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APPLICATION NUMBER: NDA 20-755

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Rumble

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CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-755

SUBMISSION DATE:

Alprostadil aqueous injection in ampoules (5, 10, and 20 μg/1 ml and 40 μg/2 ml)

07/26/96 (Original)
11/22/96 (BB No. 001)

BRAND NAME: Caverject Injection

SPONSOR: Pharmacia and Upjohn Company

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: NDA

Code: 5S

TITLE: "Review of A New Dosage Form For The Currently Marketed Caverject"

BACKGROUND:

Caverject Sterile Powder (alprostadil for Injection, 10 and 20 μg/vial) was previously submitted for review under NDA 20-379 by The Upjohn Company. The Human Pharmacokinetics and Bioavailability (PK/Bio) section of NDA 20-379 was reviewed by the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE II) and it was found acceptable on 04/28/95. Caverject Sterile Powder was approved by the Agency on 07/06/95.

Alprostadil is also known as prostaglandin E_1 (PGE_1), an endogenous compound. It is indicated for the treatment of male erectile dysfunction by intracavernosal (IC) injection. It is recommended that generally, Caverject be used no more than 3 times per week, with at least 24 hr between each use. The dose is to be individualized for each patient by careful titration under supervision by the physician. Dose titration in physician's clinic should be initiated at 1.25 or 2.5 μg of alprostadil, depending on the etiologic origins of the dysfunction and then dose increments are allowed, depending on the erectile responses. If there is a response, then there should be at least one day interval for the next dose. A dose of greater than 60 μg is not recommended. For maintenance dose, self-injection therapy by the patient can be started only after the patient is properly instructed and well-trained in the self-injection technique.

An NDA supplement (Serial No. 003) for Caverject Sterile Powder was submitted on 12/26/95 seeking approval for a lower strength, 5 μg/vial. The NDA supplement was reviewed by OCPB/DPE II and was found acceptable on 05/31/96. Please see previous reviews for NDA 20-379 for details.

SYNOPSIS:

On 07/26/96, Pharmacia-Upjohn (Upjohn after merging with Pharmacia) submitted NDA 20-755 for Caverject Injection (alprostadil aqueous injection). The sponsor is seeking approval of 4 strengths, 5, 10, and 20 μg in a 1-ml ampoule and 40 μg in a 2-ml

ampoule. The drug products are to be stored in a freezer and the patients will be instructed to transfer the solution from the pharmacy to his home freezer or refrigerator as soon as possible. Please see the proposed package insert (PI) in Attachment 1 for details. The proposed PI was constructed based on the existing PI for Caverject Sterile Powder to now include description of the new Caverject Injection formulation and specific patient handling instruction for preparation of this formulation for injection.

The 4 formulations of Caverject Injection (aqueous isotonic solution) are compositionally the same but not proportionally similar (Table 1). In addition, they are not compositionally nor proportionally the same as the previously approved Caverject sterile powder.

Table 1. Composition of Alprostadil Aqueous Injection

Ingredient	Quantity per mL				Function	Reference to Standards
	5 mcg/mL	10 mcg/mL	20 mcg/mL	40 mcg/2mL		
Alprostadil (bulk solution) (filled vial)					Active	USP 23
Sodium Chloride	8.2mg	8.2mg	8.2mg	8.2mg	For isotonicity	USP 23
Sodium Citrate (Dihydrate)	1.5mg	1.5mg	1.5mg	1.5mg	Buffer	USP 23
Water for Injection (bulk)	qs to 1mL	qs to 1mL	qs to 1mL	qs to 1mL	Diluent	USP 23
Dehydrated Alcohol	qs (approx.	qs (approx.	qs (approx.	qs (approx	For dissolution of active	USP 23
Hydrochloride Acid (10%)	qs	qs	qs	qs	pH adjustment	NF18
Sodium Hydroxide (1M)	qs	qs	qs	qs	pH adjustment	NF18

A trace amount (% w/v) of dehydrated alcohol . was added to solubilize the drug. The sponsor indicated that alprostadil had been previously proven to be stable in solution (Prostin VR). Loss of the active ingredient (alprostadil) 1) during the manufacturing process and 2) due to adsorption to ampoule and to plastic syringe for administration was noticed, i.e., 12.6% (for µg/ ml), 8.8% (for µg, ml), 6.4% (for µg ml), and 4.7% (for µg ml), therefore, overages of 9.4% (for µg ml), 5.2% (for µg/ ml), and 3.5% (for µg/ ml) were used to compensate the above loss. A commercial batch will be liters which gives an expected yield of 1-ml units or 2-ml units.

Pilot lots of the to-be-marketed 5, 10, and 20 μg/1-ml formulations were used in the pivotal clinical trial No. **M-5650-0077**. Two ongoing clinical trials are currently underway, but the 40 μg/2-ml formulation has not been tested clinically as indicated by the sponsor. The clinically tested formulations and lot Nos. used are summarized in Attachment 2.

There were no PK studies conducted for Caverject Injection. The basic PK information is cross-referenced to NDA 20-379 (Caverject Sterile Powder). Upon request on 09/09/96 by the Agency, the sponsor submitted **1)** background PK information for alprostadil that was summarized from NDA 20-379 and **2)** the proposed PI for Caverject Injection.

Note: On 11/19/96, a discussion was held between this reviewer and the reviewing medical officer (Dr. Fourcroy) regarding baseline (endogenous) plasma PGE_1 levels of 96 pg/ml reported in both PI's of Caverject Injection and Caverject Sterile Powder. A recently published article reported baseline plasma PGE_1 level of 1.2-1.8 pg/ml which is about 60 times lower than that reported by Upjohn (96 pg/ml). Dr. Fourcroy indicated that maybe the analytical method used for measuring plasma PGE_1 levels should be reported in the PI. Please see Labeling Comment No.1 for details.

RECOMMENDATION:

NDA 20-755 that was submitted by Pharmacia-Upjohn on 07/26/96 for Caverject Injection (alprostadil aqueous injection) has been reviewed by OCPB/DPE II. OCPB/DPE II is of the opinion that the PK/Bio section of NDA 20-755 is acceptable from the biopharmaceutic perspectives. The following Labeling Comments as appropriate should be conveyed to the sponsor.

COMMENTS: (Need Not to be sent to the sponsor)

1. The to-be-marketed formulations (5, 10, and 20 μg/1 ml) were used in the pivotal clinical trial No. **M-5650-0077**, therefore, there are no bioequivalence issues need to be addressed.

2. As indicated by the sponsor, the 40 μg/2 ml formulation has not been tested in the pivotal clinical trial nor in the two ongoing clinical trials. Since the 40 μg/2 ml formulation is exactly the same as the 20 μg/1 ml formulation, the above issue is less of a concern. Therefore, a waiver for conducting a PK/Bio study for the 40 μg/2 ml formulation is granted.

3. Caverject Injection and Caverject Sterile powder (for Injection) share the same information on dosage and administration in their PIs and no differences in the PK of alprostadil are expected after the direct injection (into the acting site) of alprostadil "solution" prepared from either Caverject product. Therefore, the PK information on alprosdatil for Caverject Injection that is cross-referenced to NDA 20-379, Caverject Sterile powder (for Injection), is acceptable.

Since in vivo bioavailability (BA) or BE is considered to be self-evident for the above Caverject products, based on CFR 320.22(b)(1), a waiver of the requirement for the submission of evidence obtained in vivo demonstrsting BA or BE of the above drug products is granted.

LABELING COMMENTS: (Need to be sent to the sponsor) Sent T/E DATED 10/16/97

1. Under the in the Pharmacokinetics subsection of the Clinical Pharmacology section, it is stated that following intracavernosal injection of 20 μg alprostadil, mean peripheral plasma concentrations of alprostadil at 30 and 60 min after injection (89 and 102 pg/ml, respectively) were not significantly greater than baseline levels of endogenous alprostadil (96 pg/ml).

   The above pharmacokinetic (PK) information was obtained from an independent study (No. F-8495). The study was conducted in 1989 by Dr. Van Ahlen in Germany employing 12 patients with erectile dysfunction and a combined with a method for the assay of plasma PGE_1 levels was used. It is reported in this submission that the method is less sensitive due to a high degree of crossreactivity for the antibodies used. It is also reported in the submission that the best estimate of the circulating plasma level of endogenous PGE_1 in healthy volunteers is 2.6 $\pm$ 1.9 pg/ml. The above value (2.6 $\pm$ 1.9 pg/ml) is close to that reported in a recently published article, i.e., baseline levels of PGE_1 and its two metabolites, 15-keto-PGE_0, and PGE_0 levels being 1.2-1.8 pg/ml, 4.2-6.0 pg/ml, and 0.8-1.3 pg/ml, respectively (Cawello et al, Eur. J. Clin. Pharmacol. 1994; 46:275-277). The Cawello's study employed (1) 12 healthy male volunteers and (2) a GC/MS/MS method for assay.

   Therefore, it is recommended that the sponsor explain whether a fold difference in the reported baseline plasma PGE_1 levels in patients with erectile dysfunction (Study No. F-8495) and in healthy volunteers (literature) is due to the different assay methods used and/or due to an existing difference in baseline plasma PGE_1 levels between healthy volunteers and patients with erectile dysfunction.

2. It is recommended that at the end of paragraph of in the Pharmacokinetic subsection of the Clinical Pharmacology section, a sentence be added as follows:

   It is also recommended that the above sentence be added similarly to the package insert for Caverject Sterile powder.

3. According to the available in-house data, the PK parameters of PGE_1 and its metabolites, 15-keto-PGE_0, and PGE_0, changed substantially in the patients with

either renal or hepatic impairment. Therefore, it is recommended that under of the Pharmacokinetics in Special Population in the Pharmacokinetics subsection of Clinical Pharmacology Section, the second sentence be changed to be read as follows:

4. Under the section of Contradictions, the second paragraph should be read as follows:

11/21/96
Tien-Mien Chen, Ph.D.

Division of Pharmaceutical Evaluation II

RD initialed by Angelica Dorantes, Ph.D. 12/10/96

FT initialed by Angelica Dorantes, Ph.D. 12/16/96

cc: NDA 20-755, HFD-580 (Fourcroy, Rumble), HFD-870 (M.L. Chen, Dorantes, T.M. Chen), HFD-870 for C. Bott (Drug, Reviewer, Chron).