CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-212

PHARMACOLOGY REVIEW

NDA 21-212 11/9/00

Caverject DC

Pharmacology Team Leader Review

The toxicology data discussed in Dr. Davis-Bruno's review were summaries from the Pharmacia & Upjohn NDA for Caverject (alprostadil) and the Schwartz-Pharma NDA for Edex (alprostadil/alpha-cyclodextrin). Pharmacia & Upjohn performed sufficient toxicology studies to support the safety of PGE_1 for a chronic indication in their NDA for Caverject. The preclinical safety information for alpha-cyclodextrin is based on published scientific articles and disclosable approval information for the Edex NDA 20-649. Once an excipient (which has no patent or exclusivity protection) has been approved, the safety data are available to support safety for other sponsors and other indications. As such, any sponsor can use the inactive ingredient in their drug product without submitting supporting animal safety data. Thus, no new toxicity data are needed for Pharmacia & Upjohn's NDA for alprostadil/alpha-cyclodextrin.

Alex Jordan, PhD

NDA 21-212
HFD-580

JUL 1 9 2000

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

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cc:HFD580/Davis-Bruno/Jordan/Colangelo
Submission Date: 1/21/00
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NDA 21-212
Information to sponsor: Yes ( ) No (X)
SPONSOR: Pharmacia & Upjohn, Kalamazoo, MI
Manufacturer: Pharmacia & Upjohn, Kalamazoo, MI

DRUG:
Code Name: PNU-10136, U-10136
Generic Name: Alprostadil, PGE_1
Trade Name: Caverject DC (Dual Chamber Syringe)
Chemical Name: (11α, 13E, 15S)-11,15-dihydroxy-9-oxoprost-13-en-1-oic acid
CAS Registry Number:745-65-3
Molecular Formula/ Molecular Weight: 354.49, [redacted]
Structure:

PGE_1

Alpha-cyclodextrin

[redacted]

Relevant NDAs: 18-484 (Prostin VR), 20-379 (Caverject sterile powder), 20-649 (Edex), 20-700 (MUSE, intraurethral), 20-755 (Caverject Injection; aqueous)

Drug Class: vasodilator prostaglandin (eicosanoid)

Indication: erectile dysfunction due to neurogenic, vasculogenic, psychogenic or mixed etiology or as an adjunct to other diagnostic tests of erectile dysfunction

TABLE OF CONTENTS

Clinical formulation: lyophilized PGE_1 and alpha-cyclodextrin in one chamber of dual chamber syringe (disposable delivery device) with reconstitution vehicle (benzyl alcohol, water) in the other chamber. Formulated in a 10 or 20 μg concentration. Delivery device is designed to deliver a single dose in a volume of 0.5 ml, set at 25% increments such that: 2.5, 5, 7.5, 10 μg or 5, 10, 15, 20 μg.

Ingredient	Function	10 μg Concentration		20 μg Concentration	
		Reconstituted Solution/ml	Amount/ Syringe	Reconstituted Solution/ml	Amount/ Syringe
Alprostadil (PGE_1)	Active ingredient				
α-cyclodextrin	Stabilizer				
Lactose	Diluent, tonicity modifier				
Sodium citrate	pH				
HCl	pH				
NaOH	pH				
Benzyl alcohol	Stabilizer, dissociation enhancer, sterility				
Water	Solvent				

The inactive ingredient lists benzyl alcohol as an approved excipient at concentrations of 0.001-0.9% given in soft tissue.

Route of administration: intracavernosal

PROPOSED CLINICAL PROTOCOL OR USE: The majority of patients require doses of 5-20 μg. The Caverject DC recommended dosing is ≤ 3X/ week with at least 24h between doses. Patients requiring <2.5 or >20 μg should be treated with Caverject sterile powder. The maximum recommended dose of alprostadil is 60 μg/day.

PREVIOUS CLINICAL EXPERIENCE: Alpha-cyclodextrin is currently used in alprostadil alfadex (Viridal; Edex) for intracavernosal injection with a maximum exposure of alpha-cyclodextrin of 1.3 mg (22 μg/kg). The molar ratio of alprostadil:α-cyclodextrin in Viridal are the same as Caverject DC, although the dose volume is double and concentration is half that used in Caverject DC. The inclusion of the alpha-cyclodextrin reduces the amount of lactose and dry product, a prerequisite for developing the dual chamber delivery system and allowing for storage at ambient temperature. The binding constant for the molecular complexation reaction between alprostadil and alpha-cyclodextrin has been determined; with a 10 μg injection, ~ 97% alprostadil is free immediately after injection in the flaccid state and >99% is free with tumescence. The corresponding free amounts were 94% and 99% respectively for the 20 μg concentration product. The sponsor suggests that the actual free alprostadil would be higher because of competition with blood constituents and a reduced binding constant at 37° C compared to measurements taken in the study at 27°C.

A single phase III clinical study (98-DUAL-001) was conducted to compare the safety/efficacy of alprostadil (sterile powder) with the alprostadil/α-cyclodextrin formulation used in Caverject DC. This study did not evaluate the device. This trial was an open, baseline, retrospective comparative control study of 87 patients with erectile dysfunction. Each patient used alprostadil sterile powder (2.5-20 μg) 4 weeks prior to inclusion and received the same dose of alprostadil/α-cyclodextrin for 6 weeks at home. A total of 29 adverse events reported by 14%

of patients. The most common reported event was penis disorder. Penile pain, tension and prolonged erection were most frequently reported with 22 reports by 7% of patients. Two patients reported prolonged erection of ≤ 4 h. Two patients withdrew from the study due to penile pain or ketoacidosis (unrelated to drug).

DRUG HISTORY: PGE_1 combined with α-cyclodextrin was approved at 10 and 20 μg/ml. Complete pharmacology and toxicology evaluations were performed for NDA 20-379 (PGE_1 sterile powder), NDA 20-649 (PGE_1, α-cyclodextrin) and NDA 20-755 (PGE_1 aqueous).

PGE_1 (alprostadil) is marketed for use in neonates with heart defects to maintain patency of the ductus arteriosus (Prostin VR, Upjohn). PGE_1 (intracavernosal) has been approved for treatment of erectile dysfunction (Caverject NDA 20-379 Upjohn/Pharmacia). Schwarz Pharma markets Prostavasin (PGE_1, alpha-cyclodextrin) in some foreign markets for peripheral arterial occlusive disease.

PHARMACOLOGY: Caverject DC consists of alprostadil (PGE_1) in an alpha-cyclodextrin complex which improves the stability of the PGE_1. After reconstitution, the alprostadil immediately dissociates from the alpha-cyclodextrin complex. Alpha-cyclodextrin is considered pharmacologically inert.

Prostaglandins (eicosanoids) are long chain (20 carbon), unsaturated fatty acids, endogenously synthesized from essential and dietary fatty acids. The profile of endogenous prostaglandins and their activities are tissue dependent. PGE_1 and other monoenoic acids are derived from dihomo-gamma-linoleic acid (DHLA) whereas dienoic eicosanoids (PGE_2) are converted from arachidonic acid by prostaglandin synthetase present in most human tissues including the penis.

Drug Activity Related to Proposed Indication: Studies in animals and humans have established three crucial factors for erection: increased blood flow to the cavernous arteries, cavernous smooth muscle relaxation and venous outflow restriction. Smooth muscle in the arteriolar wall and the trabecula surrounding the sinusoids constitute the controlling mechanism for erection. Smooth muscle contraction is under neural control by the cavernous nerve. The pharmacologic activity of alprostadil in treatment of impotence is mediated by its relaxing effect on cavernosal smooth muscle.

Alprostadil stimulated penile erection has been studied in rat, rabbit primate and man. PGE1 mediates erection in rats after systemic administration of pharmacologic doses, this initially led to development of PGE1 for impotence. Intracavernosal injections produce erections in primates and man by dose dependent increases in penile blood flow.

Ancillary Pharmacology Studies: Alprostadil is a potent vasodilator in most vascular beds of animal and humans. Systemic blood pressure decreases in response to systemic alprostadil administration (≤10 μg/kg) and blood flow is increased in most organs. PGE_1 increases cardiac output and mediates the vascular effects of acute inflammation. Alprostadil is a potent inhibitor of platelet aggregation. Alprostadil enhances cholinergic responses. PGE_1 stimulates bicarbonate and mucous production in the stomach of laboratory animals and has gastric cytoprotective effects against many gastric irritants. Alprostadil can also increase intestinal motility and fluid secretion. Alprostadil produces dilation of bronchial smooth muscle, relaxation of the non-pregnant human uterus, and uterine contraction in pregnant women. α-cyclodextrin is considered pharmacologically inert.

PHARMACOKINETICS/TOXICOKINETICS: PGE_1 and α-cyclodextrin rapidly dissociate upon reconstitution.

Absorption: Intravenous alpha cyclodextrin disappears rapidly from circulation with a plasma half-life of [redacted] in rats.

Distribution: The rapid distribution of radioactivity after a single intracavernous injection of 650 µg of ^{14}C-alpha-cyclodextrin was demonstrated in cynomolgus monkeys (sampled at 1, 6, 24, 186 h post dose in urine and feces) with [redacted] of the dose in the penis at 1 h. The highest radioactivity was observed in the prostate, kidney and bladder consistent with the routes of excretion (NDA 20-649).

Metabolism: Intracavernous injection of alprostadil increased endogenous levels of PGE_1 from 0.8±0.6 pg/ml to 17.6±19.2 pg/ml within 5 minutes after injection in humans. Alprostadil concentrations returned to baseline within 2 h post injection. Peripheral levels of the major circulating metabolite, 15-keto-13,14-dihydro-PGE_1 increased from 12.9±11.8 pg/ml to 434±339 pg/ml after 10 minutes post injection. Levels returned to baseline within 2h and were not associated with significant changes in heart rate or blood pressure, consistent with a low incidence of serious adverse events. Metabolites have 10% of the pharmacologic activity of PGE_1. PGE_1 is rapidly and extensively metabolized (80-90%) after the first pass through the lungs, thereby limiting systemic effects. PGE_1 metabolism involves five enzymatic reactions: dehydrogenation of C-15 hydroxyl group, reduction of the 13,14 trans double bond, β-oxidation, ω-oxidation, reduction of the 9-oxo function.

PGE_1 in aqueous solution degrades to [redacted]. Administration of IV doses of [redacted] in rats or 500 µg/kg/day in dogs for 28 days was well tolerated, indicating a large safety margin for the degradation product [redacted] (NDA20-755).

Elimination: Urinary excretion of unchanged alpha-cyclodextrin predominates (86-91%) within 6 h of intracavernous dosing and is complete within 24 h in cynomolgus monkeys (NDA 20-649). Polar metabolites of PGE_1 are predominately excreted in the urine.

TOXICOLOGY: Rapid and complete dissociation of the alprostadil/alpha cyclodextrin complex after reconstitution (immediately before injection) combined with the established safety profile of alprostadil and alpha-cyclodextrin in animals and humans preclude the need for additional nonclinical studies with Caverject DC.

Alprostadil/alpha-cyclodextrin has been tested in standard toxicity studies including repeated dose parenteral studies in rats and dogs, intracavernous studies in monkeys (26 weeks), parenteral reprotoxicity and genotoxicity assays. Daily IP injections of alprostadil/alpha-cyclodextrin in rats for 26 weeks at doses up to 50 µg/kg/day (alpha cyclodextrin 1.6 mg/kg/day) reveals no systemic toxicity. In dogs the systemic NOEL after daily 2h IV infusion for 26 weeks was between 15 and 45 µg/kg/day of alprostadil (between 0.5-1.46 mg/kg/day alpha-cyclodextrin). At doses ≥45 µg/kg/day focal testicular atrophy is present. The toxicity of intracavernosal alprostadil/alpha cyclodextrin has been evaluated in a 26 week study in cynomolgus monkeys. The NOAEL is ≥40 µg/kg/day alprostadil which corresponds to 1.3 mg/day (0.22 mg/kg/day) of alpha cyclodextrin.

The target organ of toxicity for alpha-cyclodextrin is the kidney. In rats given an acute SC dose of 1000 mg/kg, renal lesions consisting of an increase in apical vacuoles in proximal convoluted tubules, giant lysosomes and lysosomal structures deformed by crystals containing cyclodextrin were observed.

CARCINOGENICITY: not performed

REPRODUCTIVE TOXICOLOGY: In male rats IP doses of 40 to 200 μg/kg/day of alprostadil/alpha-cyclodextrin (194 μg/kg/day) had no effect on fertility (male or female) or reproductive function. This represent 2 to 10 times the maximum recommended human dose of 40 μg of PGE1 on a body weight basis.

GENETIC TOXICOLOGY: No mutagenic potential of alprostadil/alpha cyclodextrin was indicated when tested in a standard battery of genetic toxicology tests which included: Ames bacterial mutagenicity, chromosome aberration (human lymphocytes, CHO) and *in vivo* mouse micronucleus.

SPECIAL TOXICOLOGY STUDIES: The 26-week intracavernosal monkey study (PGE_1, α-cyclodextrin) revealed penile effects only. Slight inflammation of the urethral mucosa and mucosa of the glans penis was observed in both treated and control monkeys and was considered secondary to the daily injections. Granulomatous inflammation was noted with increased incidence in PGE_1 treated animals (0% C, 30% LD, 60% MD, 30% HD) The inflammation was still present after an 8 week recovery period in the 40 μg (HD) group. Fibrosis was not observed in any monkey according to the sponsor (NDA 20-649).

OVERALL SUMMARY AND EVALUATION: The toxicologic data on cyclodextrins is mainly published literature on β cyclodextrin rather than α, although they are considered structurally related and have generally low toxicity. The threshold for parenteral renal toxicity of α-cyclodextrin has not been determined, although studies with repeated SC administration have demonstrated a NOAEL= 100 mg/kg. Cyclodextrins have been shown to be non-mutagenic, non-reprotoxic and do not affect tumor growth (suggests non-carcinogenic). The content of α-cyclodextrin in Caverject DC will provide a maximal exposure of 0.649 mg/day which is similar to other approved products which do not report significant adverse events.

Alprostadil is rapidly absorbed and metabolized resulting in a significant loss of activity within minutes in all species. Systemic effects are not expected to occur with intracavernous injection of PGE1 because of the rapid metabolism and excretion of metabolites. Alprostadil is non-irritating to penile tissue of monkeys at doses (40 μg) up to 3 times the maximum human intracavernosal dose of 60 μg based on body weight comparison.

Prostaglandins have known uterotonic and abortifacient properties and are contraindicated for use in women of childbearing potential. Doses up to 0.2 mg/kg/day do not adversely alter rat spermatogenesis, a 200X margin of safety for male reproductive function.

A standard genetic toxicology test battery does not reveal any mutagenic/clastogenic potential for alprostadil/alpha-cyclodextrin. Carcinogenicity studies have not been conducted with alprostadil since the short biological half life obviates the need for these studies.

The alprostadil/alpha-cyclodextrin formulation used in Caverject DC has been demonstrated to be safe in various nonclinical and clinical tests.

Labeling Review: The pharmacology/toxicology section of the label is acceptable.

RECOMMENDATIONS: Pharmacology recommends approval.

Reviewer/Team Leader Signature of Concurrence: SAG 1/5

SAG 1/5