CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-212

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW

NDA 21-212

Drug Product:
Caverject Impulse (Alprostadil for injection)

Sponsor: Pharmacia & Upjohn

Reviewer: J. Salemme, Ph.D.

Division of Reproductive and Urologic Drug Products
(HFD-580)

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-212

2. REVIEW # 4

3. REVIEW DATE: 10-Jun-2002

4. REVIEWER: J. Salemme, Ph.D.

5. PREVIOUS DOCUMENTS:

Document	Document Date
Original NDA	20-Jan-2000
Amendment 002	31-May-2000
Amendment 008	15-Sept-2000
Amendment 012	2-Oct-2000
Amendment 013	5-Oct-2000

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment 014 – Partial response to CMC deficiencies	17-Nov-2000
Amendment 015 – Full response to Approvable Letter	12-Dec-2001
Amendment 016 – 36 month stability data	6-May-2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Pharmacia & Upjohn
Address:	7000 Portage Road Kalamazoo, MI 49001-0199
Representative:	Terry Reinstein

Chemistry Review Data Sheet

Telephone: (616) 833-8542

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Caverject Impulse
b) Non-Proprietary Name (USAN): Alprostadil for Injection
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Vasodilator, for the treatment of erectile dysfunction

11. DOSAGE FORM: lyophilized powder for injection

12. STRENGTH/POTENCY: 10 mcg or 20 mcg per 0.5 mL of sterile water for injection

13. ROUTE OF ADMINISTRATION: intracavernosal injection

14. Rx/OTC DISPENSED: X Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note25]:

X SPOTS product – Form Completed

_____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

See Chemistry Review 1 of the original NDA.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: See Original NDA Chemistry Reviews 1, 2 and 3.

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-379	Caverject Sterile Powder for Injection
NDA	20-755	Alprostadil for Injection

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	Reviewer or Comment
Biometrics	Not Requested		
EES	Satisfactory		
Pharm/Tox	Satisfactory		See original NDA.
Biopharm	Satisfactory		See original NDA.
LNC	N/A		
Methods Validation	Satisfactory		Not Required (NDA 20-379 has same methods)
OPDRA	Satisfactory	8-Aug-2001	H-J Kim, Pharm.D
EA	Satisfactory		Categorical exclusion claimed. See Chemistry Review No. 1.
Microbiology	Satisfactory		See Chemistry Review No. 1.

The Chemistry Review for NDA 21-212

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
From a CMC point of view, this NDA may be approved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance
The drug product is a new alprostadil formulation and new delivery presentation different from previously approved Pharmacia & Upjohn Caverject products. The drug product formulation contains the drug substance, alprostadil, lactose, alpha-cyclodextrin, and sodium citrate. The alpha-cyclodextrin gives chemical stability to alprostadil and allows the drug product to be stored at room temperature. The delivery presentation is a dual chamber glass cartridge used with a syringe that allows increments of the nominal dose to be delivered. The dual chamber glass cartridge contains lyophilized drug formulation in the front chamber and sterile diluent, water for injection with benzyl alcohol, in the rear chamber. The sterile diluent is transferred to the front chamber by the action of the barrel in the syringe for reconstitution of the drug product prior to injection.

Two drug product strengths, 10 mcg and 20 mcg, have been developed. The quantitative composition of the formulation after reconstitution for the 10 mcg strength is: alprostadil (—), lactose (—), alpha-cyclodextrin (—), and sodium citrate (—); for the 20 mcg strength is: alprostadil (— , lactose (—), alpha-cyclodextrin (—), and sodium citrate dihydrate (—).

The quality of the lyophilized formulation is controlled by specifications for appearance, water content, pH, assay, dose uniformity, and purity. The quality of the diluent is controlled by specifications that include a test for benzyl alcohol. The quality of the reconstituted formulation is controlled by specifications for appearance, pH, reconstitution time, particulate matter, volume of injection, and sterility. The acceptance criterion for each is considered to be adequate.

The dual chamber is made of clear [redacted] tubing, a plunger/stopper made of grey [redacted] rubber, and aluminum cap containing grey [redacted] rubber. The components are satisfactorily controlled to provide adequate protection of the drug product during shelf life. The syringe used with the glass dual chamber allows for an increment of or the total 0.5mL volume to be delivered. A small gauge needle is provided with the syringe.

The drug product is manufactured by Pharmacia & Upjohn AB, in Stockholm and Uppsala, Sweden. The Office of Compliance has determined the sites are satisfactory for the manufacture of the drug product. The tradename Caverject Impulse is accepted by OPDRA. Based on 36-month real time data and 6 months accelerated data from three primary stability batches, an expiry date of 36 months is granted.

The drug substance, alprostadil, also known as prostaglandin E1, is used in other previously approved drug products. The drug substance is manufactured by Pharmacia and Upjohn in Michigan in compliance with cGMP. The quality of the drug substance is controlled by specifications for assay, appearance, identification by IR, water content, residue on ignition, degradation products, chromium and rhodium metals, and residual solvents.

B. Description of How the Drug Product is Intended to be Used

The drug product is intended for use in the treatment of erectile dysfunction. The reconstituted drug product is intended for a single injection intracavernously. The patient may select a portion of the reconstituted formulation to inject in quarter increments of the 0.5mL volume or inject the total 0.5mL volume. The reconstituted solution may be kept at room temperature for 24 hours or kept refrigerated for seven days before the injection is performed.

The drug product may be stored at room temperature. An expiry of 36 months has been approved for drug product kept at 25°C.

C. Basis for Approvability or Not-Approval Recommendation

The deficiencies outlined in the Approvable letter issued in October 2000 have been satisfactory addressed. The Office of Compliance has determined the manufacturing sites in Sweden are acceptable for the manufacture of the drug product. Additional CMC issues outlined in the Approvable letter are discussed in this review. Most of the CMC information, however, was previously found to be acceptable and is discussed in chemistry reviews 1, 2, and 3.

III. Administrative

Executive Summary Section

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date:	J. Salemme, Ph.D.
ChemistryTeamLeaderName/Date	David T Lin, Ph.D.
ProjectManagerName/Date	Eufrecina De-Guia

C. CC Block

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Summary of Chemistry Review of NDA 21-212

A. Drug Substances:

Alprostadil is known as prostaglandin E_1 (PGE_1) and has been used in other previously approved drugs (NDA 20-379). It is manufactured by **Pharmacia & Upjohn** (DMF) **in compliance with cGMP.**

The **quality** of the drug substance is **adequately controlled** by specifications such as assay, appearance, identification by IR, water content, residue on ignition, prostaglandin A_1, prostaglandin B_1, foreign prostaglandins, 15-keto-PGE_1, chromium, rhodium, and residual solvents. The **methods** involved are **deemed to be suitable for regulatory purpose. Validation** of the methods is **not** necessary because they are the same as those previously approved.

B. Drug Product:

This is a new presentation of previously approved **Caverject** products, which utilizes a **dual chamber cartridge** containing **lyophilized powder** in the **front chamber** and **diluent** in the **rear chamber**. This dual chamber cartridge is to be used with a **device**, which can provide selected dose to the patient. The **device** is considered to be **adequate** for delivering the drug safely and effectively. The lyophilized powder in the front chamber contains alprostadil (10/20mcg), ;), α–cyclodextrin (;), and sodium citrate dihydrate (cg). The **diluent** (0.64ml) in the rear chamber contains water for injection containing **benzyl alcohol** (

The **α–cyclodextrin** is to **stabilize** the thermodynamically unstable prostagladin by forming a **complex**. However, it is claimed that as soon as the complex is reconstituted with the diluent, the drug substance is released from the complex possibly because benzyl alcohol displaces alprostadil from the complex.

The dual chamber cartridges are manufactured and supplied by **Pharmacia & Upjohn AB**, Stockholm and Upspsala, in Sweden. They are determined to be **NOT in compliance with cGMP**.

The **quality** of the **lyophilized powder** in the front chamber is controlled by specifications such as identification, appearance, water content, pH, assay, dose uniformity, and purity. The **diluent** in the rear chamber is controlled by specifications including identification for benzyl alcohol, and its assay. The **reconstituted solution** is controlled by appearance, pH, reconstitution time, sub-visible particle matter, volume of injection, endotoxin, and sterility. All **tests and specification limits** are now considered to be **adequate.**

The **dual chamber** is composed of **type 1 clear glass tubing** (DMF), plunger **stopper** which is **grey** ; **rubber** (DMF), and **aluminum cap** containing grey (1 rubber. They are all **satisfactorily controlled** to provide adequate protection of the drug product during the shelf life.

Based on 12-month real time data and 6-month accelerated data from 3 primary stability batches, an **expiry date of** is granted.

The tradename, **Caverject DC**, was **NOT** accepted by OPDRA

C. Conclusion and Recommendation:

From the chemistry point of view, I concur with the primary reviewer's recommendation of **"Approvable"** for this NDA pending resolution of the following issues:

1. Satisfactory inspection of the facilities.
2. Other minor issues
   - New tradename
   - Other editorial changes on carton/container labels

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
For the Division of reproductive and Urologic Drug Products
DNDC II, Office of New Drug Chemistry

/s/

Moo-Jhong Rhee
11/27/00 10:26:26 AM
CHEMIST

Summary of Chemistry Review of NDA 21-212

A. Drug Substances:

Alprostadil is known as prostaglandin E_1 (PGE_1) and has been used in other previously approved drugs (NDA 20-379). It is manufactured by **Pharmacia & Upjohn** ——— **in compliance with cGMP.**

The **quality** of the drug substance is **adequately controlled** by specifications such as assay, appearance, identification by IR, water content, residue on ignition, prostaglandin A_1, prostaglandin B_1, foreign prostaglandins, 15-keto-PGE_1, chromium, rhodium, and residual solvents. The **methods** involved are **deemed to be suitable for regulatory purpose. Validation** of the methods is **not** necessary because they are the same as those previously approved.

B. Drug Product:

This is a new presentation of previously approved **Caverject** products, which utilizes **a dual chamber cartridge** containing **lyophilized powder** in the **front chamber** and **diluent** in the **rear chamber.** This dual chamber cartridge is to be used with a **device**, which can provide selected dose to the patient. The **device** is considered to be **adequate** for delivering the drug safely and effectively. The lyophilized powder in the front chamber contains alprostadil (10/20mcg), lactose (——— cg), and sodium citrate (——— 3.9mcg). The **diluent** (0.64ml) in the rear chamber contains water for injection containing **benzyl alcohol** ———.

The ☐-**cyclodextrin** is to **stabilize** the thermodynamically unstable prostagladin by forming a **complex.** However, it is claimed that as soon as the complex is reconstituted with the diluent, the drug substance is released from the complex possibly because benzyl alcohol displaces alprostadil from the complex.

The dual chamber cartridges are manufactured and supplied by **Pharmacia & Upjohn AB**, Stockholm and Upspsala, in Sweden. They are determined to be **NOT in compliance with cGMP**.

The **quality** of the **lyophilized powder** in the front chamber is controlled by specifications such as identification, appearance, water content, pH, assay, dose uniformity, and purity. The **diluent** in the rear chamber is controlled by specifications including identification for benzyl alcohol, and its assay. The **reconstituted solution** is controlled by appearance, pH, reconstitution time, sub-visible particle matter, volume of injection, endotoxin, and sterility. All **tests and specification limits** are considered to be **adequate, except for** the specification for the **water content** in the lyophilized powder and **lacking information on sampling plans.** The specification for the water content **needs to be revised to** ~~% at release and~~ ~ **% during the shelf life.**

The **dual chamber** is composed of **type 1 clear** ——— **glass tubing** (DMF ——, plunger **stopper** which is **grey** ——— **rubber** (DMF ——), and **aluminum cap** containing grey ——— **rubber. They are all satisfactorily controlled** to provide adequate protection of the drug product during the shelf life.

Based on 12-month real time data and 6-month accelerated data from 3 primary stability batches, **an expiry date of** ——— is granted.

The tradename, **Caverject DC**, was **NOT** accepted by OPDRA

C. Conclusion and Recommendation:

From the chemistry point of view, I concur with the primary reviewer's recommendation of **"Approvable"** for this NDA pending resolution of the following issues:

1. Specifications for the water content in the drug product at release and during the shelf life
2. Information on the sampling plan for the regulatory tests of the drug product
3. Acceptance by the sponsor of the [redacted] expiry date
4. Satisfactory inspection of the facilities.
5. Other minor issues
   - New tradename
   - Other editorial changes on carton/container labels

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
For the Division of reproductive and Urologic Drug Products
DNDC II, Office of New Drug Chemistry

/s/

Moo-Jhong Rhee
11/16/00 01:43:24 PM
CHEMIST

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

NDA: 21-212 **Reviewer:** J. Salemme
Chemistry Review # 3

SUBMISSION TYPE	**Document Date**	**CDER Date**	**Review Date**
Original	20-Jan-2000	21-Jan-2000	15-Nov-2000

NAME AND ADDRESS OF SPONSOR
Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001

DRUG PRODUCT NAME:

Proprietary:	Caverject DC (Name not yet chosen)
Established	Alprostadil
Chem. Type/Ther. Class:	3S

PHARMACOLOGICAL CATEGORY/INDICATION: Prostaglandin, vasodilator; for the treatment of erectile dysfunction

DOSAGE FORM:	lyophilized powder for injection
STRENGTHS:	10 mcg or 20 mcg per 0.5 mL sterile water for injection
ROUTE OF ADMINISTRATION:	intracavernosal injection
Rx/OTC:	Rx
SPECIAL PRODUCTS:	lactose monohydrate

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Provided in chemistry review #1.

SUPPORTING DOCUMENTS: The complete list is provided in chemistry reviews #1 and #2.

RELATED DOCUMENTS: None

CONSULTS:

- Inspections: The establishment inspections for the US drug substance manufacturing site, and two Swedish sites, one in Stockholm for the drug product manufacture, and the other in Uppsala for the chemical and microbiological testing laboratories, were conducted. The US site was approved. The two Swedish sites had a number of deficiencies that will not be satisfactorily remedied by the PDUFA date. The Office of Compliance recommends a Withhold of the NDA based on unsatisfactory inspections of these two sites (as stated in the attached EES report on page 3).
- Microbiology: The deficiencies outlined in the Microbiology Review #1, dated 2-Aug-2000, were addressed satisfactorily as reported in the Microbiology Review #2, dated 26-Oct-2000. The NDA is recommended for approval on the basis of sterility assurance.

COMMENTS:

- This review summarizes the CMC status of this NDA at the PDUFA date of 21-Nov-2000.

CONCLUSIONS AND RECOMMENDATION:

This NDA is approvable pending satisfactory resolution of the following issues conveyed to the sponsor in a Discipline Review letter dated 14-Nov-2000 and satisfactory site inspections.

- The specification for water content at the time of release and throughout the shelf-life
- The sampling plan employed in the determination of representative sampling from drug product batches
- The shelf-life expiration date
- The selection of a tradename
- Labeling and labels of container/cartons

J. Salemme, Ph.D.
Review Chemist, HFD-580

Moo-Jhong Rhee, Ph.D.
Team Leader, HFD-580

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See p. 7 of Chemistry Review #2 for resolution of CDRH review comments.