

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20-755**

**CHEMISTRY REVIEW(S)**

OCT 27 1997

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

NDA: 20-755  
CHEMISTRY REVIEW # 3

DATE REVIEWED: 27 Oct. 1997

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	26 July 1996	2 Aug. 1996	12 Aug. 1996
AMENDMENTS	23 July 1997	24 July 1997	
	6 Oct. 1997	7 Oct. 1997	
	24 Oct. 1997		

NAME & ADDRESS OF APPLICANT: The Upjohn Company  
7000 Portage Road  
Kalamazoo, MI 49001  
(616) 329-5671

**DRUG PRODUCT NAME**

Proprietary:	Caverject Injection
Nonproprietary/Established/USAN:	Alprostadil Aqueous injection
Code Name/#:	CAS-745-65-3; U-10136 (Upjohn)
Chem.Type/Ther.Class:	3 S

**ANDA Suitability Petition / DESI / Patent Status:** N/A [if applicable]

**PHARMACOLOGICAL CATEGORY/INDICATION:** Vasodilator/ Treatment of Erectile Dysfunction

**DOSAGE FORM:** Isotonic Solution

**STRENGTHS:** 5, 10, 20 mcg/mL and 40 mcg/2 mL

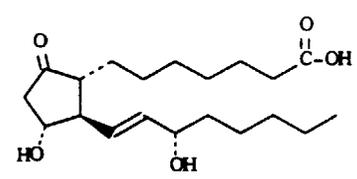
**ROUTE OF ADMINISTRATION:** Intracavernosal injection

**DISPENSED:**  Rx  OTC

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

Molecular Formula: C<sub>20</sub>H<sub>34</sub>O<sub>5</sub>

Molecular Weight: 354.49



(11α,13E,15S)-11,15-dihydroxy-9-oxoprost-13-en-1-oic acid

**SUPPORTING DOCUMENTS:**

IND		
IND		
NDA 20-379	Alprostadil for Inj. (Caverject)	Upjohn
NDA 18-484	Alprostadil inj. (Postin VR)	Upjohn
DMF		
DMF		

**RELATED DOCUMENTS (if applicable):** N/A

**CONSULTS:** Microbiology--Review #2 dated 2 June 1997 states that the application is recommended for approval on the basis of sterility assurance.

**REMARKS/COMMENTS:** This is a review of the Amendment dated 24 Oct. 1997 which is a response to the CMC and Labeling deficiencies conveyed to the Applicant on 16 Oct. 1997

**CONCLUSIONS & RECOMMENDATIONS:** NDA 20-755 may be approved from a chemistry, manufacturing and controls perspective.

Orig. NDA 20-755  
cc: HFD-580/Division File  
HFD-580/ K. Srinivasachar/Rhee/CSO

R/D Init by:

10/27/97

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K. Srinivasachar, Ph.D.  
Review Chemist  
filename: nda20755.3

OCT 14 1997

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

NDA: 20-755  
 CHEMISTRY REVIEW # 2

DATE REVIEWED: 14 Oct. 1997

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	26 July 1996	2 Aug. 1996	12 Aug. 1996
AMENDMENTS	23 July 1997	24 July 1997	
	6 Oct. 1997	7 Oct. 1997	

**NAME & ADDRESS OF APPLICANT:** The Upjohn Company  
 7000 Portage Road  
 Kalamazoo, MI 49001  
 (616) 329-5671

**DRUG PRODUCT NAME**

Proprietary:	Caverject Injection
Nonproprietary/Established/USAN:	Alprostadil Aqueous injection
Code Name/#:	CAS-745-65-3; U-10136 (Upjohn)
Chem.Type/Ther.Class:	3 S

**ANDA Suitability Petition / DESI / Patent Status:** N/A [if applicable]

**PHARMACOLOGICAL CATEGORY/INDICATION:** Vasodilator/ Treatment of Erectile Dysfunction

**DOSAGE FORM:** Isotonic Solution

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**ROUTE OF ADMINISTRATION:** Intracavernosal injection

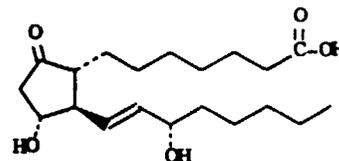
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DMF		
DMF		



**RELATED DOCUMENTS (if applicable):** N/A

**CONSULTS:** Microbiology--Review #2 dated 2 June 1997 states that the application is recommended for approval on the basis of sterility assurance.

**REMARKS/COMMENTS:** This is a review of the Amendment dated 6 Oct. 1997 which is based on the teleconference of 4 Sep. 1997 regarding stability issues and storage conditions of the drug product. This Amendment was received before the deficiencies identified in Chemistry Review # 1 were conveyed to the sponsor.

**CONCLUSIONS & RECOMMENDATIONS:** NDA 20-755 is approvable from a chemistry, manufacturing and controls viewpoint pending a satisfactory response, in the form of an Amendment from the sponsor, to the deficiencies listed

Orig. NDA 20-755  
cc: HFD-580/Division File  
HFD-580/ K. Srinivasachar/Rhee/CSO

R/D Init by:

10/14/97

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K. Srinivasachar, Ph.D.  
Review Chemist  
filename: nda20755.2

OCT - 3 1997

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

NDA: 20-755  
CHEMISTRY REVIEW # 1

DATE REVIEWED: 29 Sep. 1997

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	26 July 1996	2 Aug. 1996	12 Aug. 1996
AMENDMENT	23 July 1997	24 July 1997	

NAME & ADDRESS OF APPLICANT: The Upjohn Company  
7000 Portage Road  
Kalamazoo, MI 49001  
(616) 329-5671

**DRUG PRODUCT NAME**

Proprietary:	Caverject Injection
Nonproprietary/Established/USAN:	Alprostadil Aqueous injection
Code Name/#:	CAS-745-65-3; U-10136 (Upjohn)
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**ANDA Suitability Petition / DESI / Patent Status:** N/A [if applicable]

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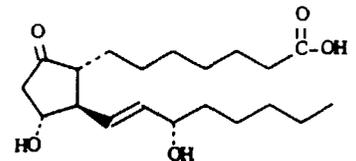
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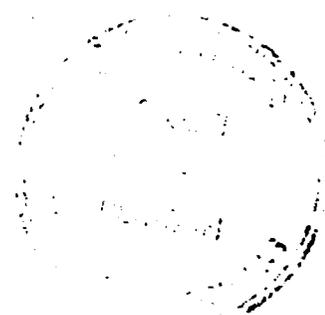
Molecular Weight: 354.49



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DMF		
DMF		



**RELATED DOCUMENTS (if applicable): N/A**

**CONSULTS:** Microbiology--Review #2 dated 2 June 1997 states that the application is recommended for approval on the basis of sterility assurance.

**REMARKS/COMMENTS:** The drug substance for this NDA, Alprostadiil, is the same as in approved NDA 18-484, Prostin VR Pediatric Sterile Solution and approved NDA 20-379, Caverject Sterile Powder, submitted by the same applicant. The prostaglandins are inherently unstable molecules and their facile degradation is of major concern in any drug product formulated with these substances. The degradation of Alprostadiil (Prostaglandin E<sub>1</sub>) is highly dependent on pH and temperature; careful control of these variables is necessary to ensure maximum potency of the drug over its shelf-life. These considerations assume even greater importance given the low concentration of drug (5, 10 and 20µg/ mL and 40 mcg/2 mL) in the formulations which the applicant proposes to market.

**CONCLUSIONS & RECOMMENDATIONS:** NDA 20-755 is approvable from a chemistry, manufacturing and controls viewpoint pending a satisfactory response, in the form of an Amendment from the sponsor, to the deficiencies listed

Orig. NDA 20-755  
cc: HFD-580/Division File  
HFD-580/ K. Srinivasachar/Rhee/CSO

R/D Init by:

10/3/97

K. Srinivasachar, Ph.D.  
Review Chemist  
filename: nda20755.1