CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-212

CORRESPONDENCE

JAN 27 2000

NDA 21-212

Pharmacia & Upjohn
Attention: Terry Reinstein
Regulatory Manager
7000 Portage Road
Kalamazoo, MI 49001

Dear Mr. Reinstein:

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

Name of Drug Product: Caverject DC (alprostadil for injection)

Therapeutic Classification: Standard (S)

Date of Application: January 20, 2000

Date of Receipt: January 21, 2000

Our Reference Number: NDA 21-212

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 21, 2000, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be November 21, 2000, and the secondary user fee goal date will be January 21, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is

not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

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

If you have any questions, call Kim Colangelo, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Terri Rumble, B.S.N.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 21-212
HFD-580/Div. Files
HFD-580/K.Colangelo/T.Rumble

DISTRICT OFFICE

Drafted by: kmc/January 24, 2000
Initialed by:
final:
filename:

ACKNOWLEDGEMENT (AC)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-212

INFORMATION REQUEST LETTER

Pharmacia & Upjohn
Attention: Terry Reinstein
Regulatory Manager
7000 Portage Road
Kalamazoo, MI 49001

Dear Mr. Reinstein:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Caverject (alprostadil for injection) Dual-Chamber Syringe.

We also refer to your submission dated August 31, 2000.

We are reviewing the proposed labeling sections of your submissions and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

1. Comments on the physician and patient package insert are attached. Recommended deletions are listed as ~~strikethrough~~ text, and added text is double-underlined.

2. Mock-up labels for the container and cartons should be submitted.

3. The statement "Keep out of reach of children" should be added to the carton label.

4. References to the originally proposed trademark Caverject "DC" have been removed. These sections can be replaced once a trademark for this product has been determined.

If you have any questions, call Kim Colangelo, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ATTACHMENT

9 pages redacted from this section of the approval package consisted of draft labeling

21 pages redacted from this section of the approval package consisted of draft labeling

22 pages redacted from this section of the approval package consisted of draft labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: October 4, 2000

FROM: Karen Lechter, HFD-42

TO: Barbara Chong, HFD-42

SUBJECT: Caverject DC PPI
NDA 21-212

Attached are two copies of the proposed PPI for Caverject DC. One tracks the changes we propose from the sponsor's original. The other is a clean copy.

We propose the following changes:

- Insert an introductory paragraph
- Simplify wording
- Use headings we propose for most new PPI's
- Group similar information

I had a number of questions. I embedded the questions in the text in brackets and italics. They deal with issues such as whether certain information should be included and how to clarify some information.

In addition to these questions, the review division should consider whether to add a warning about the possibility of needle breakage, how to avoid it, and what to do if it occurs. The division should also consider whether to warn against using other impotence medications at the same time.

cc:
HFD-42/Lechter/Ostrove/Tabak/Reading
NDA 21-212

KLechter 10/4/00
NON-RELEASABLE

Label comments from Barbara Chang DDMAC

Caverject DC labeling comments
NDA 21-212

Pharmacokinetics in Special Populations

Pediatric

Is this section necessary? It could be used as an off-label use for Caverject DC.

Clinical Studies

Study 1:

"In the double-blind phase, each dose of Caverject was significantly more effective than placebo by clinical evaluation ("full penile rigidity") and by RigiScan criteria (70% rigidity for at least 10 minutes); there was no response to placebo"
Would it be possible to quantify the results by adding the percentage of patients in each group that achieved full penile rigidity by clinical evaluation and RigiScan criteria?

in [redacted] " How is " [redacted] defined? Would it be [redacted] ?" In study 3, the same wording is used [redacted]

Study 2:
"The differences in the response rates in both the clinical and the RigiScan evaluations between each of the doses of Caverject and placebo were statistically significant."

[redacted]

Next paragraph after Study 3:

[redacted] Is that the only difference between the two formulations?

Systemic Adverse Events

"However, these changes were usually clinically unimportant; only three patients discontinued treatment because of symptomatic hypotension." Could we delete the first part of the sentence (However, these changes were usually clinically unimportant) and the word "only"?

23 pages redacted from this section of the approval package consisted of draft labeling

21 pages redacted from this section of the approval package consisted of draft labeling

3.3 FOREIGN MARKETING HISTORY

3.3.1 List of Countries where Marketed and Dates of Approval

3.3.1.1 CAVERJECT Dual Chamber

CAVERJECT DC (alprostadil for injection) is not currently marketed anywhere in the world. The

3.3.1.2 CAVERJECT Sterile Powder

CAVERJECT® Sterile Powder (alprostadil for injection; available in vials of 5, 10, 20, and 40 µg) was approved on 5 July 1995 for the treatment and diagnosis of ED (NDA 20-379). As of 7 December 1999, CAVERJECT® Sterile Powder had been approved in 71 countries worldwide (Table 3.3-1).

Table 3.3-1. Worldwide Registrations of CAVERJECT Sterile Powder (Alprostadil for Injection)

Country	Date Approved	Country	Date Approved
Argentina	June 1996	Luxembourg	September 1994
Austria	September 1995	Malaysia	April 1997
Bahrain	January 1995	Malta	January 1995
Belarus	April 1995	Mauritius	December 1997
Belgium	June 1995	Mexico	July 1995
Brazil	December 1996	Morocco	July 1995
Bulgaria	June 1996	Myanmar	July 1996
Burma	July 1996	Netherlands	June 1995
Canada	March 1996	Netherlands Antilles	March 1997
Chile	January 1996	New Zealand	February 1994
China	November 1995	Nicaragua	April 1995
Colombia	June 1995	Norway	March 1996
Costa Rica	November 1995	Pakistan	November 1994
Cyprus	March 1996	Panama	October 1995
Czech Republic	January 1995	Peru	February 1995
Denmark	January 1995	Philippines	September 1995
Dominican Republic	July 1997	Poland	March 1998
Ecuador	August 1995	Portugal	June 1994

continued

Table 3.3-1. Worldwide Registrations of CAVERJECT Sterile Powder (Alprostadil for Injection)

Country	Date Approved	Country	Date Approved
Finland	February 1994	Russian Federation	February 1995
France	September 1994	Singapore	March 1995
Germany	July 1997	Slovakia (Slovak Republic)	March 1995
Ghana	November 1995	Slovenia	November 1996
Greece	January 1996	South Africa	March 1996
Guatemala	December 1994	Spain	November 1994
Honduras	March 1995	Sweden	January 1994
Hong Kong	February 1995	Switzerland	October 1994
Hungary	June 1995	Taiwan	June 1995
Iceland	August 1995	Thailand	November 1995
Indonesia	October 1995	Trinidad And Tobago	October 1996
Ireland	March 1995	Uganda	September 1995
Israel	July 1995	Ukraine	September 1995
Italy	April 1995	United Arab Emirates	December 1995
Jamaica	May 1997	United Kingdom	March 1994
Korea, Republic Of	April 1995	United States	July 1995
Kuwait	July 1995	Venezuela	January 1996
Lithuania	October 1997		

3.3.1.3 CAVERJECT Injection

CAVERJECT® Injection [(alprostadil injection) aqueous; available in amounts of 10, 20, and 40 µg) was approved on 31 October 1997 for the treatment and diagnosis of ED (NDA 20-755). As of 7 December 1999, CAVERJECT Injection had been approved in 11 countries worldwide (Table 3.3-2).

Table 3.3-2. Worldwide Registrations of CAVERJECT Injection (Alprostadil Injection) Aqueous

Country	Approved
Australia	April 1995
Brazil	December 1996
Colombia	September 1997
Germany	February 1999
Guatemala	December 1996
Lithuania	October 1997
Nicaragua	March 1997
Singapore	October 1998
Sweden	November 1997
United States	October 1997
Venezuela	December 1995

3.3.1.4 PROSTIN VR Pediatric Sterile Solution

PROSTIN VR Pediatric® Sterile Solution (alprostadil injection, USP; available at a concentration of 500 µg/mL) was approved on 16 October 1981 for use as palliative therapy to temporarily maintain the patency of the ductus arteriosus in neonates with congenital heart defects (NDA 18-484). Alprostadil sterile solution is registered for this indication in 54 countries (Table 3.3-3) and is marketed outside the United States under the following trade names: PROSTIN™ VR, MINPROG™ PAED, PROSTIVAS™, PROLESINA™ VR, and PROSTINE™ VR.

Table 3.3-3. Worldwide Registrations of PROSTIN VR Pediatric Sterile Solution (Alprostadil Injection, USP)

Country	Approved	Country	Approved
Argentina	June 1993	Kuwait	June 1990
Australia	December 1982	Kyrgyzstan	April 1993
Austria	June 1987	Lebanon	June 1994
Belarus	March 1993	Luxembourg	June 1983
Belgium	November 1983	Malaysia	July 1997
Brazil	October 1988	Netherlands	January 1985
Bulgaria	April 1994	New Zealand	March 1982
Canada	February 1982	Norway	May 1987
Central African Republic	June 1994	Philippines	August 1992
Chile	September 1986	Poland	November 1989
Colombia	September 1986	Portugal	March 1985
Cyprus	January 1994	Qatar	March 1988
Czech Republic	June 1983	Russian Federation	March 1992
Denmark	February 1984	Saudi Arabia	January 1993
Finland	December 1985	Singapore	July 1989
France	April 1982	Slovakia (Slovak Republic)	June 1983
Germany	May 1983	Slovenia	September 1995
Ghana	June 1993	South Africa	February 1983
Greece	January 1983	Spain	May 1983
Hong Kong	June 1984	Sweden	June 1986
Hungary	January 1991	Switzerland	January 1983
India	February 1999	Taiwan	February 1989
Indonesia	March 1993	Thailand	February 1992
Israel	January 1984	Tunisia	June 1992
Italy	July 1987	United Arab Emirates	October 1993
Jamaica	July 1987	United Kingdom	July 1981
Korea, Republic Of	May 1994	United States	October 1981

3.3.2 List of Countries where Approvals Are Pending and Dates of Applications

3.3.3 Information from Regulatory Bodies Refusing Drug Approval on Grounds of Safety

To date, no regulatory agency has withdrawn or rejected CAVERJECT for safety reasons.

Kim

SEP 1 9 2000

NDA 21-212

DISCIPLINE REVIEW LETTER

Pharmacia & Upjohn
Attention: Terry Reinstein
Regulatory Manager
7000 Portage Road
Kalamazoo, MI 49001

Dear Mr. Reinstein:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Caverject (alprostadil for injection) Dual-Chamber Syringe.

We also refer to your submission dated May 31, 2000.

Our review of the Chemistry section of your submission is complete, and we have identified the following deficiencies:

1. Deficiencies have been noted for ——— ; and will be separately addressed with the DMF holder.

2. Information is needed on the packaging and storage conditions used during shipment of the drug substance.

3. Certificates of Analysis (COAs) for the batches of drug substance used in manufacturing the drug product are needed.

4. Primary stability data for six batches to 6-months at 40°C/75% RH show that during a six month period, the percent water increases from an initial value of — to — . This accelerated data can be used to estimate that at 25°C by about 18 months, the amount of water present will be approximately — Therefore, the specification for the amount of water to be — at time of release is not sufficient to allow for any water increase that will occur during the expiration period. The specification for water needs to be revised to include a release specification of not more than (NMT) —% and a through shelf-life specification of NMT —

5. A detailed procedure for the measurement of volume of injection needs to be provided.

6. A sampling procedure for the analysis of the drug product needs to be provided.

7. The sterility of the wiping tissues to be used with the drug product needs to be established.

8. The proposed expiration date of ——— is not acceptable. A ——— expiration date can be granted based on the 6-months real-time and 6-months accelerated data submitted for the primary stability batches.

9. The Stability Commitment needs to be revised to state that the expiration date will be extended based on full real-time stability data from the first three commercial lots.

10. Table C provided in your Stability Commitment indicates that the 6- and 18-month test intervals will not be carried out if the shelf-life exceeds two years. All time intervals should be carried out for any batches in stability. The Stability Commitment needs to be revised accordingly.

11. A new proprietary name for this product should be submitted.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Kim Colangelo, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader for the
Division of Reproductive and
Urologic Drug Products, (HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 21-212
HFD-580/Div. Files
HFD-580/K.Colangelo
HFD-580/M.Rhee/J.Salemme
HFD-820/J.Gibbs
DISTRICT OFFICE

Drafted by: kmc/September 13, 2000
Initialed by: Rumble, 09.13.00; Salemme, 09.14.00; Rhee, 09.15.00; Allen, 09.18.00
final: Colangelo, 09.18.00
filename: c:\data\nda\21-212\drcmc.doc

DISCIPLINE REVIEW LETTER (DR)

151

NDA 21-212

DISCIPLINE REVIEW LETTER

AUG 2 5 2000

Pharmacia & Upjohn
Attention: Terry Reinstein
Regulatory Manager
7000 Portage Road
Kalamazoo, MI 49001

Dear Mr. Reinstein:

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

We also refer to your submission dated June 15, 2000.

Our review of the Microbiology section of your submission is complete, and we have identified the following deficiencies:

1. It appears that following filling of front cartridge chamber the cartridges must pass through the [redacted] area prior to being loaded into the freeze-dryer. Following the freeze-dry cycle the open cartridges must again pass through a [redacted] prior to capping of the front chamber and filling of the rear chamber. It is not clear what steps are taken to protect the filled, but uncapped, cartridges from microbiological contamination during transit to and from the freeze-dryer. The methods used to protect the open cartridges should be provided. These methods should include protocols and results from any validation experiments for equipment used to accomplish this.

2. Only one equipment load pattern is described for sterilization in [redacted] It should be clarified whether this is the only load to be sterilized using this equipment. If not, validation data for each load sterilized using this equipment should be specified and validation data provided for each load processed using this equipment.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to this issue during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Kim Colangelo, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/s/

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader for the
Division of Reproductive and
Urologic Drug Products, (HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 21-212
HFD-580/Div. Files
HFD-580/K.Colangelo/M.Rhee/J.Salemme
HFD-805/P.Cooney/P.Stinavage
HFD-820/J.Gibbs
DISTRICT OFFICE

Drafted by: kmc/August 22, 2000
Initialed by: Stinavage, Cooney, 08.24.00; Rhee, 08.25.00
final: Colangelo, 08.25.00
filename: c:\data\nda\21-212\drmicro.doc

DISCIPLINE REVIEW LETTER (DR)

DUPLICATE

HIRSCH

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA
Telephone: (616) 833-4000

Pharmacia & Upjohn

NDA ORIG AMENDMENT

May 24, 2002

RECEIVED
MAY 28 2002
HFD-580/CDER

Division of Reproductive and Urologic Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Division Document Room
5600 Fishers Lane
Rockville, MD 20857

N-15L

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

Amendment
Revised Insert Labeling

Dear Sir or Madam:

Please refer to Pharmacia & Upjohn (P&U) correspondence dated December 10, 2001 for the NDA referenced above and the telephone contact of May 16, 2002 between FDA (Eufrecina Deguia) and P&U (Terry Reinstein). The purpose of this amendment is to provide a revised package insert with modified patient instructions, in accordance with Dr. Hirsch's request (as per the telephone contact) that the word "usually" be removed from line 649 in the underline/strikeout version of the Patient Instructions.

We agree with Dr. Hirsch's request; therefore, please refer to the attachments provided with this correspondence for revised insert labeling. The proposed insert is provided in two formats. **Attachment 1** is presented in underline/strikeout showing the changes versus FDA's text per the approvable letter dated November 20, 2000 (including P&U's comments/rationale for the proposed text), plus the change on line 649 in the patient instructions. **Attachment 2** provides for a clean copy of the aforementioned underline/strikeout version; line 580 in this attachment corresponds to the change on line 649 of Attachment 1. Also, please note "Caverject * *" is used throughout the proposed insert wherever the final tradename for the product will appear, once approved.

If you have any questions regarding the information provided, please contact me at (616) 833-8542, or by fax at (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY

for Terry Reinstein

Terry L. Reinstein, R. Ph.
Regulatory Manager

Desk Copy: Eufrecina Deguia , CSO/Division of Reproductive and Urologic Drug Products (HFD-580)

DUPLICATE

Pharmacia & Upjohn

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA
Telephone: (616) 833-4000

May 6, 2002

RECEIVED
MAY 0 8 2002
HFD-580/CDER

BC
NDA ORIG AMENDMENT

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

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

Amendment No. 016
Response to FDA Request for CMC Information – Updated Stability Data

Dear Sir or Madam:

We are amending our NDA 21-212 for Caverject Dual Chamber Syringe in response to a request from FDA Consumer Safety Officer, Ms. Eufrecina Deguia, on March 18, 2002. Ms. Deguia asked that Pharmacia submit 36-month stability data for the product as soon as the data were available. In order to provide complete data for both the 10 mcg and 20 mcg strengths of the product for review by FDA prior to the action date for this application of June 12, 2002, Pharmacia agreed to respond by the middle of May.

The attached stability report contains data through 36 months in support of our request for 36-month expiration dating for both strengths of the product.

Please contact Terry Reinstein at (616) 833-8542, if there are questions. Send all correspondence addressed to Unit 0633-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Terry L. Reinstein, R.Ph.
Regulatory Manager
Regulatory Affairs

TLR:SEH

Attachments

ORIGINAL

Pharmacia & Upjohn

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA
Telephone: (616) 833-4000

December 10, 2001

Division of Reproductive and Urologic Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Division Document Room
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT

RE: NDA 21-212
CAVERJECT Dual-Chamber Syringe
(Alprostadil for injection)

Amendment
Complete Response to Approvable Letter

Dear Sir or Madam:

Please refer to the FDA correspondence dated November 20, 2000, in which you provided an approvable response for NDA 21-212. In addition, your correspondence identified deficiencies that remain pending, which must be addressed by Pharmacia & Upjohn (P&U) before this NDA may be approved. Therefore, the purpose of this correspondence is to amend NDA 21-212 in order to provide a complete response to the deficiencies noted in the approvable letter.

P&U's responses to the items listed in your November 20, 2000 letter are provided below. For ease of review, pending deficiencies identified in the approvable letter are shown in bold text, followed by our response.

Item no. 1:
Until actual data are provided to demonstrate that the water content will not significantly affect the drug product during the shelf-life, specifications for water content need to be implemented as follows: NMT [redacted] at release and NMT [redacted] % during shelf-life.

P&U Response:
A response to this deficiency was previously submitted to NDA 21-212 on November 17, 2000 as amendment no. 14 (see ***Attachment 1***). For your convenience, the following is a reiteration of that response:

We agree to accept the time of release and shelf-life limits cited by the reviewer, NMT [redacted] and NMT [redacted] %, respectively. Since multiple replicates are routinely run for this test, the limits will be applied to the average result.

Item no. 2:
Provide a brief overall description of the sampling plan(s) for production batches and selection of the sub-samples for analysis. Evaluation should consider the adequacy of the sampling process (e.g. beginning, middle, end) and the number of samples per production batch.

P&U Response:
A response to this deficiency was previously submitted to NDA 21-212 on November 17, 2000 as amendment no. 14 (see ***Attachment 1***).

Item no. 3:
Based on 12 months of stability data at 25 C and 6 months at 40 C, an —— expiration period can be granted.

P&U Response:
P&U previously acknowledged this notification in our response submitted to NDA 21-212 on November 17, 2000 as amendment no. 14. However since that time, additional stability data are now available to support a 36-month expiration period for each strength of CAVERJECT Dual Chamber Syringe (see ***Attachment 2***), also known as CAVERJECT IMPULSE (see page 3 of this correspondence for additional information concerning this tradename).

Item no. 4:
In addition, it will be necessary for you to submit revised draft labeling for the drug. The labeling should be identical in content to the attached labeling (text for the package insert and text for the patient package insert). Carton labels must be revised to include the statement "Keep out of reach of children."

P&U Response:
Please refer to ***Attachment 3*** of this correspondence for revised insert labeling. The proposed insert is provided in two formats; one is in underline/strikeout showing the changes versus FDA's text per the approvable letter dated November 20, 2000, which also includes P&U's comments/rationale for the proposed changes. The second format provides for a "clean" copy of the aforementioned underline/strikeout version. Also, please note "Caverject **" is used throughout the proposed insert wherever the final tradename for the drug product will appear, once approved.

Please refer to ***Attachment 4*** of this correspondence for the manuscript version of the revised carton labeling, which includes the statement "Keep out of reach of children."

Item no. 5:
During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the inspector. Satisfactory inspections will be required before this application may be approved.

P&U Response:
The deficiencies noted during the June/July 2000 FDA inspections of our manufacturing facility have been addressed. We are prepared for a reinspection.

Item no. 6:
Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. **Details of any significant changes or findings.**

2. **Summary of worldwide experience on the safety of this drug.**

3. **English translations of any approved foreign labeling not previously submitted.**

4. **Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.**

P&U Response:
Please refer to ***Attachment 5*** of this correspondence, which contains the NDA Safety Update as requested in points no. 1, 2, and 4 above.

Regarding point no. 3, please refer to ***Attachment 6*** for the English translations for all approved foreign labeling of this drug product (Europe and Brazil).

Tradename:
Please refer to our correspondence dated November 21, 2001 submitted to IND 38,269 (serial no. 122), in which we appeal for the use of CAVERJECT IMPULSE™ as the proprietary name for the product. We would appreciate FDA's consideration of this appeal at the earliest possible opportunity.

If you have any questions regarding the contents of this submission, please contact me at (616) 833-8542 or Dan Chirby at (616) 833-9411, or by fax at (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY

for Terry Reinstein

Terry L. Reinstein, R. Ph.
Regulatory Manager

Desk Copy: Dornette Spell-LeSane, CSO/Division of Reproductive and Urologic Drug Products (HFD-580)

Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

October 5, 2000

DUPLICATE

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

CMC AMENDMENT
BC

Re: NDA 21-212
CAVERJECT® DC
alprostadil for injection

Amendment No. 013
Response to FDA Request for
CMC Information - Chemistry

Dear Sir or Madam:

We are amending our NDA 21-212 for Caverject DC to provide responses to items 6 and 7 in FDA's discipline review letter of September 19, 2000. Our initial response to deficiencies noted in the September 19 letter was submitted in our Amendment No. 012 dated October 2, 2000.

For ease of review, each original question is shown in italics, followed by our response. Tables, figures and attachments are numbered to be consistent with the question with which they are associated.

Question 6
A sampling procedure for the analysis of the drug product needs to be provided.

Response
The sampling procedure for the drug product is included as Attachment 6.

Question 7
The sterility of the wiping tissues to be used with the drug product needs to be established.

Response
The wiping tissues are not claimed to be sterile. The tissues are described in Part 2.F.5.c of Item 4A of the NDA.

As discussed with Ms. Kim Colangelo, FDA Project Manager, we are awaiting clarification from the FDA of the deficiencies noted in item 1 of your September 19 letter. Note that Pharmacia & Upjohn (P&U) provided responses to questions concerning the drug substanc in our Amendment No. 002 dated May 31, 2000. Additionally, as conveyed to Ms. Colangelo, we are actively engaged in a selection process for a new proprietary name (item 11) and will submit this information to the agency as soon as it becomes available.

Please contact Terry Reinstein at (616) 833-8542, if there are questions. Send all correspondence addressed to Unit 0633-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Terry L. Reinstein, R.Ph.
Regulatory Manager
Regulatory Affairs

TLR:kmv

Attachments

Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

October 2, 2000

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

DUPLICATE

Re: NDA 21-212
CAVERJECT® DC
alprostadil for injection

ORIG AMENDMENT

BC

Amendment No. 012
Response to FDA Request for CMC Information - Chemistry

Dear Sir or Madam:

We are amending our NDA 21-212 for Caverject DC to provide a partial response to FDA's discipline review letter of September 19, 2000. Reference is also made to our submission of May 31, 2000 (our amendment No. 002). Pharmacia & Upjohn will provide responses to the remaining items (as noted below) as soon as they are available.

With regard to the item 4 deficiency concerning water specifications, we would like to request a teleconference with the reviewer if the proposed specifications are deemed unacceptable.

For ease of review, each original question is shown in italics, followed by the proposed response. Tables, figures and attachments are numbered to be consistent with the question with which they are associated.

Question 1
Deficiencies have been noted for DMF [redacted] *and will be separately addressed with the DMF holder.*

Response
No response required at this time.

Question 2
Information is needed on the packaging and storage conditions used during shipment of the drug substance.

Response
The immediate packaging is an appropriately sized amber USP Type III glass bottle with a [redacted]) lined cap, as described in the NDA (Item 4A Part 1.C.11).

Alprostadil is shipped according to a standard procedure established for exporting chemicals. The portion of the procedure which applies to materials like alprostadil which require refrigerated storage is excerpted below.

1. Material should not be left unrefrigerated longer than two hours.
2. Carbon Dioxide Solid is used to keep the material cold during shipment.
3. All boxes or containers used for shipment of Carbon Dioxide Solid must be packed in insulated boxes designed for that use. Boxes should be marked with appropriate labels, (e.g., "Carbon Dioxide Solid") and must be in compliance with the appropriate hazardous article specifications sheet.
4. Protect the material from direct contact to the Carbon Dioxide Solid. Make sure there is an appropriate amount of Carbon Dioxide Solid for the shipment destination.
5. If an order is not shipped the day it is packed, it must be placed in a cold room or freezer until it is released for shipment and the Carbon Dioxide Solid must be repacked the day the order is shipped.

Question 3
Certificates of Analysis (COAs) for the batches of drug substance used in manufacturing the drug product are needed.

Response
Certificates of Analysis for lots 57610-51 (produced as Kalamazoo lot 11ATP) and 57428-51 (produced as Kalamazoo lot 51ACJ) were included as the first 4 pages of Appendix 3.3 to Part 4A of NDA 21-212. Copies are included as Attachment 3

Question 4
Primary stability data for six batches to 6-months at 40°C/75% RH show that during a six month period the percent water increases from an initial value of — to —. This accelerated data can be used to estimate that at 25°C by about 18 months, the amount of water present will be approximately —. Therefore, the specification for the amount of water to be —, at time of release is not sufficient to allow for any water increase that will occur during the expiration period. The specification for water needs to be revised to include a release specification of not more than (NMT) — and a through shelf life specification of NMT —

Response
Updated 25°C/60%RH water data for the six registration stability lots are given below. Data are available through 18 months for five of the lots; the sixth lot, manufactured later, has data through 12 months. Data from 40°C/75%RH studies are repeated for comparison.

Table 4.3 Chemical Stability of CAVERJECT DCS (20 µg strength) as a Function of Water Content at 40°C

Time (month)	0.5% Water	1.2% Water	2.0% Water	3.0% Water	4.4% Water
	PGE_1[a]	PGE_1[a]	PGE_1[a]	PGE_1[a]	PGE_1[a]
0.00					
0.50					
1.00					
1.67					
2.07					
3.00					
4.00					
6.00					

[a] - µg/mL

Figure 4.1 **Formation of the Major Degradation Product ( ) for CAVERJECT DCS as a function of Time at 40°C for Freeze-Dried Samples at Various Moisture Contents**

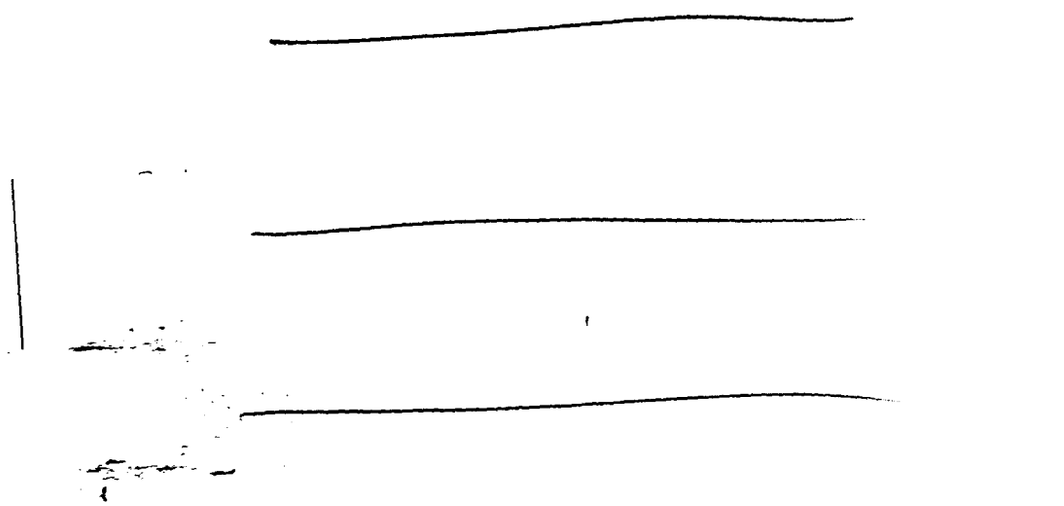
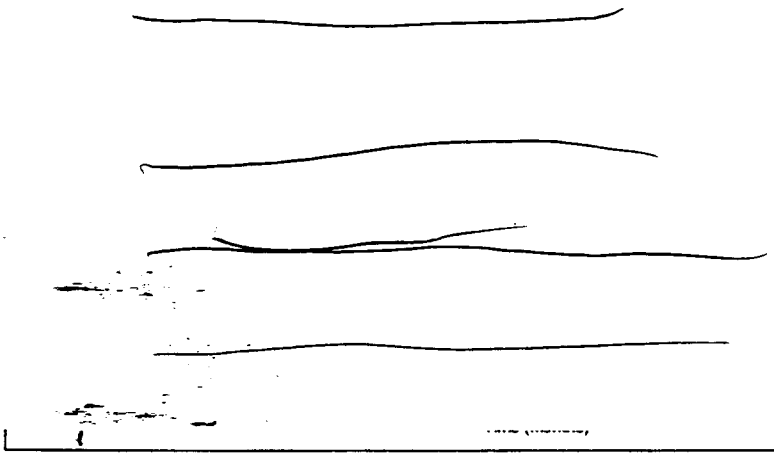


Table 4.4 Chemical Stability of CAVERJECT DCS (20 μg strength) as a Function of Water Content at 25°C

Time (month)	0.5% Water PGE_1[a]	1.2% Water PGE_1[a]	2.0% Water PGE_1[a]	3.0% Water PGE_1[a]	4.4% Water PGE_1[a]
0.00					
1.00					
2.07					
4.00					
6.00					
9.37					
12.1					

[a] - μg/mL

Figure 4.2 Formation of the Major Degradation Product for CAVERJECT DCS as a function of Time at 25°C for Freeze-Dried Samples at Various Moisture Contents



The data from samples made with the highest water content are particularly interesting. Although it is clear that the rate of degradation (measured by the increase in the amount of) is much greater for samples with an initial water content of 4.4% than for those with 0.5% water, it is still less than 0.7% of the labeled amount of alprostadil in 12 months (average content at 12.1 months minus average at initial). This is equivalent to an increase of content of less than 1.5% of the labeled amount of alprostadil over the proposed 24 month expiration interval for a lot with an initial water content as high as 4.0%.

Table 4.1 Updated Water Data from Registration Stability Lots							
Strength		10 µg	10 µg	10 µg	20 µg	20 µg	20 µg
Lot		27589-51	27657-51	28710-51	27313-51	27423-51	27771-51
Condition	Months	Water (%)	Water (%)	Water (%)	Water (%)	Water (%)	Water (%)
initial	00						
		ave: 0.9	ave: 1.0	ave: 1.0	ave: 1.1	ave: 1.0	ave: 1.2
25°C/60%RH	06						
	12						
	18						
40°C/75%RH	04						
	06						

The increases in water content are summarized below.

Table 4.2 Increase in Water Content* of Caverject DC Samples Upon Storage at 25°C/60%RH		
Interval	Average	High
6 months	0.3%	
12 months	0.5%	
18 months	0.8%	

* average for each lot at the interval minus average at initial testing

The trend in water content is upward, but the rate of increase is quite modest at 25°C/60%RH. The available data suggest that the increase in water content during room temperature storage for the proposed expiration interval can be estimated at about 1%.

We are also able to provide additional data from the scientific stability which investigated the impact of varying initial water content (to % on chemical stability). This information was presented in Part 2.A.2.e (Effect of Residual Water) of the NDA. It is repeated below in tabular and graphical format with additional data through 12 months at 25°C and with minor corrections in the time intervals (1.5 → 1.67 and 2.0 → 2.07 months at 40°C; 2.0 → 2.07 months at 25°C).

We ask that the reviewer reconsider our proposal for a 4.0% upper limit on water at the time of release with no limit throughout the shelf life. We believe that the quality of the product throughout the shelf life is adequately controlled by the shelf life limits of the other quality characteristics. The data above from the scientific stability study show that long term exposure to water content above 4% water does not compromise the chemical stability of the product. The test results from the registration stability lots show that the water increase expected for samples stored at 25°C/60%RH for 24 months is only about 1%.

We would also like to inform the reviewer regarding the capability of the lyophilization process. Tables 4.5 and 4.6 show data gathered during validation of the freeze drying process and the transfer and capping process, respectively. Table 4.7 shows the water results from the batch testing for the process validation lots.

Table 4.5. Freeze Drying Process Results: Water Content
(Data From Qualification Number 40-1273)

[illegible]	[illegible]	[illegible]	[illegible] content [illegible]
32080-51	20 µg	32 L (40000 cylinders)	Shelf 2 corner
			Shelf 2 middle
			Shelf 6 corner
			Shelf 6 middle
			Shelf 10 corner
			Shelf 10 middle
32126-51	20 µg	47 L (60000 cylinders)	Shelf 2 corner
			Shelf 2 middle
			Shelf 6 corner
			Shelf 6 middle
			Shelf 10 corner
			Shelf 10 middle
32212-51	20 µg	47 L (60000 cylinders)	Shelf 2 corner
			Shelf 2 middle
			Shelf 6 corner
			Shelf 6 middle
			Shelf 10 corner
			Shelf 10 middle
32227-51	10 µg	47 L (60000 cylinders)	Shelf 2 corner
			Shelf 2 middle
			Shelf 6 corner
			Shelf 6 middle
			Shelf 10 corner
			Shelf 10 middle
32226-51	10 µg	32 L (40000 cylinders)	Shelf 2 corner
			Shelf 2 middle
			Shelf 6 corner
			Shelf 6 middle
			Shelf 10 corner
			Shelf 10 middle
32299-51	10 µg	32 L (40000 cylinders)	Shelf 2 corner
			Shelf 2 middle
			Shelf 6 corner
			Shelf 6 middle
			Shelf 10 corner

Table 4.5. Freeze Drying Process Results: Water Content
(Data From Qualification Number 40-1273)

			Shelf 10 middle	

* Batch size volume is for front chamber solution

Table 4.6. Transfer and Capping Water Content Results
(Data From Qualification Number 40-1273)

32080-51	20 µg	32 L (40000 cylinders)	Beginning	
			Middle	
			End	
			15 hours**	
32126-51	20 µg	47 L (60000 cylinders)	Beginning	
			Middle	
			End	
			15 hours**	
32212-51	20 µg	47 L (60000 cyl)	Beginning	
			Middle	
			End	
			15 hours**	
32227-51	10 µg	47 L (60000 cylinders)	Beginning	
			Middle	
			End	
			15 hours**	
32226-51	10 µg	32 L (40000 cylinders)	Beginning	
			Middle	
			End	
			15 hours **	
32299-51	10 µg	32 L (40000 cylinders)	Beginning	
			Middle	
			End	
			15 hours**	

* Batch size volume is for front chamber solution
** Samples were left uncapped 15 hours after unloading of freeze dryer, to check moisture uptake during this time

Table 4.7 Release Testing Results for Process Validation Lots of Caverject DC		
Strength	Lot ID	Result
10 µg	Trade # 657-037 Batch # 32227	
	Trade # 656-980 Batch # 32226	
	Trade # 656-980 Batch # 32299	
20 µg	Trade # 656-997 Batch # 32080	
	Trade # 657-044 Batch # 32126	
	Trade # 657-044 Batch # 32212	

Most water results are below 1.5%, but results as high as % were observed. Averages of the individual results reported in Tables 4.5 and 4.6 were as high as 1.6%.

The reformulated product provides improved convenience and safety (i.e., sterility assurance) for the patient because its dual-chamber design eliminates the need to reconstitute with diluent from an external source. The reduced mass of the lyophilized cake which supports use of the dual-chamber syringe makes the product more susceptible to increases in water content (i.e., 1 mg of water is equal to nearly 2% of the mass of the cake). The presence of the α-cyclodextrin dramatically improves chemical stability compared to the currently marketed Caverject Sterile Powder, even upon prolonged exposure to water content above 4%. We ask that the new Caverject formulations not be constrained with water specifications which would limit our ability to obtain longer expiration dating (e.g., 48 months when sufficient data are available) relative to the current formulations despite the improved stability relative to the current formulations.

Question 5
A detailed procedure for the measurement of volume of injection needs to be provided.

Response
The volume of injection is calculated based on the mass of reconstituted solution which is delivered after reconstitution in a manner consistent with actual use. The diluent which is left behind (i.e., between the two plunger stoppers) is not included. The reconstituted solution which remains in the needle is not included. The procedure is described below.

Question 11

A new proprietary name for this product should be submitted.

Response

A separate response will be submitted.

Please contact Terry Reinstein at (616) 833-8542, if there are questions. Send all correspondence addressed to Unit 0633-298-113.

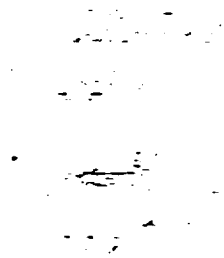
Sincerely,

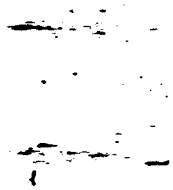
PHARMACIA & UPJOHN COMPANY

Terry L. Reinstein, R.Ph.
Regulatory Manager
Regulatory Affairs

TLR:lmf

Attachments





Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

September 27, 2000

ORIG AMENDMENT

13C

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

DUPLICATE

Re: NDA 21-212
CAVERJECT® DC
alprostadil for injection

Amendment No. 011
Response to FDA Request for Product Samples

Dear Sir or Madam:

We are amending our NDA 21-212 for Caverject DC to provide samples of the Caverject DC syringe system. Enclosed are two samples. One is a complete unit including the syringe device containing the dual-chamber cartridge, with lyophilized powder and diluent, and the accompanying needle. Also enclosed is the syringe device without the dual-chamber cartridge.

Please contact Terry Reinstein at (616) 833-8542, if there are questions. Send all correspondence addressed to Unit 0633-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Terry L. Reinstein, R.Ph.
Regulatory Manager
Regulatory Affairs

TLR:lmf

Attachments

Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

DUPLICATE

September 21, 2000

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

Re: NDA 21-212
CAVERJECT® DC
alprostadil for injection

ORIG AMENDMENT

PI

Amendment No. 010
Response to FDA Request for CMC Information – Microbiology

Dear Sir or Madam:

We are amending our NDA 21-212 for Caverject DC in response to FDA's letter of August 25, 2000. Reference is also made to our submission of June 15, 2000 (our Amendment No. 003). The following information addresses the two deficiencies noted during the agency's review of the Microbiology Section of our NDA submission. For ease of review, each original question is shown in italics, followed by our response.

Question 1

It appears that following filling of front cartridge chamber the cartridges must pass through the ——— area prior to being loaded into the freeze-dryer. Following the freeze-dry cycle the open cartridges must again pass through a ——— area prior to capping of the front chamber and filling of the rear chamber. It is not clear what steps are taken to protect the filled, but uncapped, cartridges from microbiological contamination during transit to and from the freeze-dryer. The methods used to protect the open cartridges should be provided. These methods should include protocols and results from any validation experiments for equipment used to accomplish this.

Response:

The open cartridges are protected from microbiological contamination by use of a sealed transport carrier during the transport through the ——— area before and after freeze-drying. The attached document (00-2249) describes the use of the sealed transport carriers. Protocols and results from validation experiments are included.

Please see the floor diagram which was included in NDA 21-212, Item 4, Attachment II.I.1 of Part II.I for the location of room numbers referenced in the response.

Question 2

Only one equipment load pattern is described for sterilization in Getinge Autoclave, model : [redacted] equipment # [redacted]. It should be clarified whether this is the only load to be sterilized using this equipment. If not, validation data for each load sterilized using this equipment should be specified and validation data provided for each load processed using this equipment.

Response:

This is the only load pattern comprising articles used in the manufacturing process of Caverject DC.

Please contact Terry Reinstein at (616) 833-8542, if there are questions. Send all correspondence addressed to Unit 0633-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Terry L. Reinstein, R.Ph.
Regulatory Manager
Regulatory Affairs

TLR:crdt

Attachments

DUPLICATE

Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

September 18, 2000

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

SU

Re: NDA 21-212
CAVERJECT® DC
alprostadil for injection

Amendment No. 009
4-Month Safety Update Report

Dear Sir/Madam:

We are amending our NDA 21-212 to provide a 4-month Safety Update Report for Caverject DC. This report includes relevant safety data obtained since the filing of NDA 21-212 on January 20, 2000. Since that time, data has become available from two completed non-IND studies; one (139-URO-0089-0003) that was requested by the German health authorities, and a second "convenience" study (139-URO-0089-004) used to assess patient satisfaction with the Caverject DC system. As part of this report, we have reviewed Pharmacia & Upjohn's database of spontaneously reported medical events for CAVERJECT® Sterile Powder and CAVERJECT® Injection. Since we were unable to submit this report in May, we extended the cut-off date for the review of the spontaneous database through the period ending July 31, 2000.

Please contact Terry Reinstein at (616) 833-8542, if there are questions. Send all correspondence addressed to Unit 0633-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Terry L. Reinstein, R.Ph.
Regulatory Manager
Regulatory Affairs

TLR:crdt

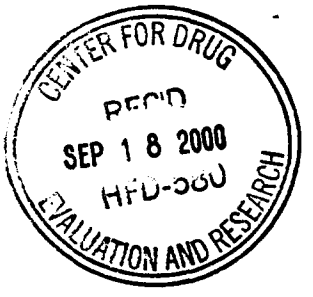
Attachments

DUPLICATE

Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

September 15, 2000



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

BC
ORIG AMENDMENT

Re: NDA 21-212
CAVERJECT® DC
alprostadil for injection

Amendment No. 008
Response to FDA Request for CMC Information – Updated Stability Data

Dear Sir/Madam:

We are amending our NDA 21-212 for Caverject DC in response to a request on September 8, 2000 from Ms. Kim Colangelo, Project Manager, HFD-580. Ms. Colangelo requested that Pharmacia & Upjohn provide as much real-time stability data as possible in support of our pending application. Enclosed are data through 12 months for all three lots of the 20 µg strength and for two lots of the 10 µg strength. One of the 10 µg lots has data only through 9 months. This report does not contain results for subvisible particulate matter. Data for the subvisible particulate matter test will be included in future updates.

Please contact Terry Reinstein at (616) 833-8542, if there are questions. Send all correspondence addressed to Unit 0633-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Terry L. Reinstein, R.Ph.
Regulatory Manager
Regulatory Affairs

TLR:mlw
Attachments

DUPLICATE

Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

September 14, 2000

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

Bm
ORIG AMENDMENT

Re: NDA 21-212
CAVERJECT® DC
alprostadil for injection

Amendment No. 007;Addendum to Amendment No. 004
Response to FDA Request for Clinical Information – Adverse Event Narrative

Dear Sir/Madam:

On August 28, 2000, Pharmacia & Upjohn provided all of the case report forms that were completed for patient #124 from the clinical study conducted under protocol 98-DUAL-001. On September 6, we submitted a narrative for two adverse events experienced by this patient: temporary cardiac insufficiency and reddening of the injection site. At the request of FDA, we have contacted the investigator at the site where this patient was enrolled and obtained the following information concerning this patient's experience.

> One hour after the injection, the patient experienced difficulty in breathing and a feeling of having fluid in his lungs. These symptoms resolved. Two to three hours after the occurrence of the first episode, at bedtime, he experienced the same symptoms once again, but only for a short period. The patient slept during the night and the next day had no symptoms at all.

We have learned that this patient has moved and changed his telephone number, so it is unlikely we can obtain any further details.

Please contact Terry Reinstein at (616) 833-8542, if there are questions. Send all correspondence addressed to Unit 0633-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Terry L. Reinstein, R.Ph.
Regulatory Manager
Regulatory Affairs

TLR:mlw

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

ORIGINAL

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

Noted + included as part of my NDA review
MH 9/13/00

September 6, 2000

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

ORIG AMENDMENT

BM

9/15/00

Re: NDA 21-212
CAVERJECT® DC
alprostadil for injection

Addendum to Amendment No. 004
Response to FDA Request for Clinical Information – Adverse Event Narrative

Dear Sir/Madam:

We are submitting additional information to our NDA 21-212 for Caverject DC in response to a request on August 14, 2000 from Ms. Kim Colangelo, Project Manager, HFD-580. On August 28, we provided all of the case report forms that were completed for patient #124 from the clinical study conducted under protocol 98-DUAL-001. To complete Ms. Colangelo's request of August 14, we are now submitting a narrative for two adverse events experienced by this patient: temporary cardiac insufficiency and reddening of the injection site.

The enclosed description is based upon the information provided in the case report forms. We have contacted the investigator at the site in Germany where this patient was enrolled in an attempt to obtain further details; specifically, the amount of time between the injection of Caverject DC and the onset of the cardiac insufficiency, the initial symptoms reported or exhibited by the patient, and the course of the patient's condition during the hour from the onset of this event until recovery. We will provide additional information if, and when, it is received from the investigator.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.L. ☐ MEMO

KMC 9/15/00
CSO INITIALS DATE

Please contact Terry Reinstein at (616) 833-8542, if there are questions. Send all correspondence addressed to Unit 0633-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Terry L. Reinstein, R.Ph.
Regulatory Manager
Regulatory Affairs

TLR:SEH
Attachments

DUPLICATE

Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

August 31, 2000

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

ORIG AMENDMENT

BL

RE: NDA 21-212
CAVERJECT ® DC
alprostadil for injection

Amendment No. 005
Revision of Proposed Package Insert

Dear Sir/Madam:

We are amending our NDA 21-212 for Caverject DC in response to a request on August 11, 2000 from Ms. Kim Colangelo, Project Manager, HFD-580. Ms. Colangelo noted that we had not included information in our proposed package insert regarding the clinical study conducted under protocol 98-DUAL-001 in support of this application.

Enclosed are both a "clean" copy (version A) and "strikeout" copy (version B) of the revised package insert which includes the addition of the requested change. We are also providing you with two diskettes containing these same copies. Please note that the Clinical Studies Section of the proposed package insert submitted in our original application was provided in an "Appendix A". In the enclosed copies of the revised package insert, the Clinical Studies Section has been inserted after the Clinical Pharmacology Section.

Please contact Terry Reinstein at (616) 833-8542, if there are questions. Send all correspondence addressed to Unit 0633-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Terry L. Reinstein, R.Ph.
Regulatory Manager
Regulatory Affairs

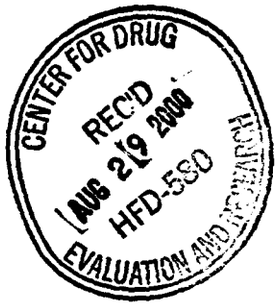
TLR:mlw
Attachment

Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

August 28, 2000

DUPLICATE



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

RE: NDA 21-212
CAVERJECT ® DC
alprostadil for injection

ORIG AMENDMENT
BM

Amendment No. 004
Response to FDA Request for Clinical Information – Case Report Forms

Dear Sir/Madam:

We are amending our NDA 21-212 for Caverject DC in response to a request on August 14, 2000 from Ms. Kim Colangelo, Project Manager, HFD-580. Ms. Colangelo asked that we provide all of the case report forms that were completed for patient #124 from the clinical study conducted under protocol 98-DUAL-001. Included as part of the case report forms is the International Index of Erectile Function (IIEF) questionnaire. Since patient #124 was located in [redacted], the completed IIEF appears in [redacted] For convenience, I am including a blank copy of the IIEF in English.

Please contact Terry Reinstein at (616) 833-8542, if there are questions. Send all correspondence addressed to Unit 0633-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Terry L. Reinstein, R.Ph.
Regulatory Manager
Regulatory Affairs

TLR:lmf

Attachment

ORIGINAL

Pharmacia&Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

August 14, 2000

NEW CORRESP

Roy A. Blay, Ph.D.
Office of Medical Policy, Division of Scientific Investigations,
Good Clinical Practices Branch I , HFD-46
7520 Standish Place
Rockville, MD 20855

N/C

Re: NDA 21-212
CAVERJECT® DC
alprostadil for injection

General Correspondence
Response to Inquiry

Dear Dr. Blay:

I am writing in follow-up to your telephone conversation of August 1, 2000 with Mr. Daniel Chirby, my colleague in Regulatory Affairs at Pharmacia & Upjohn. You had contacted Mr. Chirby to request background information in preparation for the inspection of two clinical sites at which we conducted a Caverject DC study under Protocol 98-DUAL-001. These sites are located in Green Belt, Maryland and San Antonio, Texas. The principal investigators at these sites were Dr. Myron Murdock and Dr. David Ray Talley, respectively.

Enclosed you will find a separate volume for each site that contains the primary information you requested. In addition, we are supplying a second volume for each site that contains the monitoring survey information.

Within the primary information, there are no cover letters for protocol amendments since no amendments were made to the original protocol. Likewise, since this was an open-label, historical-design study, there was no randomization list utilized for either site. Although we have included a list of concomitant medications for the patients at each of the sites, there were no patients at either of these two sites who experienced serious adverse events. Additionally, as noted in the protocol (9.3 and 9.4) laboratory efficacy and safety assessments were not applicable.

Included in your request for monitoring survey information was the following question: *When monitoring was conducted, were original records reviewed?* The answer to that question, as it applies to both sites, is yes.

If you require any additional information, or need clarification of the material being provided with this communication, please don't hesitate to contact me at (616) 833-8542. Send all correspondence addressed to Unit 0633-298-113.

Sincerely,

Terry L. Reinstein, R.Ph.
Regulatory Affairs
Regulatory Manager

TLR/crdt

Enclosures

cc: FDA/Division of Reproductive/Urologic
Document Control Room

REVIEWS COMPLETED

☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS 8/22/00 DATE

Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

June 21, 2000

DUPLICATE

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

RE: NDA 21-212
CAVERJECT ® DC
alprostadil for injection

ORIG AMENDMENT
BM

Addendum to Amendment No. 001
Response to FDA Request

Dear Sir/Madam:

We are submitting additional information regarding clinical trial patient #111 as an addendum to amendment number 001 to our NDA 21-212 for Caverject DC. Amendment number 001 was originally submitted on May 2, 2000. During a telephone conversation on May 11, 2000 between Ms. Kim Colangelo (FDA) and Mr. Terry Reinstein (Pharmacia & Upjohn), Ms. Colangelo requested the following information (in bold type). Our response follows each item.

1. The date of the patient's last use of Caverject in relation to his hospital admission

The date of last known administration of Caverject was during the patient's second clinic visit on June 4, 1999. It is not known whether the patient used Caverject again between that date and July 9, 1999, the day ~~the patient~~ was hospitalized. At last contact with the patient on August 17, 1999, he could not remember whether he used Caverject between June 4 and July 9.

2. The date of hospital admission

The patient was admitted to the hospital on July 9, 1999.

3. Result of cerebrospinal fluid culture, if done

According to the hospital summary, an attempt was made to culture the cerebrospinal fluid. However, no bacteria could be cultured and identified. (See page 3 of the hospital summary already submitted.) The diagnosis of bacterial meningitis was made by the hospital based upon improvement of the patient following antibiotic therapy.

4. The method of detecting bacteria in the cerebrospinal fluid (e.g., microscopy or gram stain)

See item 3 above.

Please contact Terry Reinstein at (616) 833-8542, if there are questions. Send all correspondence addressed to Unit 0633-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Terry L. Reinstein, R.Ph.
Regulatory Manager
Regulatory Affairs

TLR:kmv

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
NDA 21-212

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Pharmacia & Upjohn Company	June 21, 2000
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(616) 833-8542	(616) 833-8237

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State,ZIP Code, telephone & FAX number)* IF APPLICABLE
7000 Portage Road Kalamazoo, Michigan 49001	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Alprostadil for Injection	CAVERJECT DC

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Powder for reconstitution for injection	10 mcg, 20 mcg	Injection

(PROPOSED) INDICATION(S) FOR USE: For the treatment and diagnosis of erectile dysfunction ED) via intracavernosal injection.

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION
Addendum to Amendment No. 001 - Response to FDA Request

PROPOSED MARKETING STATUS (check one) ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 | THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telepone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA 20-379 / NDA 20-755

MFs

EF

Y 1/1/00

Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

June 15, 2000

ORIGINAL

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

RE: **NDA 21-212**
CAVERJECT ® DC
alprostadil for injection

ORIG AMENDMENT

BC

Amendment No. 003
CMC Information – Additional Autoclave

Dear Sir/Madam:

We are amending our NDA 21-212 for Caverject DC to include a summary report of the thermal and microbiological qualification of an additional autoclave used to sterilize various utensils for the aseptic filling of drug products, including Caverject DC. Also included in this amendment is a new version of the location of equipment used in the aseptic processing of Caverject DC. It has been revised to include this additional autoclave. This information was inadvertently omitted from Item 4. of our original filing dated January 20, 2000.

Please contact Terry Reinstein at (616) 833-8542, if there are questions. Send all correspondence addressed to Unit 0633-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Terry L. Reinstein, R.Ph.
Regulatory Manager
Regulatory Affairs

TLR:mlw

Attachment

REVIEWS COMPLETED · Re CMC revised
CSO ACTION:
☐ LETTER ☒ N.A.L ☐ MEMO
CMC 11/15/00
CSO INITIALS DATE

Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

DUPLICATE

May 31, 2000

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

ORIG AMENDMENT
BC

RE: NDA 21-212
CAVERJECT ® DC
alprostadil for injection

Amendment No. 002
Response to FDA Request for CMC Information

Dear Sir/Madam:

We are amending our NDA 21-212 for Caverject DC in response to a request for additional information or clarification of material concerning the drug substance in our original submission. Ms. Kim Colangelo, HFD-580, made this request during a telephone call on April 26, 2000. Our responses appear after each of the agency's comments, which are italicized for ease of review.

1. *The specifications for PGE_2 that were submitted in the application do not match the specifications in our DMF (—— for PGE_2.*

The specifications for PGE_2 which is used in the synthesis of alprostadil for Caverject Sterile Powder were filed in NDA 20-379 (Appendix 4 in Amendment 10, February 20, 1995) (Appendix 4 attached) as a result of our response to an FDA letter dated February 10, 1995. The specifications for PGE_2 filed in NDA 20-379 are also suitable for the production of alprostadil as described in the Caverject DC application. Some of these specifications are different from the specifications for PGE_2 as described in DMF —. Specifications for water, residue on ignition, and optical rotation are more restrictive for the PGE_2 starting material than in DMF —while the limits on related prostaglandins are comparable.

Clarification of the testing is provided in our responses to questions 2, 3, and 4 below. The testing and specifications for PGE_2, which is used as a starting material for synthesis of alprostadil, will be revised to include these clarifications.

2. *Could not find in the application the solvent used to determine optical rotation.*

The Specific Optical Rotation (as is) (by USP method <781 S>) is determined in a solution of

3. *Asked for the meaning of "ROI".*

"ROI" is used as the abbreviation for "Residue on Ignition."

4. *What are the specific degradants of PGE_2 that were tested for, i.e. what isomers are quantified?*

The degradants (determined by r , are and ; the % limit for degradation products applies to the sum of the and . The isomers (determined by , are : ; the limit for isomers applies to the sum of the isomers.

5. *The drug substance is produced in the U.S. and shipped to Sweden. What identification or acceptance test is conducted upon arrival in Sweden?*

Upon arrival in Stockholm, the identity of the drug substance is confirmed by the identification test described on the registration specifications page for the drug substance.

Please contact Terry Reinstein at (616) 833-8542, if there are questions. Send all correspondence addressed to Unit 0633-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Terry L. Reinstein, R.Ph.
Regulatory Manager
Regulatory Affairs

TLR:lmf

Attachments

DUPLICATE

Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

ORIG AMENDMENT

BM

May 2, 2000

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

RE: NDA 21-212
CAVERJECT ® DC
alprostadil for injection

Amendment No. 001
Response to FDA Request

Dear Sir/Madam:

We are amending our NDA 21-212 for Caverject DC in order to provide a more complete narrative for clinical trial patient #111, including pertinent hospital summaries. This information was requested by Ms. Kim Colangelo, HFD-580 during a telephone conversation on March 10, 2000 with Mr. Greg Brier, Regulatory Manager, at Pharmacia & Upjohn.

Enclosed is a four-page summary for this patient. The original text of the summary is available upon request.

Please contact Terry Reinstein at (616) 833-8542, if there are questions. Send all correspondence addressed to Unit 0633-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Terry L. Reinstein, R.Ph.
Regulatory Manager
Regulatory Affairs

TLR:lmf

Attachment

Pharmacia&Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

January 20, 2000

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

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

Original Submission of New Drug Application

Dear Sir/Madam:

Under the provisions of 21CFR 314.50, Pharmacia & Upjohn (P&U) is submitting a New Drug Application, NDA 21-212, for CAVERJECT DC (alprostadil for injection), indicated for the treatment and diagnosis of erectile dysfunction (ED) via intracavernosal injection. P&U currently markets CAVERJECT® Sterile Powder (alprostadil for injection) approved under NDA 20-379 and CAVERJECT® Injection (alprostadil injection) aqueous approved under NDA 20-755.

CAVERJECT DC (alprostadil for injection) will be available in 10 and 20 mcg strengths and uses a device consisting of a pre-filled dual chamber cartridge injection system that allows simple reconstitution. Once the alprostadil is reconstituted, the dual chamber device provides for a patient adjustable dose of 2.5, 5, 7.5, or 10 mcg of alprostadil for the 10 mcg presentation, and 5, 10, 15, or 20 mcg of alprostadil for the 20 mcg presentation. An enhanced formulation involving the use of α-cyclodextrin has been developed for CAVERJECT DC, allowing for a reduction in the maximum injection volume to 0.5 ml and storage of the product at ambient temperatures.

In accordance with recommendations from the Division of Reproductive & Urological Drug Products, copies of the summaries for the Nonclinical Pharmacology and Toxicology Section, Human Pharmacokinetics and Bioavailability Section, and Clinical Data Section from NDA 20-379 have been provided as a reference to their respective Sections of this NDA. Detailed information pertaining to toxicology and clinical experience with CAVERJECT is made by reference to data previously submitted and evaluated in NDA 20-379 for CAVERJECT Sterile Powder (alprostadil for injection), which was approved July 5, 1995.

Clinical Information

The clinical information for this indication consist of one open-label, baseline-retrospective crossover study (Protocol 98-DUAL-001) of patients with ED. The primary objective of this study was to demonstrate that CAVERJECT Sterile Powder and CAVERJECT DC produce comparable efficacy results when self-injected intracavernosally, in the home situation, and at the same dose levels, in patients with ED who were on stable treatment with CAVERJECT Sterile Powder.

Pediatric Waiver

Pursuant to the provisions of 21CFR 314.55, P&U is requesting a full waiver from conducting a pediatric assessment. CAVERJECT DC, which is indicated for the treatment and diagnosis of ED via intracavernosal injection, does not represent a meaning therapeutic benefit in the pediatric population.

Application format

This application consist of 19 paper volumes as described in the following outline:

Item	Description	Volume Number(s)
Cover Letter		1.1
Attachment 1	Form FDA 356h	1.1
Attachment 2	Abbreviated NDA Table of Contents	1.1
Attachment 3	Item 13/14 Patent Information	1.1
Attachment 4	Item 16 Debarment Certification	1.1
Attachment 5	Item 17 Certification of CMC Field Copy	1.1
Attachment 6	Item 18 User Fee Cover Sheet	1.1
Attachment 7	Item 19 Financial Certification Disclosure	1.1
CD-ROM	Item 11 Case Report Tabulations (electronic format)	1.1
	Item 12 Case Report Forms (electronic format)	1.1
Item 1	Application Index	1.1
Item 2	Labeling	1.2
Item 3	Application Summary	1.3
Item 4	Chemistry Section	1.4 – 1.8
Item 5	Nonclinical Pharmacology and Toxicology Section	1.9 – 1.12
Item 6	Human Pharmacokinetics and Bioavailability Section ...	1.13 – 1.15
Item 7	Clinical Microbiology Section	N / A
Item 8	Clinical Data Section	1.16 – 1.19
Item 9	Safety Update Report	N/A
Item 10	Statistical Section	1.16 – 1.19

The Overall Index for the application is located in Volume 1.1. An abbreviated Table of Contents is provided in Attachment 2 of this letter. The first volume of each Item contains a comprehensive table of contents for that Item. Each volume within an Item is also prefaced with a table of contents specific to that volume.

The volumes are sequentially numbered within each item. Each volume also bears an overall volume number on the binder cover. The overall volume numbers are NOT used for cross-referencing.

Submission information

Data are being provided in either print or electronic format, as described below and on the abbreviated Table of Contents located in Attachment 2.

- The paper submission consists of archival and review copies of all volumes for Items 1, 2, 3, 4, 5, 6, and 8/10. Two review copies of Item 8/10 are provided for the Clinical and Statistical reviews, respectively.

- As previously requested, we are providing 3 Desk Copies of the Application Index (Vol. 1.1) and 2 Desk Copies of the Application Summary Sections (Vol. 1.3). Additional Desk Copies will be provided upon request.

- An archival and a review copy of Item 11 Case Report Tabulations and Item 12 Case Report Forms are being submitted in electronic form only and are provided as SAS transport files. The CD-ROM provided in Volume 1.1, which contains data for the one study, has a root directory named N21212. PDF files of Item 11 and 12 are located in subdirectory CRT and CRF respectively. The total size of these electronic files is 4.2 megabytes. In addition, a copy of this letter (*cover.pdf*), Form 356h (*356h.pdf*), and the abbreviated Table of Contents (*ndatoc.pdf*) are provided in the root directory N21212. Proposed labeling in MS Word 97 format (*manuscript version – dc1-7a2.doc*), (*annotated version – dc1-7c2.doc*), (*underlined strikout version – dc1-7b2.doc*), and (*device & carton labeling – noninsrt.doc*) are included on the same CD-ROM, which is located in Volume 1.1, in the subdirectory named LABELING. The CD-ROM has been scanned with Network Associate's McAfee Virus Scan for Windows version 4.0.3 to verify that it is free of viruses.

Please contact Terry L. Reinstein at (616) 833-8542, if you have any questions during the interim. Send all correspondence addressed to Unit 0633-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Gregory A. Brown/for

Terry L. Reinstein, R.Ph.
Regulatory Manager
Regulatory Affairs

TLR:kmv

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-212

Pharmacia & Upjohn
Attention: Terry Reinstein, R.Ph.
Regulatory Manager
7000 Portage Road
Kalamazoo, MI 49001

Dear Ms. Reinstein:

We acknowledge receipt on January 21, 2000 of your January 20, 2000 resubmission to your new drug application (NDA) for CAVERJECT Dual-Chamber Syringe (alprotadil for injection).

This resubmission contains additional chemistry and labeling information submitted in response to our November 20, 2000 action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is June 12, 2002.

If you have any questions, call me at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier, B.S.
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Jennifer L. Mercier
1/2/02 09:49:01 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-212

DISCIPLINE REVIEW LETTER

Pharmacia & Upjohn
Attention: Terry Reinstein
Regulatory Manager
7000 Portage Road
Kalamazoo, MI 49001

Dear Mr. Reinstein:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Caverject (alprostadil for injection) Dual Chamber Syringe.

We also refer to your submissions dated May 31, September 15, and October 2 and 5, 2000.

Our review of the your responses to our letter dated September 19, 2000, is complete, and we have identified the following deficiencies:

1. The deficiencies noted in DMF — for PGE_2 are addressed in the application. Therefore, no additional information regarding PGE_2 is needed to support NDA 21-212.

2. Until actual data are provided to demonstrate that the water content will not significantly affect the drug product during the shelf-life, specifications for water content need to be implemented as follows: NMT —% at release and NMT —% during the shelf-life.

3. Based on 12 months of stability data at 25°C and 6 months at 40°C, an 18-month expiration period can be granted.

4. A new trademark for this product needs to be provided.

5. Provide a brief overall description of the sampling plan(s) for production batches and selection of sub-samples for analyses. Evaluation should consider the adequacy of the sampling process (e.g., beginning, middle, end) and the number of samples per production batch.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Kim Colangelo, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader for the
Division of Reproductive and
Urologic Drug Products, (HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

/s/

Moo-Jhong Rhee
11/14/00 03:00:20 PM

[redacted]

Application #(s):	NDA 21-212
Document Type:	NDA Letter
Document Group:	Information Request Letters
Document Name:	Discipline review letter for a pending NDA
Letter Code:	NDA-E2
COMIS Decision:	DR: DISCIPLINE REVIEW
Drafted by:	kmc/November 7, 2000
Revised by:	Salemme, Rhee, 11.07.00
Initialed by:	Rumble, 11.07.00; Allen, 11.13.00,
Finalized:	Colangelo, 11.14.00
Filename:	C:\data\nda\21-212\dr2cmc.doc
DFS Key Words:	
Notes:	
Linking Instructions:	Link this letter to the incoming documents that were reviewed.

[redacted]

[redacted]

pplication #(s):	NDA 21-212
)ocument Type:	NDA Letter
ıcument Group:	Information Request Letters
)ocument Name:	Information request letter for a pending NDA
Letter Code:	NDA-E1
:OMIS Decision:	IR: INFORMATION REQUEST
Drafted by:	kmc/November 6, 2000
Revised by:	Rumble, 11.01.00; Salemme, 11.02.00
Initialed by:	Rhee, Hirsch, 11.02.00; Shames, 11.03.00; Allen, 11.06.00
Finalized:	Colangelo, 11.06.00
Filename:	C:\data\nda\21-212\irlabel.doc
DFS Key Words:	
Notes:	
nking Instructions:	Link this letter to the incoming document containing the information requiring further clarification.

[redacted]

sexual function. Regarding the modifications, the EIR states, "With respect to the primary endpoints I [the FDA inspector] noted that in some cases the patient's evaluation was changed after the evaluation had been completed by the individual....I asked Mr. Geppert [the study coordinator] why the answers were changed. He stated that these individuals had initially interpreted the question incorrectly and that after some discussion and full understanding of the question the correct and more accurate answer was given." The study protocol makes no provision for modification of subjects' responses by study personnel. The exhibits collected at the site for these subjects that were related to the primary efficacy endpoint were limited to baseline data, and thus, the impact on the primary efficacy endpoint cannot be conclusively determined. These observations raise a concern regarding efficacy data for these subjects from this site.

Review of the records also indicated that the investigational drug was dispensed 27 days after completing the preceding study, a difference of only one day from that required by the protocol. Since the half-life of the test article is measured in minutes, a 27-day washout period is sufficient and would not affect the findings of the study. This deficiency was omitted from the letter. However, upon review of the inspection report, it was noted as a deficiency in the letter to Dr. Talley that the clinical coordinator, who was responsible for conducting substantial portions of the study, was not listed on the Form 1572. This deficiency was not noted in the inspector's report.

The issue of data modification is brought to the attention of the medical officer. DSI suggests that the review division determine whether the data provided by this site be used in support of this application.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The data submitted in support of this NDA by Dr. Murdock are acceptable. We recommend that the review division make a judgement as to whether the data from Dr. Talley are acceptable.

Follow-up action: A VAI-R letter is being issued to Dr. Talley requesting his response to the issues outlined in the letter. Upon receipt, Dr. Talley's response should be reviewed for adequacy.

Roy Blay, Ph.D., Clinical Reviewer
DSI/GCPBI

CONCURRENCE:

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