	DISCOUNT	NET AMOUNT
99005576	01/12/2000	15195102	285,740.00	0.00	285,740.00

Check #	[illegible]	[illegible]	[illegible]	Check Amount
10184821	01/18/2000	102459	FOOD & DRUG ADMINISTRATION	285,740.00

80-1990 10/

THE BACK OF THIS DOCUMENT HAS AN ARTIFICIAL WATERMARK. HOLD AT ANGLE TO VIEW.

PHARMACIA & UPJOHN CO.
8320-243-74
KALAMAZOO MI 49001-0199

No. 10184821

62-20
311

DATE
01/18/2000

PAY TWO HUNDRED EIGHTY-FIVE THOUSAND SEVEN HUNDRED FORTY USD

AMOUNT

VOID

FOOD

PAY TO

SIGNATURE

1Gim

MAY – 2 2000

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 3/1/00	**DUE DATE:** 5/1/00	**OPDRA CONSULT #:** 00-0064

TO:
Susan Allen, M.D.
Acting Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH:
Kim Colangelo
Project Manager, DRUDP
HFD-580

PRODUCT NAME: **Caverject DC** **(alprostadil for injection) 10 mcg and 20 mcg.** **NDA#:** 21-212	**MANUFACTURER:** Pharmacia & Upjohn

SAFETY EVALUATOR: Peter Tam, RPh.

OPDRA RECOMMENDATION:
OPDRA does not recommend the use of the suffix "DC" with the proprietary name, Caverject.

5/2/2000

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

5/4/00

Peter Honig, MD
Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 4/20/00

NDA#: 21-212

NAME OF DRUG: Caverject DC
(alprostadil for injection) 10 mcg and 20 mcg

NDA HOLDER: Pharmacia & Upjohn

I. INTRODUCTION:

This consult is in response to a 3/1/00 request by the Division of Reproductive and Urologic Drug Products, to review the proposed proprietary drug name, Caverject DC, regarding potential name confusion with other proprietary/generic drug names. Container label and container labeling were reviewed for possible interventions in minimizing medication errors.

PRODUCT INFORMATION

Alprostadil is currently marketed as Caverject Sterile Powder and Caverject Injection. The applicant wants to introduce a new packaging configuration as a single-dose, dual chamber syringe system, called Caverject DC.

Caverject DC (alprostadil for injection) is indicated for the treatment of erectile dysfunction due to neurogenic, vasculogenic, and psychogenic or mixed etiology.

Alprostadil is rapidly converted to compounds which are further metabolized prior to excretion. The metabolites of alprostadil are excreted primarily by the kidney, with almost 90% of an administered intravenous dose excreted in urine within 24 hours post-dose. The remainder of the dose is excreted in the feces.

Caverject DC will be available as a disposable, single-dose, dual chamber syringe system. The system includes a glass cartridge which contains sterile, freeze-dried alprostadil in the front chamber and sterile bacteriostatic water for injection in the rear chamber. Caverject DC will be available in two strengths for intracavernosal administration, 10 mcg/0.5 mL and 20 mcg/0.5 mL.

II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound alike or look alike to Caverject DC to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

The expert panel consists of members of OPDRA's medication error Safety Evaluator Staff and a representative from the Division of Drug Marketing, Advertising and Communications (DDMAC).

The expert panel did not like the suffix "DC" after the proprietary name. Qualification of the proprietary name through the use of letter prefixes or suffixes should be avoided since this might lead to misinterpretation resulting medication errors. In addition, the term "DC" is a standard medication abbreviation for discontinuing a medication. Therefore, the use of common or standard medication abbreviation in a proprietary name may result in misunderstanding of prescription orders.

---

[1] MICROMEDEX Healthcare Intranet Series, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc).

[2] American Drug Index, online version, Facts and Comparisons, St. Louis, MO.

[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[4] Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

[5] WWW location http://www.uspto.gov/tmdb/index.html.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

These studies were conducted by OPDRA and involved 94 health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Caverject DC with other drug names due to the similarity in handwriting and verbal pronunciation of the name. Inpatient order and outpatient prescriptions were written, each consisting of (known/unknown) drug products and a prescription for Caverject DC (see below). These prescriptions were scanned into a computer and were then delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

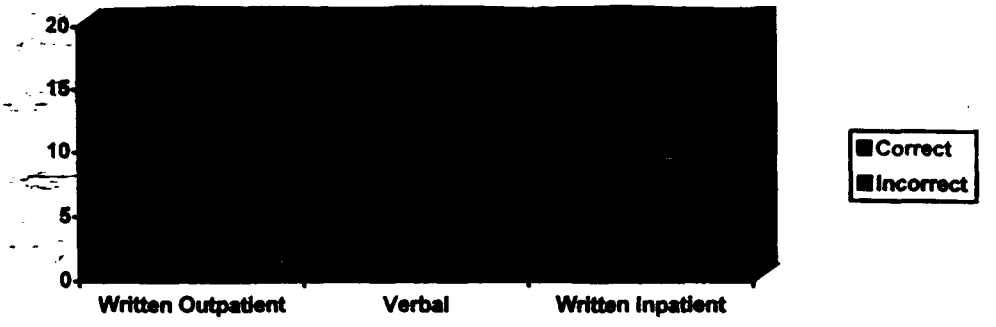
Outpatient RX: Caverject DC As directed	Caverject DC As directed
Inpatient RX: Caverject DC as directed	

2. Results:

The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Outpatient	34	24 (71%)	18	6
Verbal	29	12 (41%)	10	2
Written Inpatient	31	17(55%)	9	8
Total	94	53(56%)	37 (70%)	16 (30%)



Seventy percent of the participants responded with the correct name, Caverject DC. The incorrect written and verbal responses are as follows in Table II.

	Incorrectly Interpreted
Written Outpatient	Caverzect
	Coverject
	Caverjak
	*Caverject discontinue as directed (2)
Written Inpatient	*Caverject discontinue as directed
	Careject (2)
	Cavijject
	Cavejject (2)
	Carreject (2)
Verbal	Phonetic Variable Responses
	Caberject
	Kavriziak

* "DC" interpreted as discontinue order

C. SAFETY EVALUATOR RISK ASSESSMENT

Results of the verbal and written analysis studies show 37 participants interpreted the proprietary name, Caverject DC correctly. As the expert panel predicted, two participants in the outpatient prescription study interpreted "DC" as standard medical abbreviation to discontinue the medication. One participant in inpatient study also interpreted "DC" to discontinue the drug. These findings are significant since our sample size is small. Our results confirm the concerns expressed by the expert panel about the suffix "DC" in a proprietary name and may pose a potential safety risk.

Two scenarios may happen; one in inpatient setting and the other in outpatient setting.

a) Inpatient setting:

Discharged medications; Caverject DC as directed, ASA 81 mg, Rescula 1 gtt ou bid and Prednisone 5 mg bid.

The above discharged medication Rx could be interpreted, as 1) Caverject is the discharged medication physician ordered and the rest Rx are discontinued. 2) Only Caverject Rx is discontinued.

b) Outpatient setting:

In outpatient physician office settings, similar scenario could be unfolded as follows in patient's office chart:

Patient Rx: Caverject DC as directed, Prednisone 5 mg bid and Adalat CC daily.

The above Rx could be interpreted by office nursing personnel as 1) discontinued Caverject, 2) only Caverject Rx is needed and the rest medications are discontinued.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

We have no comments.

IV. RECOMMENDATIONS:

1. OPDRA does not recommend the use of the suffix "DC" with the proprietary name, Caverject .

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Peter Tam, RPh. at 301-827-3241

5/4/51

Peter Tam, RPh.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

5/4/51

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

CC:

NDA – 21-212
Office Files
HFD-580; Kim Colangelo, Project Manager DRUDP
HFD-580; Susan Allen M.D., Acting Division Director, DRUDP
HFD-042; Mark Askine, Senior Regulatory Review Officer, DDMAC (Electronic Only)
HFD-440; Denise Toyer, Safety Evaluator, DDREII, OPDRA
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Director, OPDRA (Electronic Only)
HFD-002; Murray Lumpkin, Deputy Center Director for Review Management (Electronic Only)

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: August 8, 2001	**DUE DATE:** September 10, 2001	**OPDRA CONSULT #:** 01-0172

TO: Susan Allen, M.D.
Acting Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Dornette Spell-LeSane
Project Manager
HFD-580

PRODUCT NAME: Caverject Impulse (Alprostadil for Injection; 10 mcg and 20 mcg) **NDA #:** 21-212	**NDA SPONSOR:** Pharmacia & Upjohn

SAFETY EVALUATOR: Hye-Joo Kim, Pharm.D.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), OPDRA conducted a review of the proposed proprietary name "Caverject Impulse" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: From a safety perspective, OPDRA has no objection to the proprietary name, "Caverject Impulse." However, DDMAC has found the name objectionable from an advertising and promotional perspective.

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Postmarketing Drug Risk Assessment (OPDRA)

HFD-400; Parklawn Building Room 15B-32

FDA Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: **August 20, 2001**

NDA NUMBER: **21-212**

NAME OF DRUG: **Caverject Impulse**
(Alprostadil for Injection;
10 mcg and 20 mcg)

NDA SPONSOR: **Pharmacia & Upjohn**

I. INTRODUCTION

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580) for assessment of the proprietary name, *Caverject Impulse*. OPDRA completed a Proprietary Name Review for this product on April 20, 2000 and did not recommend the use of the proprietary name, "Caverject DC" (See OPDRA Consult 00-0064).

The sponsor, Pharmacia & Upjohn, currently markets the following Caverject products:

Caverject (alprostadil sterile powder): 5, 10, 20, 40 mcg

Caverject Impulse is an addition to the Caverject product line currently marketed by Pharmacia & Upjohn. Caverject Impulse is indicated for the treatment of erectile dysfunction due to neurogenic, vasculogenic, and psychogenic or mixed etiology. The proposed product, Caverject Impulse, contains α-cyclodextrin, which reduces the maximum injection volume to 0.5 mL and permits storage of the product at ambient temperatures. In addition, the proposed product has improved sterility assurance. Furthermore, unlike the current Caverject, the proposed cartridge injection system allows for simple reconstitution; it does not have to be reconstituted in a vial with diluent from an external source, followed by transfer of the vial contents to a syringe prior to injection. Caverject Impulse will be available in two strengths for intracavernosal administration, 10 mcg/0.5 mL and 20 mcg/mL. It will be available as a disposable, single-dose, and dual chamber syringe system. The system includes a glass cartridge, which contains sterile, freeze-dried alprostadil in the front chamber and sterile bacteriostatic water for injection in the rear chamber.

II. RISK ASSESSMENT

The standard OPDRA proprietary name review was not conducted for this consult because "Caverject" has been utilized in the U.S. marketplace. An Expert Panel discussion was conducted to address concerns with the use of the modifier "Impulse". In addition, the Adverse Event

Reporting System (AERS) database was searched to determine if there is any current confusion with the use of the proprietary name "Caverject."

A. EXPERT PANEL DISCUSSION

A discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name *Caverject Impulse*. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA's Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

The OPDRA Expert Panel concluded that the modifier, "Impulse", does not convey anything about the proposed product and that it does not accurately describe the new formulation. However, the panel found the modifier, "Impulse," acceptable.

In addition, a representative from DDMAC had the following comments: First, the name could be misleading because "Impulse" implies that it is fast-acting or has an immediate effect. Therefore, DDMAC is concerned that the name would overstate the product's efficacy. Second, doctors may forget the second word of the proposed name and thus confuse the proposed product, Caverject Impulse, with the currently available product, Caverject.

B. AERS and DORS DATABASE SEARCHES

We searched the *FDA Adverse Event Reporting System (AERS)* database for all postmarketing safety reports of medication errors associated with Caverject. The Meddra Preferred Term (PT), "Drug Maladministration," and the drug names, "alprostadil%" and "Caverject" were used to perform the searches.

This search strategy retrieved zero medication error reports of name confusion involving Caverject.

C. SAFETY EVALUATOR RISK ASSESSMENT

Caverject was approved on July 6, 1995, but the Agency has not received any medication error reports of name confusion involving Caverject. Therefore, there is no substantial evidence to warrant a name change. OPDRA will continue to monitor post-marketing medication errors in association with the proprietary name, Caverject.

The proposed product, Caverject Impulse, contains the same active ingredient, alprostadil, as the currently available product, Caverject. However, the proposed product, Caverject Impulse, contains α-cyclodextrin, which reduces the maximum injection volume to 0.5 mL and permits storage of the product at ambient temperatures. In addition, the proposed product has improved sterility assurance. Furthermore, unlike the current Caverject, the proposed cartridge injection system allows for simple reconstitution. The sponsor added the modifier "Impulse" to the name, Caverject, in order to differentiate the currently available Caverject product from the proposed product. However, the sponsor failed to provide any justification for the modifier "Impulse."

The OPDRA Expert Panel concluded that the modifier, "Impulse", does not convey anything about the proposed product and that it does not accurately describe the new formulation. However, the panel found the modifier, "Impulse" acceptable. Since there is no approved product name that utilizes the modifier, "Impulse", in conjunction with the proprietary name, it should not be misinterpreted and lead to medication errors.

DDMAC objected to the name, Caverject Impulse, because "Impulse" makes a misleading claim about the drug product. Specifically, "Impulse" implies that it is fast acting or has an immediate effect and thus, the name would overstate the product's efficacy. DDMAC was also concerned that doctors may forget or omit "Impulse" and thus confuse Caverject Impulse with the current Caverject product.

We acknowledge DDMAC's concern that confusion may occur between the existing product and a new product if doctors omit "Impulse." However, the current Caverject product and the proposed product, Caverject Impulse, have the same active ingredient and strengths. Furthermore, we expect the sponsor to provide sufficient education prior to availability of this product to familiarize health care practitioners with this new product.

IV. RECOMMENDATIONS

From a safety perspective, OPDRA has no objection to the proprietary name, "Caverject Impulse." However, DDMAC has found the name objectionable from an advertising and promotional perspective.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Hye-Joo Kim, Pharm.D. at 301-827-0925.

Hye-Joo Kim, Pharm.D.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

cc: NDA 21-212
HFD-580: Division Files/Dornette Spell-LeSane, Project Manager
HFD-580: Susan Allen, Acting Director, Division of Reproductive and Urologic Drug Products
HFD-400: Jerry Phillips, Associate Director, OPDRA
HFD-400: Hye-Joo Kim, Safety Evaluator, OPDRA
HFD-400: Sammie Beam, Project Manager, OPDRA

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Hye-Joo Kim
8/24/01 10:00:07 AM
PHARMACIST

Jerry Phillips
8/24/01 10:06:08 AM
DIRECTOR

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21212/000**
Stamp: **21-JAN-2000** Regulatory Due: **12-JUN-2002**
Applicant: **PHARMACIA AND UPJOHN**
7000 PORTAGE RD
KALAMAZOO, MI 490010199

Priority: **3S** Org Code: **580**
Action Goal: District Goal: **22-SEP-2000**
Brand Name: **CAVERJECT DC (ALPROSTADIL) 10/20MCG INJ**
Established Name:
Generic Name: **ALPROSTADIL**
Dosage Form: **INJ (INJECTION)**
Strength: **10 AND 20 MCG**

FDA Contacts: **J. SALEMME (HFD-580) 301-827-7270 , Review Chemist**

Overall Recommendation:

ACCEPTABLE on 10-JUN-2002 by S. ADAMS (HFD-324) 301-594-0095
WITHHOLD on 15-NOV-2000 by EGASM

Establishment: **9691013**
PHARMACIA AND UPJOHN AB
S 112 87
STOCKHOLM, 87, , SW
DMF No:
AADA No:

Profile: **SVL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **10-JUN-2002**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment: **1810189**
PHARMACIA AND UPJOHN CO
7000 PORTAGE RD
KALAMAZOO, MI 49001
DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **03-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment: **9610566**
PHARMACIA DIAGNOSTIC AB
RAPSGATAN PLANT, RAPSGATAN 7
UPPSALA, , SW
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **10-JUN-2002**
Decision: **ACCEPTABLE**
Responsibilities: **INTERMEDIATE MANUFACTURER**

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Reason: **DISTRICT RECOMMENDATION**

Application 21-212 HFD-580

K1.1A

N21212

NAME: CAVERJECT (alprostadil for injection) Dual Chamber Syringe

APPLICANT: Pharmacia & Upjohn

RFC. 06/19/02 9:34 AM

CHEMICAL & THERAPEUTIC CLASS: 3/S

Review Cycles

Review Cycle: 1 **Submission Date: January 20, 2000** **Receipt Date: January 21, 2000** **Goal Date: November 21, 2000** **Action: AE**	**Review Cycle: 2** **Submission Date:** Dec. 10, 2001 **Receipt Date:** Dec. 12, 2001 **Goal Date:** June 12, 2002 **Action:** APPROVAL
Review Cycle: 3 **Submission Date:** **Receipt Date:** **Goal Date:** **Action:**	**Review Cycle: 4** **Submission Date:** **Receipt Date:** **Goal Date:** **Action:**

CORE REVIEW TEAM MEMBERS

PROJECT MANAGER/ CSO : ~~Kim Colangelo~~ / F. DEGUIA **Phone # & Office Room #: x74252, 17B-45**
MEDICAL: Mark Hirsch, MD
CHEMISTRY: Jean Salemme, PhD
PHARM/TOX: Karen Davis-Bruno, PhD
BIOPHARMACEUTICS: Venkat Jarugula, PhD
BIOMETRICS: ~~N/A~~
OTHER: Microbiology (Sterility): Paul Stinavage, PhD **CDRH: Von Nakayama**

Volume 1 of 1

NDA 21-212
Concurrence Page;

Susan Allen, M.D., M.P.H., Division Director (HFD-580)	/S/
Dan Shames, M.D., Acting Deputy Director (HFD-580)	/S/
Mark Hirsch, M.D., ~~Acting Urology Team Leader~~ Medical officer (HFD-580)	/S/
Alex Jordan, Ph.D., Pharmacology Team Leader (HFD-580)	/S/
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, (HFD-580)	/S/
Jean Salemme, Ph.D., Chemist, (HFD-580)	/S/
Ameeta Parekh, Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader (HFD-580)	/S/
Venkat Jarugula, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer (HFD--580)	/S/
Peter Cooney, Ph.D., Microbiology Team Leader (HFD-805)	/S/
Paul Stinavage, Ph.D., Microbiology Reviewer (HFD-805)	/S/
Terri Rumble, BSN, Chief Project Management Staff (HFD-580)	/S/

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21212	Efficacy Supplement Type SE-	Supplement Number
Drug: Caverject (alprostadil for injection)	Applicant: Pharmacia and Upjohn	
RPM: Eufrecina DeGuia	HFD-580	Phone # 301-827-4260
Application Type: (x) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name): 20-379 and NDA 20755	

❖ Application Classifications:	
• Review priority	(x) Standard ( ) Priority
• Chem class (NDAs only)	3 S
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	June 12, 2002 (resubmission)
❖ Special programs (indicate all that apply)	( ) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(x) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (x) No
• This application is on the AIP	( ) Yes ( ) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(x) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(x) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III x IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	(x) Verified

Exclusivity (approvals only)	
• Exclusivity summary	
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	x Yes, Application #_NDA 20379 and NDA 20755 ( ) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	June 11, 2002
❖ Actions	
• Proposed action	(x)AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE (November 10, 2000)
• Status of advertising (approvals only)	(x) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(x) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	x
• Original applicant-proposed labeling	x
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	x
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	X - Caverject Sterile Powder
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	x
❖ Memoranda and Telecons	x
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	October 1, 1998
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	

Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	X (June 10, 2002); November 13, 2000
❖ Clinical review(s) *(indicate date for each review)*	X (6-10-02)
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	X (included in MO review)
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	x
❖ Statistical review(s) *(indicate date for each review)*	N/A
❖ Biopharmaceutical review(s) *(indicate date for each review)*	11-15-00
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X
• Bioequivalence studies	N/A
CMC review(s) *(indicate date for each review)*	06-10-02; 11-27-00; 11-16-00; 11-06-00; 9-12-00
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	Included in Chem Review #1 p. 38
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	11-17-00; 07-27-00;
❖ Facilities inspection (provide EER report)	Date completed: (x) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed (x) Requested ( ) Not yet requested
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	11-09-00
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

45 Day Meeting Checklist
PROJECT MANAGEMENT

ITEM	YES	NO	COMMENT
1) Do any of the following apply to this application (i.e., if YES, the application MUST BE REFUSED TO FILE under 314.100 (e) and there is no filing over protest):			
a. Is the drug product already covered by an approved application?		X	
b. Does the submission purport to be an abbreviated application under 314.55; however the drug product is not one for which FDA has made a finding that an abbreviated application is acceptable under 314.55(b)?		X	
c. Is the drug product subject to licensing by FDA under the Public Service Act and Subchapter F of Chapter I of Title 21 of the CFR?		X	
2) Do any of the following apply to this application (i.e., if NO, the application MAY BE REFUSED TO FILE under 314.100 (d) and there is the potential for filing over protest):			
a. Does the application contain a completed application form as required under 314.50 or 314.55?	X		

ITEM	YES	NO	COMMENT
b. On its face, does the application contain the sections of an application required by regulation and Center guidelines?	X		
c. Has the applicant submitted a complete environmental assessment which addresses each of the items specified in the applicable format under 25.31 or has the applicant submitted evidence to establish that the product is subject to categorical exclusion under 25.24 of the CFR?	X		
d. On its face, is the NDA formatted in compliance with Center guidelines including integrated efficacy and safety summaries?	X		
e. Is the NDA indexed and paginated?	X		
f. On its face, is the NDA legible?	X		
g. Has the applicant submitted all required copies of the submission and various sections of the submission?	X		
h. Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussion with the sponsor?			

Colangelo

NDA FILEABILITY CHECKLIST

NDA Number: 21-212 **Applicant:** Pharmacia & Upjohn **Stamp Date:** 21-Jan-00
Drug Name: Caverject DC (alprostadil for injection)

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Has stability data and analysis been provided to support the requested expiration date?	X		A review issue will be real time data is provided for 6 months at 40°C and 25°C. The Sponsor has data for a similar formulation (same excipients; different ratios) for 36 mo/25° and 6 mo/40° they want to use to support a 2 yr shelf life.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			A pre-NDA meeting was not held. A meeting held with regard to NDA 20-379 outlined the plans for the new formulation and dual cartridge and syringe.
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		A review issue will be that the sponsor has provided validation of all methods in NDA 20-379. The methods used in this NDA will be compared to those used in 20-379 to determine if they are exactly the same.
15	Is a separate microbiological section included?		X	NA; however, sterility sections provided within the CMC Section will be provided to Microbiology for Consult
16	Is a separate Device section included?	X		The device is a new device. A Consult to CDRH will be needed.
17	Have all DMF References Been Identified	X		

Conclusion:
IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) Yes X

Review Chemist: Jean Salemme, Ph.D Date 3-21-00
Team Leader: Moo-Jhong Rhee, Ph.D. Date: 3/21/00

NDA 21-212
HFD-580/Division File
HFD-580/MJRhee/JSalemme
HFD-580/KColangelo

DEPARTMENT OF HEALTH AND HUMAN SERVICES **MEMORANDUM**

Food and Drug Administration
Office of Device Evaluation
9200 Corporate Avenue

CONSULTATION REVIEW

Date: July 24, 2000

To: CDER/Division of Reproductive and Urologic Drug Products (HFD-580)

Thru: Branch Chief,
Patricia Cricenti

From: Scientific Reviewer/HFZ-480

Document No: NDA 21-212
Company Name: Pharmacia & Upjohn
Device: Caverject® DC (alprostadil for injection)

Indications for Use:
The treatment and diagnosis of erectile dysfunction (ED) via intracavernosal injection.

This consult is an evaluation of the device component of a syringe system for the reconstitution and delivery of 10 and 20mcg strengths of Caverject DC from prefilled cartridges.

The Caverject syringe system ("syringe") is a single dose, disposable hypodermic syringe containing a prefilled glass cartridge that is inaccessible to the patient. The syringe body is made of a copolymer plastic and has molded ABS finger grips, and a polypropen threaded plunger rod. The body houses the drug cartridge and has a cutout window through which the cartridge can be seen. The tip of the syringe body is threaded to accept the pen needle (29G, 0.33x12.7mm) that is provided with the syringe. The cartridge is a dual chambered container made of type 1 ——— glass filled with sterile, freeze-dried Caveject DC powder in the front chamber, and sterile bacteriostatic water for injection in the back chamber. The front end of the cartridge is sealed with a ——— rubber stopper covered with an aluminum cap. The back end has a ——— rubber stopper that functions as a plunger. The rubber stoppers are surface treated with ——— and comply with the USP physicochemical tests for elastomeric closures for injection.

The syringe is intended for the delivery of a single dose, selected by the patient using the plunger rod and a dose scale printed along the side of the cartridge. The selection of a partial dose results in a residual drug volume in the cartridge. The syringe operates in the same manner as a conventional syringe, except that the plunger rod is designed to lock in place after it has been depressed. This design feature discourages, but does not prevent, the reuse of the syringe for subsequent doses of the residual drug. Patients can select one of four doses from each cartridge: 2.5, 5, 7.5, or 10mcg for the 10mcg cartridge; 5, 10, 15, or 20mcg for the 20mcg cartridge. Dose strength is based on the volumetric delivery of the reconstituted drug product. The cartridge has a fill volume of 0.64mL and use volume of 0.5mL.

Dose accuracy was tested to the specifications of ISO 11608-1.3 (pen injectors for medical use, part 1), with results presented in volume 1, beginning on page 342. Dose accuracy testing was for delivery volumes of 0.125mL, 0.25mL, 0.375mL, and 0.50mL, quantities that correspond to the four selectable doses (in mcg) that are available from the 10mcg and 20mcg cartridges. Dose accuracy testing was conducted with 200 20mcg cartridges, and the sponsor stated that dose accuracy was approved for 5mcg, 10mcg, 15mcg, and 20mcg. The acceptance standard is a delivered dose within 90-110% of an identified nominal dose.

The sponsor assumed the dose accuracy of the 10mcg cartridge based on the testing of the 20mcg cartridge. The sponsor stated that the doses available from the 10mcg and 20mcg strengths, when expressed in mL, are identical. The dose accuracy of the 2.5mcg and 7.5mcg strengths, where volume variances can have greater impact, was not supported by data. Dose accuracy testing normally includes the low, mid, and high dosage range, and the lack of the 2.5mcg low dose testing is inconsistent with the sponsor's conclusion that the device meets ISO requirements, or supports the accuracy of the syringe in delivering a 2.5mcg dose.

Conclusion:

The Caverject DC injection device does not raise any new issues in terms of intended use, technological characteristics, or any new questions of safety, and effectiveness when used as intended and according to labeling. The design and functionality of the Caverject DC injection device are substantially equivalent to legally marketed syringe devices. However, the sponsor should be asked to:

> Provide dose accuracy test results for the 2.5mcg or data to demonstrate that the expected 2.5mcg dose is within the 90-110% range of an indicated dose of 2.5mcg. The lack of data for the low (2.5mcg) level does not support the use of the syringe for that dose, although the accuracy of the 2.5mcg dose can be extrapolated from the existing data.
>
> Include more prominent warnings/cautions against the reuse of the syringe, regardless of the quantity of unused drug in the cartridge. The syringe is designed as a single use device that retains a drug residual if the entire content of the cartridge is not injected; it appears possible that the plunger rod can be manipulated to reuse the syringe to administer the residual quantities. The ability to reuse the syringe is inconsistent with its labeling.

If you have any questions, please call me at (301) 594-1287.

Von Nakayama

Redacted 19

pages of trade

secret and/or

confidential

commercial

information

ITEM	YES	NO	COMMENT
I. Does the application contain a statement that all nonclinical laboratory studies was conducted in compliance with the requirements set forth in Part 58 or a statement why a study was not conducted in compliance with those requirements?	X		
j. If required, has the applicant submitted carcinogenicity studies?	✓		
k. On its face, does the application contain at least two adequate and well-controlled clinical trials?		X	
l. Does the application contain a statement that all clinical trials were conducted in accord with the IRB/Declaration of Helsinki provisions of the CFR?	✓		
m. Have all articles/study repots been submitted either in English or translated into English?	✓		
n. Has the applicant submitted draft labeling in compliance with 210.56 and 210.57 of the CFR?	X		
3. From a project management perspective, is this NDA fileable? If "no", please state on reverse why it is not.	X		

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3-6-00

[redacted]

Application #(s):	NDA 21-212
Document Type:	NDA Letter
Document Group:	Approval Letters
Document Name:	Approval letter based on enclosed/submitted labeling text
Letter Code:	NDA-I1
COMIS Decision:	AP: APPROVAL
Drafted by:	ed/June 11, 2002
Revised by:	
Initialed by:	MHirsch,DShames061102
Finalized:	
Filename:	NDA21-21.DOC
DFS Key Words:	
Notes:	
Linking Instructions:	If this is the first action on the application, link the outgoing letter to the N, RS, AR, or FO coded incoming document, as appropriate. Otherwise, the outgoing letter must be linked to the major amendment submitted in response to the previous action le

[redacted]

[redacted]

Application #(s):	NDA 21-212
Document Type:	NDA Letter
Document Group:	Approvable Letters
Document Name:	Approvable letter - Misc. deficiencies and labeling revisions listed in letter
Letter Code:	NDA-H4
COMIS Decision:	AE: APPROVABLE
Drafted by:	kmc/November 7, 2000
Revised by:	Allen, 11.20.00
Initialed by:	Jordan, Jarugula, 11.14.00; Cooney, Stinavage, Rumble, Hirsch, Rhee, Salemme, 11.17.00; Parekh, Shames, 11.20.00
Finalized:	Colangelo, 11.20.00
Filename:	C:\data\nda\21-212\ae000.doc
DFS Key Words:	
Notes:	
Linking Instructions:	If this is the first action on the application, link the outgoing letter to the N, RS, AR, or FO coded incoming document, as appropriate. Otherwise, the outgoing letter must be linked to the major amendment submitted in response to the previous action letter. In addition, the outgoing document should also link to all associated amendments and correspondences included in the action. Do NOT link this letter to any amendments that were not reviewed for this review cycle (i.e., amendments where the review was deferred to the next review cycle).

[redacted]

Deputy Division Director/Group Leader Memorandum

NDA 21-212

Date NDA submitted: January 20, 2000
Date NDA received: January 21, 2000
Draft review completed: November 7, 2000
Revisions completed: November 13, 2000

Sponsor:	Pharmacia & Upjohn Company 7000 Portage Road Kalamazoo, MI 49001
Drug:	**Generic**: alprostadil for injection **Proposed Trade**: CAVERJECT DC **Chemical**: [11α, 13E, 15S]-11,15-dihydroxy-9-oxoprost-13-en-1-oic acid.
Route:	intracavernosal
Dosage form:	injection
Strength:	10 and 20 micrograms
Proposed indication:	treatment of erectile dysfunction

Regulatory Background

CAVERJECT Sterile Powder was approved for the treatment of erectile dysfunction on July 6, 1995. In order to improve patient convenience and ease-of-use, the sponsor developed a second CAVERJECT formulation, known as CAVERJECT Injection (alprostadil aqueous). This product was approved on November 30, 1997. CAVERJECT Injection is supplied as a frozen liquid, rather than a powder, and therefore does not require reconstitution. However, it must be kept frozen until the patient intends to use it, and then it must be slowly thawed.

Pharmacia has continued to pursue formulation changes to CAVERJECT in the hope of improving ease of use. On October 1, 1998, Pharmacia met with the Division to discuss a new formulation of CAVERJECT to be delivered in a new dual-chamber injection device. The new formulation would contain alpha-cyclodextrin, an excipient used to improve stability and reduce dry volume. By adding alpha-cyclodextrin, the sponsor would be able to reduce the amount of lactose and fit the dry drug substance in the front chamber of the new dual-chamber syringe. The diluent in this system is benzyl alcohol and water. The entire system can be stored at room temperature.

Alprostadil alphadex (containing alpha-cyclodextrin) is already approved for the treatment of ED as the drug product EDEX (Schwarz Pharma). The lyophilized powder and device of

EDEX are essentially the same as in Caverject DC. However, the EDEX diluent is saline and benzyl alcohol, while the Caverject DC diluent is water and benzyl alcohol.

At an October 1, 1998 meeting with the Division, the sponsor stated their intention not to pursue any additional clinical testing for the new formulation. However, at that time, the sponsor was informed that a major formulation change would require a bioequivalence study. The sponsor and Division agreed that a typical bioequivalence study was not feasible in this circumstance due to rapid metabolism of alprostadil in the penile tissues, rapid first-pass clearance in the lungs, and lack of measurable plasma levels.

Therefore, the Division agreed to a "modified" bioequivalence study based on the pharmacodynamic endpoint of success in obtaining an erection sufficient for intercourse. In addition, a rough comparison of the safety of the two formulations would be conducted. The sponsor submitted the final protocol (98-DUAL-001) on April 26, 1999 and the study was initiated on May 3, 1999. The Division and sponsor agreed that the final study report for 98-DUAL-001 would serve as the major clinical support for the new formulation.

Clinical Assesment

98-DUAL-001: This was an open-label, crossover study conducted in 60 men with erectile dysfunction. The objective of this study was to demonstrate that two formulations of alprostadil (alprostadil sterile powder and alprostadil/α-cyclodextrin) produced comparable pharmacodynamic effects when injected intracavernosally at the same dose levels. The dual chamber injection device was not used in this study.

The CDRH reviewer states that "The CAVERJECT DC injection device does not raise any new questions of safety and effectiveness when used as intended and according to labeling. The device and functionality of the CAVERJECT DC injection device are substantially equivalent to legally marketed syringe devices." The primary medical reviewer states that "the objective of this particular study, therefore, was to demonstrate pharmacodynamic equivalence of the two formulations, but NOT to assess the performance of the dual-chamber injector device."

Overall, the primary medical reviewer believes "that the results of this study demonstrate that alprostadil sterile powder and alprostadil/α-cyclodextrin induce comparable erectile responses when administered at comparable doses. In terms of safety, there were no new obvious safety concerns noted in the alprostadil/α-cyclodextrin group compared to the alprostadil sterile powder group".

Reviewer's Comment: I agree with the primary medical reviewer that study 98-DUAL-001 provides substantial evidence that alprostadil sterile powder and alprostadil/α-cyclodextrin sterile powder are "bioequivalent" (pharmacodynamically equivalent).

Non-Clinical Assessments

Pharmacotoxicology: Non-clinical studies with CAVERJECT DC were not performed. The sponsor believes that the safety of the drug substance (alprostadil) is very well known and the Pharmtox. reviewer agrees. In support of the safety of alprostadil/alpha-cyclodextrin

and alpha-cyclodextrin alone, the sponsor submitted published scientific articles and disclosable approval information from the Edex NDA 20-649 (Schwarz-Pharma).

The toxicology data discussed in the Pharmtox review were summaries from the Pharmacia & Upjohn NDA for Caverject (alprostadil) and the Schwartz-Pharma NDA for Edex (alprostadil/alpha-cyclodextrin). Pharmacia & Upjohn performed sufficient toxicology studies to support the safety of PGE_1 for a chronic indication in their original NDA for Caverject. The preclinical safety information for alpha-cyclodextrin, an excipient in this product, is based on published scientific articles and disclosable approval information for the Edex NDA 20-649. Once an excipient (which has no patent or exclusivity protection) has been approved, the safety data are available to support safety for other sponsors and other indications. As such, any sponsor can use the inactive ingredient in their drug product without submitting supporting animal safety data. Thus, no new toxicity data are needed for Pharmacia & Upjohn's NDA for alprostadil/alpha-cyclodextrin.

Reviewer's comment: I agree with the Pharmtox recommendation of approval.

Chemistry, CDRH, and Microbiology Issues: As previously mentioned, the **CDRH** reviewer found no problems with the proposed device. The **Microbiology** reviewer stated that the application "is recommended for approval on the basis of sterility assurance".

OPDRA and the Division concurred that the suggested tradename was **not appropriate** as DC could be misconstrued as "discontinue". The sponsor was informed of our opinion during a tcon. on 5/11/00, a chemistry review letter on 9/19/00 and an IR labeling letter of 10/6/00.

Facilities Inspection: Agency inspectors recommended **withholding approval** of this NDA because of significant deficiencies at the finished dosage manufacturing site in Stockholm and an intermediate manufacturing plant in Uppsala.

The **Chemistry reviewer** concluded that the NDA is **approvable** pending satisfactory review of responses to each of the following issues:

1. Specifications of drug product water content during release and during shelf life testing
2. Sampling plan for drug product
3. Shelf-~~life~~ expiration date
4. Tradename (see below)
5. Unsatisfactory facility inspections

A response to ~~the first three~~ issues above was received on 11/20/00. The Division elected to defer review of this information.

Clinical Pharmacology: No additional studies to evaluate the pharmacokinetics of the new alprostadil/alpha-cyclodextrin formulation have been performed. Such studies were not undertaken because they were thought to be of limited value for the following reasons:

1. Systemic levels of alprostadil are unlikely to reflect the pharmacodynamic effects in the corpora cavernosum
2. Prior studies characterizing systemic plasma concentrations and metabolites after intracavernosal administration have been submitted, and
3. The dissociation of alprostadil from the alprostadil/alpha-cyclodextrin complex is [redacted] and cyclodextrin would not be expected to result in differences in alprostadil disposition when compared to other formulations with identical amounts of alprostadil.

In support of #3, the sponsor submitted the results from a single, non-clinical study which determined the binding constant for the molecular complexation between alprostadil and alpha-cyclodextrin and used that value to estimate the percentage of alprostadil free upon injection of alprostadil/alpha-cyclodextrin. This study confirmed the sponsor's assertion regarding a lack of effect of alpha-cyclodextrin on alprostadil disposition.

In lieu of a standard bioequivalence study, the sponsor conducted Study 98-DUAL-001, a controlled clinical trial that was designed in accord with the Division's recommendations.

Reviewer's comment: The OCPB reviewer and team leader recommended that NDA 21-212 for Caverject DC is acceptable (for approval). I agree with their recommendation.

Labeling Issues: The Division and DDMAC sent Labeling comments for the PPI and PI with my concurrence on 11/6/00. The key issue was that "Following a single use, the injection device and any remaining solution should be properly discarded". **As of 11/20/00 there was no response from the sponsor** to the Division's version of the label.

DSI issues: Findings from DSI inspections of two clinical sites were acceptable by DSI and/or the Division.

Conclusions: This application is approvable pending the resolution of the following Deficiencies and issues:

1. **Unacceptable facilities inspections at manufacturing sites in Stockholm and Uppsala Sweden.**
2. **Agreement with the sponsor on final labeling**
3. **Resolution of additional four (1-4) chemistry deficiencies sited above**

Regulatory Action: A regulatory letter should inform the sponsor that the application is approvable pending resolution of the above deficiencies and issues.

Daniel A. Shames MD
Deputy Director, DRUDP
CDER/FDA

/s/

Daniel A. Shames
11/20/00 05:04:27 PM
MEDICAL OFFICER

Susan Allen
11/21/00 11:39:29 AM
MEDICAL OFFICER
I concur.

Meeting Minutes

Date: January 14, 2002 **Time:** 2:00 – 3:00 PM **Location:** 17B-43

NDA: 21-212 **Indication:** Treatment or diagnosis of Erectile Dysfunction via intracavernosal injection

Drug Name: CAVERJECT IMPULSE® (alprostadil for injection) Dual Chamber Syringe

Sponsor: Pharmacia & Upjohn Company

Meeting Type: Filing Meeting

Meeting Chair: Mark Hirsch, M.D.

Meeting Recorder: Jennifer Mercier

FDA Attendees:
Mark Hirsch, M.D. – Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)
David Lin, Ph.D. – Team Leader, Division of New Drug Chemistry II (DNDCII) @ DRUDP (HFD-580)
Jean Salemme, Ph.D. – Chemist, DNDCII @ DRUDP (HFD-580)
Leslie Stephens, M.P.H. – Regulatory Health Coordinator, DRUDP (HFD-580)
Jennifer Mercier – Regulatory Project Manager, DRUDP (HFD-580)

Background:
CAVERJECT IMPULSE® (alprostadil for injection) Dual-Chamber Syringe was originally submitted on January 20, 2000 to the Division for review. An Approvable (AE) letter was issued on November 20, 2000 requiring the sponsor to resubmit with the following information: the water content in the drug product and the sampling plan for stability. The sponsor submitted the response to approvable letter for review on December 10, 2001, received December 12, 2001. The PDUFA goal date for this application is June 12, 2002. The action package should be to the Medical Team Leader by May 22, 2002 and to the Division Director for sign off on June 5, 2002.

Purpose of the Meeting: To discuss the adequacy of the complete response to the Approvable letter sent to the sponsor on November 20, 2000.

Discussion:
Clinical
- The application is fileable.
- The tradename and the label need to be reviewed in this cycle.

- A safety update was submitted with this response and will be reviewed.

Chemistry

- The application is fileable.
- In the first review cycle, the sponsor failed the manufacturing inspection; a re-inspection has been requested.
- The sponsor has submitted 24 months of stability data and requests a 36 mointh expiry. We will need to review the 36 month stability data, so the sponsor should be asked to provide these data when they become available. (Based on the dates the stability studies were started, March 1999, the 36 month data should be available sometime after March 2002.)

Decisions Made:

- The submission is fileable.

Action Items:

- Set up regular status meetings.
- Complete reviews prior to May 22, 2002
- Medical Officer (M. Hirsch) to contact DDMAC regarding their objection to tradename (done on 1/16/02 – M. Askine has no substantial objection to the tradename, CAVERJECT IMPULSE – sponsor notified that the tradename is acceptable on 1/18/02).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mark S. Hirsch
2/14/02 01:27:44 PM

Meeting Minutes

Date: October 2, 2000 **Time:** 1:00-2:00 PM EST **Location:** Parklawn; 17B-43

NDA 21-212 **Drug:** Caverject Dual-Chamber Syringe

Indication: erectile dysfunction **Sponsor:** Pharmacia & Upjohn

Type of Meeting: Status/Team Meeting

Attendees:
Dan Shames, MD – Acting Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Mark Hirsch, MD – Medical Officer/Acting Urology Team Leader, DRUDP (HFD-580)
Ashok Batra, MD – Medical Officer, DRUDP (HFD-580)
Jean Salemme, PhD – Chemistry Reviewer, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Venkat Jarugula, PhD – Clinical Pharmacology/Biopharmaceutics Reviewer, Division of Pharmaceutical Evaluation II @ DRUDP (HFD-580)
Kim Colangelo - Regulatory Project Manager, DRUDP (HFD-580)
Barbara Chong, PharmD – Regulatory Reviewer, Division of Drug Marketing, Advertisting and Communications (DDMAC; HFD-42)

Meeting Objective: To discuss the status of the review of NDA 21-212 for Caverject for the treatment of erectile dysfunction. The primary PDUFA goal is November 21, 2000. Reviews, including secondary sign-off, are due November 3, 2000.

Discussion:
Clinical
- review is complete, including the Safety Update
- the syringe prototype was received; changes to the patient package insert will be made if necessary
- inspections of the Clinical sites are pending; Division of Scientific Investigations stated that inspections will be completed by November 7, 2000

Chemistry
- the first review is complete and a Discipline Review letter was sent; responses are expected by October 6, 2000
- Pharmacia & Upjohn (P&U) was asked to declare if the alcohol swabs to be supplied in the kit are considered sterile; P&U responded verbally that they are not sterile; the written response will be consulted to Microbiology for confirmation that this is not a sterility concern
- manufacturing site inspections are still pending; Dr. Salemme will follow-up on the status of responses

Clinical Pharmacology/Biopharmaceutics

- review is ongoing; a labeling review is not needed

DDMAC

- comments on the package insert and patient package insert will be sent to DRUDP by October 6, 2000

Action Items:

- reviews including secondary sign-off will be provided to Ms. Colangelo by November 3, 2000
- Dr. Hirsch will update the revisions to the patient package insert if needed based on the prototype syringe submitted by P&U
- Ms. Colangelo will consult the P&U response regarding alcohol swab sterility to Microbiology upon receipt
- Dr. Salemme will check on the status of the facility inspections *[the inspector report from one of the two Swedish sites was received this week, the other inspector report is pending; Dr. Salemme was advised to contact the reviewer at the end of October for an update; 10.04.00]*
- Dr. Chong will forward comments on the package and patient package inserts to Ms. Colangelo by October 6, 2000

Minutes Preparer **Concurrence, Chair**

cc:
Original NDA 21-212
HFD-580/DivFile
HFD-580/Colangelo/Shames/Hirsch/M.Rhee/J.Salemme/A.Jordan/A.Parekh/V.Jarugula
HFD-580/L.Kammerman
HFD-42/B.Chong
HFD-805/P.Stinavage

drafted: Colangelo, 10.05.00
concurrence: Hirsch, 10.05.00; Chong, 10.12.00; Shames, Salemme, Jarugula, 10.17.00
final: Colangelo, 10.19.00

MINUTES

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Meeting Minutes

Date: September 11, 2000 **Time:** 1:00-2:00 PM EST **Location:** Parklawn; 17B-43

NDA 21-212 **Drug:** Caverject DC (alprostadil for injection)

Indication: erectile dysfunction **Sponsor:** Pharmacia & Upjohn

Type of Meeting: Status/Team Meeting

Attendees:
Dan Shames, MD – Acting Deputy Director, DRUDP (HFD-580)
Mark Hirsch, MD – Medical Officer/Acting Urology Team Leader, DRUDP (HFD-580)
Ashok Batra, MD - Medical Officer, DRUDP (HFD-580)
Moo-Jhong Rhee, PhD – Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Jean Salemme, PhD – Chemistry Reviewer, DNDC II @ DRUDP (HFD-580)
Kim Colangelo - Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss the status of the review of NDA 21-212 for Caverject DC, dual chamber syringe, for the treatment of erectile dysfunction.

Background: Caverject DC is a new formulation of alprostadil powder in a new syringe. The dual chamber syringe was not used in the clinical trial. One trial was conducted in 87 patients to support the safety and efficacy of this product. The primary goal date for this application is November 21, 2000.

Discussion:
Pending Items

- the requested syringe prototype was requested August 11, 2000, and is expected the week of September 11, 2000
- a safety update report has not been submitted; this will be an approvability issue if not submitted prior to action
- a new proposed trademark has not been submitted (Pharmacia & Upjohn [P&U] was notified of the recommendation against "Caverject DC" on May 11, 2000); P&U reports that they have an independent marketing consultant developing alternatives; they anticipate submission of a new proposed trademark prior to the action date; approval cannot be withheld if a trademark has not been submitted, and a sponsor can notify us post-approval of the trademark to be used (without prior agreement)
- real-time stability data was requested on September 1, 2000; P&U has indicated that they have 12-month real-time data (without the particulate analysis) which will be submitted the week of September 11, 2000; the particulate analysis and 18-month data will be submitted when available
- it is possible to take an action before the pending information is received if the reviews are complete; the pending information would then be listed as deficiencies

Chemistry

- one facility inspection is pending and another site had a 483 issued; whether the deficiencies can be addressed prior to the goal date is not known; Dr. Salemme will follow-up with Compliance regarding the 483
- the CMC review is complete

Clinical Pharmacology/Biopharmaceutics

- a brief review is pending (per e-mail from Dr. Venkat Jarugula)
- an *in vitro* study on the dissociation of alprostadil from α-cyclodextrin (Study A0028158) was submitted; Ms. Colangelo will confirm that Dr. Jarugula will review this study

Clinical

- the review is complete except for the pending safety update report
- two clinical site inspections were requested and are pending; Ms. Colangelo will contact Mr. Roy Blay of DSI to follow-up on the status

Labeling

- electronic labeling was received and is now available on the N:drive for revisions by the team; Ms. Colangelo will send out an e-mail with directions to notify the team

Action Items:

- Dr. Salemme will contact Compliance regarding the outstanding facility inspection *[Compliance recommends checking back in a month; the investigator's report is pending and needs to be compared to P&U's responses to the 483; 09.11.00]*
- Ms. Colangelo will confirm the review of Study A0028158 with Dr. Jarugula *[Dr. Jarugula will review, 09.14.00]*
- Ms. Colangelo will contact Mr. Blay regarding the pending clinical site inspections *[inspections are pending, but will be completed prior to November 7, 2000; 09.12.00]*
- Ms. Colangelo will e-mail the review team regarding labeling revisions *[done, 09.11.00]*

Minutes Preparer | **Concurrence, Chair**

cc:
Original NDA 21-212
HFD-580/DivFile
HFD-580/Colangelo/Shames/Hirsch/M.Rhee/J.Salemme/A.Jordan/A.Parekh/V.Jarugula

drafted: Colangelo, 09.14.00
concurrence: Hirsch, 09.14.00; Rhee, 09.18.00; Salemme, Shames, 09.26.00
final: Colangelo, 09.27.00
MINUTES

COLANGELO

Meeting Minutes

Date: August 7, 2000 **Time:** 2:00-3:00 PM EST **Location:** Parklawn; 17B-43

NDA 21-212 **Drug:** Caverject DC (alprostadil for injection)

Indication: erectile dysfunction **Sponsor:** Pharmacia & Upjohn

Type of Meeting: Status/Team Meeting

Attendees:
Susan Allen, MD, MPH – Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Dan Shames, MD – Acting Deputy Director, DRUDP (HFD-580)
Mark Hirsch, MD – Medical Officer/Acting Urology Team Leader, DRUDP (HFD-580)
Karen Davis-Bruno, PhD – Pharmacology/Toxicology Reviewer, DRUDP (HFD-580)
Moo-Jhong Rhee, PhD – Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Jean Salemme, PhD – Chemistry Reviewer, DNDC II @ DRUDP (HFD-580)
Venkat Jarugula, PhD – Clinical Pharmacology/Biopharmaceutics Reviewer, Division of Pharmaceutical Evaluation II @ DRUDP (HFD-580)
Paul Stinavage, PhD – Microbiology Reviewer, Office of New Drug Chemistry (HFD-805)
Kim Colangelo - Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss the status of the review of NDA 21-212 for Caverject DC, dual chamber syringe, for the treatment of erectile dysfunction.

Background: Caverject DC is a new formulation of alprostadil powder in a new syringe. The dual chamber syringe was not used in the clinical trial. One trial was conducted in 87 patients to support the safety and efficacy of this product. The primary goal date for this application is November 21, 2000.

Discussion:
Clinical
- the primary review is approximately 75% complete and likely to recommend approval
- a consult to the Center for Devices and Radiological Health revealed that there was no additional risk with the proposed injector (device), nor were there concerns regarding the use of another syringe type in the clinical trial
- the study done (98-DUAL-001) was not described in the proposed package insert

Chemistry
- the primary review is completed and pending secondary sign-off
- deficiencies identified:
  - the real-time stability data provided (six months) do not support the proposed two-year shelf-life
  - a water limit specification should be provided for the end of shelf-life
  - a Certificate of Analysis is needed from the US site

- distinction of the type of alcohol swab included in the kit (i.e., sterile or non-sterile) will be requested.
- the proposed trademark of "Caverject DC" was rejected by the Office of Post-Marketing Drug Risk Assessment and DRUDP; Pharmacia & Upjohn (P&U) has been notified, but has not responded with a new proposal
- the syringe has the drug product (powder) in the front of the syringe, and the sterile water diluent (preserved) in the back; the plunger is depressed to mix the contents of the two chambers; P&U has addressed consistency in product delivery, but not potential re-use of the product; the clinical team agrees that this can be addressed in the label

Microbiology
- the review is completed, with two deficiencies identified
- problems were identified with the Swedish manufacturing site, including computer and sterility problems; a 483 (notice of violation) was issued

Clinical Pharmacology/Biopharmaceutics
- efficacy support is based on pharmacodynamics; instead of a waiver for measurement of blood levels, DRUDP agreed to allow pharmacodynamic support as the basis for approval

Pharmacology/Toxicology
- the review is completed and pending secondary sign-off
- the proposed labeling is acceptable

Action Items:
- Ms. Colangelo will contact P&U to request the following:
  - a description of Study 98-DUAL-001 in the package insert
  - a prototype of the dual-chamber syringe
- Ms. Colangelo will draft a "Discipline Review" letter with Microbiology deficiencies

Sig.
Minutes Preparer

Sig.
Concurrence, Chair

cc:
Original NDA 21-212
HFD-580/DivFile
HFD-580/Colangelo/Shames/Hirsch/M.Rhee/J.Salemme/A.Jordan/A.Parekh/V.Jarugula

drafted: Colangelo, 08.24.00
concurrence: Hirsch, Shames, 08.24.00; Davis-Bruno, Rhee, 08.25.00; Stinavage, Jarugula, 08.29.00; Salemme, 09.06.00; Allen, 09.08.00
final: Colangelo, 09.12.00
MINUTES

Meeting Minutes

Date: March 6, 2000 **Time:** 12:30 PM EST **Location:** PKLN 17B-45

NDA 21-212 **Drug:** Caverject DC Dual Chamber Syringe **Indication:** erectile dysfunction

Sponsor: Pharmacia & Upjohn **Type of Meeting:** Filing

Meeting Chair: Susan Allen, MD, MPH **Meeting Recorder:** Kim Colangelo

FDA Attendees:
Susan Allen, MD, MPH – Acting Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Dan Shames, MD – Urology Team Leader, DRUDP (HFD-580)
Mark Hirsch, MD – Medical Officer, DRUDP (HFD-580)
Moo-Jhong Rhee, PhD, Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Jean Salemme, PhD, Chemistry Reviewer, DNDC II @ DRUDP (HFD-580)
Lisa Kammerman, PhD – Statistics Team Leader, Division of Biometrics II @ DRUDP (HFD-580)
Terri Rumble, BSN – Chief, Project Management Staff, DRUDP (HFD-580)
Kim Colangelo, BS Project Manager, DRUDP (HFD-580)
Roy Blay, PhD – Good Clinical Practices Branch I, Division of Scientific Investigations (HFD-46)

Meeting Objective: To determine the fileability of NDA 21-212 for Caverject DC Dual-Chamber Syringe, indicated for the treatment of erectile dysfunction.

Background: The Dual-Chamber Syringe contains the same active ingredient, alprostadil, as in other approved injectables for the treatment of erectile dysfunction (ED). In addition to the new syringe, alpha-cyclodextrin has been added to the formulation. Alprostadil and alpha-cyclodextrin are also contained in the approved product Edex®, also indicated for the treatment of ED. A bioequivalence study could not be performed since alprostadil levels are not quantifiable with either formulation. DRUDP agreed to a single study to show pharmacodynamic equivalency to Caverject Sterile Powder (NDA 20-379). The study enrolled 85 men in an open-label trial, with 12 doses given over a six-week period. The efficacy appears to be equivalent to Caverject Sterile Powder. The addition of alpha-cyclodextrin to the formulation was intended to decrease the volume of the injected product, thereby theoretically decreasing the pain of injection. The syringe has a dial for dose selection.

Discussion:
Clinical
- the application is fileable
- the Agency should be alert for claims comparing the Dual-Chamber Syringe to other formulations
- clinical sites should be inspected; preferred sites include one in Germany (30 patients), where an incident with bacterial meningitis was reported; justification for the overseas inspection will be

Colangelo

Teleconference Minutes

Date: April 25, 2000 **Time:** 4:40 PM **Location:** Parklawn 17B-45

NDA 21-212 **Drug:** Caverject DC **Indication:** erectile dysfunction

Sponsor: Pharmacia & Upjohn **Type of Meeting:** Information Request

FDA Attendee: Kim Colangelo – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (HFD-580)

External Attendees: Terry Reinstein – Regulatory Manager, Pharmacia & Upjohn

Meeting Objective: To request additional chemistry information needed for the review of NDA 21-212 for Caverject DC.

Requests:

- drug substance clarification requested:
  - PGE 1 is produced from PGE 2; the specifications in the NDA for PGE 2 do not match those provided in the DMF referenced for PGE 2 (also held by Pharmacia & Upjohn); these need to be reconciled
  - the solvent used in the optical rotation test needs to be specified
  - the acronym "ROI" needs to be defined
  - the degradants (isomers) quantified in the specifications for PGE 2 need to be specified
- drug substance is manufactured in the US and shipped to Sweden to produce the drug product; an identity test for the drug substance upon arrival in Sweden needs to be specified

Action Items:

- Pharmacia & Upjohn will provide the requested information
- a record of this teleconference will be provided within 30 days

/S/

Minutes Preparer and Chair

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcomes.

cc:
Original NDA 21-212
HFD-580/DivFile
HFD-580/KColangelo/JSalemme

drafted: Colangelo, 05.09.00
concurrence: Salemme, 05.09.00; Rumble, 05.11.00
final: Colangelo, 05.18.00
MINUTES

cc:
Original NDA 21-212,
HFD-580/DivFile
HFD-580/Colangelo

drafted: Colangelo, 05.23.00
concurrence: Rumble, 05.24.00
final: Colangelo, 05.25.00

MINUTES

Colangelo

Teleconference Minutes

Date: May 11, 2000 **Time:** 2:10 PM EDT **Location:** Parklawn 17B-45

NDA 21-212 **Drug:** Caverject DC (alprostadil) **Indication:** erectile dysfunction

Sponsor: Pharmacia & Upjohn **Type of Meeting:** Guidance/Request for Information

FDA Attendee: Kim Colangelo – Regulatory Project Manager, Division of Reproductive and Urologic Drug Products (HFD-580)

External Attendees: Terry Reinstein – Regulatory Manager, Pharmacia & Upjohn

Meeting Objective: To convey recommendations and a request for additional information for the review of NDA 21-212.

Discussion:

- Pharmacia & Upjohn (P&U) stated that information requested for the CMC review on April 25, 2000, would be submitted in the near future
- autoclave information that was inadvertently omitted from the NDA should be submitted for review as soon as possible; P&U stated that this information would be submitted by the end of May 2000
- the Office of Post-Marketing Drug Risk Assessment (OPDRA) has returned a recommendation for the proposed trademark of "Caverject DC"; OPDRA has recommended that the proposed trademark be changed because of possible confusion with the abbreviation "DC", which is commonly used to mean "discontinue"; the DRUDP Clinical Review Team concurs with the recommendation, and requests the P&U propose an alternate trademark
- DRUDP was notified that the Swedish facility was not ready for inspection; this raises concerns following telephone communication by Mr. Greg Briar on March 21, 2000, in which DRUDP was informed that all sites were ready; P&U will follow-up on this issue
- information requested on Patient #111 was submitted on May 2, 2000; additional information requested:
  - the date of the patient's last use of Caverject in relation to his hospital admission
  - the date of hospital admission
  - result of a cerebrospinal fluid culture, if done
  - the method of detecting bacteria in the cerebrospinal fluid (e.g., microscopy or gram stain)

Action Items:

- P&U will provide responses to the above issues as soon as they are available
- minutes of this discussion will be provided to P&U within 30 days

Note to Sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcomes.

NDA 21-212 Amendment

~~Medical~~ Team Leader's Memorandum: Response to Approvable Letter

Date submitted: December 10, 2001
Date received: December 12, 2001
Date of memo: June 10, 2002

Sponsor: Pharmacia & Upjohn
Drug product: Alprostadil for Injection
Proposed tradename: Caverject Impulse™
Dosage strengths: 10 mcgs and 20 mcgs
Indication: Treatment of erectile dysfunction

Executive summary: The purpose of this memo is to provide my recommendation to the Division Director regarding regulatory action for this application. The Office of Compliance has made a final recommendation of "acceptable" for the manufacturing sites for this NDA. There are no outstanding clinical issues. Based upon this final Compliance recommendation, I recommend the issuance of an **approval** letter.

Brief background:
Please see my primary medical officer's review of May 10, 2002 for a more detailed background.

NDA 21-212 was originally submitted on January 20, 2000. The application described a novel formulation of CAVERJECT. The alprostadil was linked to alpha-cyclodextrin in order to make the dry drug product smaller in volume and more stable on the shelf. In accomplishing these formulation objectives, the drug product could then be placed into one end of a dual-chamber syringe, making for better patient convenience. On November 20, 2000, DRUDP issued an approvable letter for NDA 21-212. The approvable letter contained three numbered approvable items, all related to CMC deficiencies. In addition, inspections of the manufacturing sites for the NDA were not satisfactory.

The sponsor was told that the three CMC deficiencies required response and the manufacturing sites must undergo satisfactory inspections. In addition, revised draft labeling, revised carton labeling, and a safety update was requested. The sponsor submitted a complete response to these items on December 10, 2001.

Clinical issues:
The clinical safety update contained the final report for a single clinical trial (Protocol 136-URO-0089). No new safety concerns were evident from these results. Use of the novel formulation in dual-chamber syringe was effective and well-tolerated. Updated safety information for CAVERJECT ~~Sterile Powder~~ did not reveal any new safety concerns.

Revised labeling was submitted and was generally acceptable. On May 16, 2002, the sponsor was asked to change a single sentence in the patient package insert regarding the use of CAVERJECT in combination with other products for erectile dysfunction (ED). The sponsor wished to state that combination therapy for ED was "usually" not recommended. Given the lack of safety data for combination use, I object to the word "usually". Sponsor agreed to revise the label accordingly on May 24, 2002. Their final label, as submitted in Attachment 2 of the May 24th submission, is considered acceptable.

The tradename, Caverject Impulse, was considered acceptable by Office of Drug Safety despite some concerns about a possible promotional aspect expressed by the DDMAC representative. DDMAC ultimately decided not to oppose the use of the proposed tradename. I accept it as safe and not misleading.

Chemistry, manufacturing and controls (CMC) issues:
According to Drs. Salemme and Lin, all three individually listed CMC issues have been resolved. DRUDP is able to offer the sponsor a 36-month expiry date.

The carton labeling has been revised in an acceptable fashion to include the recommended statement "Keep out of the reach of children."

Repeat inspections of the two Pharmacia manufacturing facilities (at Stragnas and Stockholm) were completed on February 25 and February 20, 2002, respectively. The inspector recommended a continued withhold for NDA 21-212 based on general GMP deviations at both facilities. Two FDA form 483's were issued. Pharmacia responded to these deficiencies by letter to the Office of Compliance on April 25, 2002. On June 10, 2002, we received the final "acceptable" recommendation from the Office of Compliance.

Other issues
I am aware of no other outstanding issues for this application at this time. The NDA should be approved.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mark S. Hirsch
6/10/02 04:02:47 PM
MEDICAL OFFICER

Daniel A. Shames
6/11/02 12:38:18 PM
MEDICAL OFFICER

MEMORANDUM Colangelo

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: November 17, 2000

TO: Kim Colangelo., Regulatory Project Manager, HFD-580
Mark Hirsch, M.D. Medical Officer, HFD-580
Division of Reproductive and Urologic Drug Products, HFD-580

THROUGH: John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations

FROM: Roy Blay, Ph.D.,
Senior Regulatory Review Officer
Good Clinical Practices Branch 1, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-212

APPLICANT: Pharmacia & Upjohn

DRUG: Caverject Dual Chamber™ (alprostadil for injection)

THERAPEUTIC CLASSIFICATION: 3(S)

INDICATION: Treatment of erectile dysfunction

REVIEW DIVISION GOAL DATE: November 7, 2000
ACTION GOAL DATE (PDUFA Date): November 21, 2000

I. BACKGROUND:

The goal of inspection included validation of submitted data and compliance of study activities with Federal regulations and good clinical practices. Among the study elements reviewed for compliance were subject record accuracy, appropriate informed consent, appropriate use of inclusion/exclusion criteria, adherence to protocol, randomization procedures, and documentation of serious adverse events. The indication for this drug is the treatment of erectile dysfunction.

II. RESULTS (by site):

NAME	CITY, STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION/ FILE NUMBER
Myron Murdock, M.D.	Greenbelt, MD	12 Sept 00	25 Oct 00	VAI/010223
David Talley, M.D.	San Antonio, TX	12 Sept 00	16 Oct 00	VAI-R/010214

Site #1
Myron Murdock, M.D.
Urology Associates
7500 Hanover Parkway, Suite 206
Greenbelt, MD 20770
Acceptable

a. The field investigator inspected the study-related records for all 21 of the subjects enrolled at Dr. Murdock's site.

b. There were no limitations on the inspection.

c. A 483 was issued for failure to document through laboratory testing whether subjects met exclusion criteria, failure to document in writing that subjects had used Caverject powder in the four weeks previous to this study, and failure to include a sub-investigator on the Form 1572. After reviewing the protocol and Dr. Murdock's responses, it was determined that laboratory documentation of whether or not subjects met exclusion criteria (i.e., uncontrolled diabetes $\geq$ 10 mmol/L) was required by protocol, and this deficiency is included in the letter to the investigator. Oral responses by the subjects to questions regarding a history of hepatitis B and C and HIV were documented by the investigator and considered adequate. This deficiency from the 483 was omitted from the letter to the investigator. The protocol did not require written documentation of the use of Caverject powder. The other deficiency noted in the letter to the investigator was failure to include the name of an associate who assisted in the conduct of the investigation.

Site #2
David Talley, M.D.
7909 Fredericksburg Road
Urology San Antonio Research
San Antonio, Texas 78207
May Be Acceptable

a. The field inspector inspected the study-related records for all 15 of the subjects entered into the study at Dr. Talley's site.

b. There were no limitations on the inspection.

c. A Form 483 was issued for enrolling a subject within four weeks of being treated with another investigational drug.

Examination of the exhibits shows that the baseline evaluations (International Index of Erectile Function [IIEF]) completed by subject #s 1201, 1202, and 1204, were modified for these three subjects. Fourteen responses that directly impact the primary efficacy endpoint were revised, apparently by the study coordinator. The initial responses for each of these questions indicated a minimal or moderate degree of sexual function. After modification, these responses in almost all cases indicated a much higher level of

DISTRIBUTION:

NDA 21-212
HFD-45/Division File
HFD-46/Program Management Staff (electronic copy)
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HFD-46/Huff
HFD-46/CIB File #s 010223 and 010214
HFD-46/Reading File

MEMORANDUM

DATE: September 21, 2000

FROM: Roy Blay, Ph.D., Good Clinical Practices Branch I, DSI
HFD-46, MPN1, Room 107,
Phone: 827-7378
Fax: 827-5290

TO: Kim Colangelo, PM, HFD-580

SUBJECT: Clinical Inspections for Pending NDA# 21-212

Clinical inspection assignment have been issued to verify data that were reported by clinical investigators from important study sites and were submitted by the sponsor in support of drug claims for this NDA.

Inspection assignments were issued for the following pending NDA:

Drug: Caverject Dual Chamber

Sponsor: Pharmacia & Upjohn

NDA #: 21-212

The following investigators' clinical studies will be inspected:

Protocol #	Name of Investigator	Domestic	Foreign
98-DUAL-00	Myron Murdock, MD	Greenbelt, MD	
98-DUAL-001)	David Talley, MD	San Antonio, TX	

Please notify me ASAP if you disagree with this selection.

When the inspection reports (EIRs) come in from the field, you will be notified only if there is a problem. Otherwise, you will not be notified again unless the PM requests a final summary.

MEMORANDUM

Date: July 21 ~~March 16~~, 2000

To: Roy Blay, PhD, GCPB Reviewer/HFD-46

Through: David LePay, Director, DSI/HFD-45
Lana Pauls, MPH, Associate Director, Review Division/HFD-580

From: Kim Colangelo, Review Division PM/HFD-580

Subject: Request for Clinical Inspections
NDA 21-212
Pharmacia & Upjohn
Caverject DC (alprostadil sterile powder) Dual Chamber Syringe

Section A: Protocol/Site Identification

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Indication	Protocol #	Site (Name and Address)
Erectile dysfunction	98-DUAL-001	Myron Murdock, MD 7500 Hanover Parkway Suite 206 Greenbelt, MD 20770
Erectile dysfunction	98-DUAL-001	David Ray Talley, MD Urology San Antonio Research 4410 Medical Drive Suite 330 San Antonio, TX 78229

International inspection requests (Section B) or requests for five or more inspections (Section C) require sign-off by the ORM Division Director and forwarding through the Director, DSI.

Section B (optional): International Inspections

We have requested inspections because (please check appropriate statements):

____ There are insufficient domestic data; or

____ Only foreign data are submitted to support an application; or

____ Domestic and foreign data show conflicting results pertinent to decision-making; or

____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations.

____ Other_____

Section C (optional): Five or More Inspections

We have requested these sites for inspection (international and/or domestic) because of the following reasons (justify and prioritize sites).

Section D: Goal Date for Completion

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) November 7, 2000. We intend to issue an action letter on this application by (action goal date) November 21, 2000.

Should you require any additional information, please contact Kim Colangelo, 301-827-4260

Concurrence: (if necessary)
Mark Hirsch, Acting Urology Team Leader, 07.21.00
Lana Pauls, Associate Director, 07.21.00

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HFD-580/Division File
HFD-580/KColangelo
HFD-46/RBlay
HFD-45/Program Management Staff

/s/

Terri F. Rumble
11/6/00 04:50:26 PM