CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-212

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA:	21-212
Drug:	Caverject DC (alprostadil) 10/20 μg injection
Sponsor:	Pharmacia & Upjohn Company
Date of Submission:	01/21/00
Type of Submission:	Original NDA
Reviewer:	Venkateswar R. Jarugula, Ph.D.

SYNOPSIS

Alprostadil sterile powder (Caverject® Sterile powder; prostaglandin E_1, PGE_1) has been on the market in the United States since 1995 for the indication of treatment of erectile dysfunction (ED) due to the neurogenic, vasculogenic, psychogenic, or mixed etiology (NDA 20-379). In the present NDA, the sponsor is seeking approval for Caverject DC, a dual chamber cartridge system, which is a prefilled disposable syringe containing the active ingredient alprostadil in the form of an inclusion complex with α-cyclodextrin.

This is a new NDA. Although the active ingredient is same, since it is made into a complex with α-cyclodextrin, this is considered a major formulation change. Typically, a pharmacokinetic bioequivalence study is conducted to support the post approval formulation change such as this. However, since the efficacy of Caverject is by local mechanism and not due to systemic exposure of the drug, it was agreed upon by the FDA and the sponsor to conduct a clinical (pharmacodynamic) study to demonstrate comparable safety and efficacy between the approved Caverject sterile powder for injection and the proposed Caverject DC.

For the Human Pharmacokinetics and Biopharmaceutics section, sponsor referred to the pharmacokinetic information submitted in the approved NDA 20-379 and summarized the same information in the present NDA. This information was already reviewed by Dr. David Udo from Office of Clinical Pharmacology and Biopharmaceutics (Please refer to Original Review dated 12/22/94).

Sponsor did not conduct any pharmacokinetic studies with Caverject DC and requested waiver for such studies based on the following rationale:

- Systemic levels of alprostadil are unlikely to reflect the pharmacodynamic effects in the corpus cavernosum (site of action).

- Prior studies characterizing systemic plasma levels of alprostadil and its metabolites after intra-cavernosal injection have been submitted previously in NDA 20-379.

- The dissociation of alprostadil from inclusion complex with α-cyclodextrin is [redacted] and cyclodextrin would not be expected to result in differences in alprostadil disposition when compared to the approved Caverject sterile powder.

It was noted from the Clinical Pharmacology and Biopharmaceutics review dated 12/22/94 that the pharmacokinetic information reported in the current labeling was indeed obtained following administration of alprostadil in the form of a complex with α-cyclodextrin. Therefore, sponsor's request for waiver of additional pharmacokinetic studies is acceptable because of the above mentioned reasons. In accordance with 21 CFR 320.24(b)(3), a clinical study showing comparable safety and efficacy profile between Caverject DC and approved Caverject, in lieu of a traditional pharmacokinetic bioequiavelence study, is acceptable for this NDA (please refer to Dr. Mark Hirsch's review for details on the clinical study).

RECOMMENDATION

Section 6 of NDA 21-212 for Caverject DC is acceptable from Clinical Pharmacology and Biopharmaceutics perspective.

Venkateswar R. Jarugula, Ph.D.

RD initialed by Ameeta Parekh, Ph.D., Team Leader _____

FT signed by Ameeta Parekh, Ph.D. Team Leader _____

cc: NDA 21-212, HFD-580 (Hirsch, Colangelo), HFD-870 (Malinowski, Parekh, Jarugula), CDR (B.Murphy for Drug).

CPB briefing ; Drs. J.Hunt, A.Parekh, and M. Hirsch.

SUMMARY

The key questions for this NDA are:

What are the formulation changes in the proposed product compared to approved Caverject?
What data is needed to support the new formulation, Caverject DC?
Is the sponsor's rational for lack of pharmacokinetic data and a bioequivalence assessment appropriate?

What are the formulation changes in the proposed product (Caverject DC) compared to approved Caverject?

Caverject DC is a pre-filled disposable syringe which contains the active ingredient alsprostadil in the form of an inclusion complex with α-cyclodextrin, which is considered to be a safe excipient that is currently used in Scwartz Pharma's alprostadil alfadex EDEX). According to the sponsor, by including α-cyclodextrin in the formulation and reducing the amount of lactose, the amount of dry substance (volume) is reduced without reduction in the stability of the active ingredient. The reduced amount of dry substance was prerequisite to develop the dual chamber presentation and to allow for storage at ambient temperature. The dual chamber syringe contains lyophilized powder with active ingredient in one chamber and reconstitution vehicle in the other chamber. The drug concentration after reconstitution was doubled in comparison to the approved Caverject. Two formulation strengths (10 and 20 µg) have been developed for Caverject DC.

The composition of the Caverject DC and Caverject sterile powder:

Ingredient	Caverject DC		Cavejct Sterile powder	
	10 µg	20µg	10 µg	20µg
Lyophilized powder				
Alprostadil*				
α-cyclodextrin*				
Lactose$				
Sodium citrate$				
Hydrochloric acid Solution				
Sodium hydrochloride solution				
Reconstitution Vehicle				
Benzyl alcohol*				
Water for injection				

*Adjusted for potency $Amounts determined on an anhydrous basis

^ Deliverable amount is 10 or 20 µg after losses due to adsorption on the vial and syringe are taken into account.

Each 10 or 20 µg strength dual chamber is reconstituted by mixing 0.6 ml of the rear chamber with the front chamber contents. It is reported that only 0.60 ml of the 0.64ml total volume in the rear chamber is transferred to the front chamber in the reconstitution process. The volume of the reconstituted solution in the syringe is 0.64 ml, which allows 0.5 ml to be delivered to the patient.
The Caverject DC, disposable delivery device, can be preset by the user to deliver solution volumes of 0.125, 0.25, 0.375, and 0.5 ml.

The primary differences in formulation of Caverject DC compared to the approved Caverject are:

- Alprostadil in Caverject DC is complexed with α-cyclodextrin
- Concentration of alprostadil in Caverject DC (10, 20 µg/0.5 m) is double compared to Caverject sterile powder.

What data is needed to support the new formulation, Caverject DC?

Typically, a pharmacokinetic bioequivalence assessment between the new and approved formulations is conducted to support the approval of new formulation if there are major changes such as noted above. However, since the efficacy of alprostadil is due to its local action rather than systemic action, a traditional bioequivalence study is not feasible. Therefore, it was agreed by the FDA and the sponsor that a clinical (pharmacodynamic) study would be conducted comparing the safety and efficacy of Caverject DC to the approved Caverject in erectile dysfunction patients.

The clinical (pharmacodynamic) study (98-DUAL-001) conducted in support of Caverject DC was an open–label, crossover study in 87 current users of Caverject sterile powder. The study results demonstrated that two formulations are equivalent in terms of efficacy and safety. Please refer to Medical Officer's review for details on this study.

Is the sponsor's rationale for lack of pharmacokinetic data and bioequivalence assessment appropriate?

As discussed above, since the pharmacological activity of Caverject is due to its local action, sponsor appropriately submitted a clinical (pharmacodynamic) study in lieu of a bioequivalence study.

Sponsor did not attempt to measure systemic levels of alprostadil and requested a waiver for measuring blood levels with the new formulation for the following reasons:

- Systemic levels of alprostadil are unlikely to reflect the pharmacodynamic effects in the corpus cavernosum (site of action).

- Prior studies characterizing systemic plasma levels of alprostadil and its metabolites after intra-cavernosal injection have been submitted previously in NDA 20-379.

- The dissociation of alprostadil from inclusion complex with α-cyclodextrin is [redacted] and cyclodextrin would not be expected to result in differences in alprostadil disposition when compared to other formulations containing identical amounts of alprostadil. (An in vitro binding study was submitted in support of this conclusion).

According to the current approved label for Caverject, following intracavernosal administration of 20 μg, mean peripheral plasma concentrations of alprostadil at 30 and 60 minutes after injection (89 and 102 pg/ml, respectively) were not significantly greater than baseline levels of endogenous alprostadil (96 pg/ml). Alprostadil is rapidly converted to compounds, which are further metabolized prior to excretion. Following intracavernosal administration of 20 μg Caverject, peripheral levels of the major circulating metabolite 13,14 dihydro-15-oxo-PGE1, increased to reach peak level at 30 minutes after injection and returned to predose levels by 60 minutes after injection. Thus intracavernosal administration of Caverject results in limited systemic exposure. These pharmacokinetic results (excerpted from the label) were actually obtained following intracavernosal administration of alprostadil in the form of inclusion complex with α-cyclodextrin (please refer to CP&B review dated 12/22/94).

***In Vitro* study to determine the binding constant for complexation between alprostadil and α-cyclodextrin**

An *in vitro* experiment was conducted with the objectives of 1) determining the binding constant for the molecular complexation reaction between alprostadil (PGE1) and α-cyclodextrin and 2) to estimate the percent of PGE1 free upon reconstitution and subsequent injection and dilution.

It was assumed based on preliminary NMR experiments and known information in the literature that the stochiometric reaction is 1:1 complexation.

The equilibrium binding constant for the molecular complexation between PGE1 and α-cyclodextrin was determined by using [redacted] This determination was based on chemical shift of the [redacted] .. Since the observed chemical shift of these protons varies linearly as a function of the amount of PGE1 bound, a binding isotherm was generated. A binding isotherm by NMR is a curve of the observed chemical shift vs. free ligand concentration. The binding constant or stability constant was obtained from the binding curve through the application of nonlinear regression analysis.

The equilibrium binding constant for the molecular complexation between alprostadil and α-cyclodextrin was determined in this study to be [redacted] at 27°C in aqueous solution. Using the average blood volume in the vasculature of the penis, the % alprostadil that is free was estimated to be [redacted] % after initial dilution (dilution in 10 ml volume under flaccid condition) and nearly [redacted] after the subsequent dilution (in 50 ml under erectile condition). The estimate of percentage free alprostadil from Caverject DC was similar to

that from EDEX, a competing product (cycoldextrin complex) from Schwartz-Pharma, used as a comparator in the study.

The results of the in vitro study show that alprostadil rapidly dissociates from the inclusion complex, and basically the drug will be almost 100 % free upon reconstitution and intracavernosal administration. Therefore, alprostadil in Caverject DC is not likely to have a different systemic exposure than the approved Caverject. Thus, based on the in vitro binding data and on the reasons sited previously, sponsor's request to waive the submission of pharmacokinetic data for Caverject DC is acceptable.

/s/

Venkateswar Jarugula
11/15/00 02:56:14 PM
BIOPHARMACEUTICS

Ameeta Parekh
11/15/00 03:01:17 PM
BIOPHARMACEUTICS
I concur.