CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-755

PHARMACOLOGY REVIEW(S)

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Div: Division of Reproductive & Urologic
Drug Products, HFD-580

Reviewer: Jeri El-Hage, Ph.D.

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Review of Pharmacology and Toxicology Data

Drug: Alprostadil Aqueous Injection, Caverject
Prostaglandin E_1 (PGE 1)

Sponsor: Pharmacia & Upjohn, Kalamazoo, MI 49001-0199

Chemical name: (11a, 13E, 15S)-11,15-dihydroxy-9-oxoprost-13-en-1-oic acid

Related INDs/NDAs: IND NDA 20-379 Caverject
NDA 18-484 Prostin VR

Formulation: 5, 10, 20 microgram/ml and mcg/ ml sodium citrate buffer (specifications for inactive ingredients were not provided in Pharmacology section).

Indication: Erectile Dysfunction

Background: This NDA is for a formulation change from a lyophilized powder to an aqueous solution. The dosage strengths are the same as those approved for NDA 20-379. Complete evaluation of the pharmacology and toxicology data was performed for NDA 20-379. A two week bridging toxicity study was performed to compare intra penile irritation with the new and old formulations. PGA 1 is a metabolic product of PGE1 stored in aqueous solution and data from several toxicity studies conducted with PGA1 were also provided. New toxicology data are reviewed below.

14-Day Intra penile Local Irritation Study in Cynomolgus Monkeys (Study 92-192, lot# 502AS)

The study was conducted according to GLP in the Safety Pharmacology Dept., Upjohn Co., Kalamazoo, MI. The study was conducted June 15-26, 1992 and was conducted to evaluate and compare the local tissue irritation effects of intra penile injections of PGE 1.

Adult male cynomolgous monkeys (n = 3/dose) were administered 3 ug PGE1 (20 ug/ml concentration) three times per week for 2 weeks as three formulations as follows:
1. Vehicle control -0 ug PGE1 in citrate buffer
2. Sterile, freeze-dried PGE1 powder in bacteriostatic water.
3. Frozen aqueous solution of PGE1 in citrate buffer.
4. Prostin VR pediatric solution diluted with % sodium chloride.

No treatment-related changes in body weights, organ weights, or gross necropsy were observed. Histologic examination was performed on penile tissue only.

Clinical signs- diarrhea was observed on 5/14 days in one monkey treated with PGE1 aqueous solution. A raised focus on the penis and subcutaneous bleeding were also observed once in one monkey in each PGE1 treated group.

Penile histology- Lesions in the penis occurred at a similar frequency and severity in control and PGE 1-treated monkeys. Mononuclear and polynuclear leukocyte infiltration was observed in the corpus cavernosum and corpus spongiosum of most monkeys and was thought to be a result of the injection procedure since it has also been observed in placebo and treated groups in previous intra penile toxicity studies.

Conclusion-Penile lesions observed in this study were minimal to mild in severity and were consistent with the observations in the long-term penile irritation studies with PGE1. The incidence and severity of penile lesions were comparable in vehicle and treated monkeys suggesting the findings were secondary to the injection procedure. PGE1 in the formulations tested displayed no evidence of local tissue irritative properties.

Toxicity Data for PGA 1

Acute Toxicity

Species/Strain	Route	LD 50, mg/kg	Results
Rat, SD n= 5 males/dose	iv	98	Deaths occurred within 2-30 min at doses ≥ 100 mg/kg. Prostration and rapid respiration with ≥ 63 mg/kg
Mouse, ICR n = 5/sex/dose	iv	22.5	Deaths between 2-30 min at doses ≥5 mg/kg. Prostration, rapid respiration, foam at mouth and nose at doses ≥ 5 mg/kg.

Five-Day Continuous Intravenous Toxicity of PGA1 (study 430/72/7263, lots 10178-FHL-60, 10446-FHL-125)

The study was conducted in 1972 by Upjohn (non-GLP). Sprague Dawley rats (n = 6/sex/group) were administered vehicle, 2 ug/kg/min PGA1 + 20 ug/kg/min dopamine HCl, or 4 ug/kg/min PGA1 + 40 ug/kg/min dopamine by continuous intravenous infusion for 5 days.

Mortality/Signs - none

Body weight - Modest body weight loss (5-15 gms) was observed in all groups except control females. The body weight loss was not significantly different between control and treated groups.

Food consumption/ clinical chemistry/urinalysis - not measured.

Hematology/Organ weights - unremarkable

Histopathology-
Lungs- mottled/congested 0/12 C, 3/12 LD, 1/12 HD
Pancreas - periarteritis (necrotizing arteritis) - 5/6 M, 4/6 F HD
Stomach- periarteritis 3/6 M, 4/6 F HD
Heart - Thrombus 1 LD M, 1 HD F

Summary and Conclusions- Continuous intravenous administration of the low dose levels of PGA1/dopamine were generally well-tolerated producing no mortality or clinical signs. Modest decreases in body weight were observed in most groups and were believed to be secondary to the stress of the chronic intravenous infusion procedure. Mottled/congested lungs were observed infrequently in treated rats (3 LD, 1 HD). Continuous administration of the high dose of 4 ug/kg/min PGA1 plus 40 ug/kg/min dopamine for five days produced necrotizing arteritis in the pancreas and stomach of 5/6 male and 4/6 female rats.

Subacute Intravenous Toxicity of PGA1 in the Rat (study 23.01-1/67; lot #8370-JMB-9X)
Sprague Dawley rats (n = 2/sex in controls and 4/sex in treated groups) were administered vehicle or 0.2 mg/kg PGA1 intravenously over 5 minutes 10 times per day for 28 days.
Mortality/signs- none

Body weight/food consumption- slight decrease in gain in males and slight increase in gain in females (statistics not performed). No changes in food consumption.

Hematology- modest increase (25%) in leukocyte counts in treated males. No effects on hematocrit, RBC, or other WBC.

Clinical chemistry/urinalysis - unremarkable (*** clinical chemistry data were not provided).

Organ weights -unremarkable

Histopathology- There were no drug-related histologic changes in the lungs, liver, kidney, heart or reproductive organs. The frequency of vacuolar degeneration of acinar cells was increased in the lacrimal glands of treated rats (1/4 C, 5/8 treated rats).

Conclusions- Administration of 2 mg/kg/day PGA1 (0.2 mg/kg as iv infusion 10 times per day) for 28 days was well-tolerated producing no deaths or clinical signs. No drug-related changes in hematology, organ weights or histopathology were observed.

Subacute Intravenous Toxicity of PGA1 in the Dog (study 7330-001, lot #8370-JMB-9X)

Beagle dogs (n = 1/sex for controls and 2/sex for treated) were administered 0 or 0.5 mg/kg PGA1 intravenously (0.1 mg/kg 5 times per day)for 28 days.

There was a statement that there were no drug-related mortality or signs. Data were not provided.

Body weight/food consumption- unremarkable

Hematology - unremarkable

Organ weights - unremarkable

Histopathology- unremarkable

Acute Intra-arterial Infusion Study in Dogs (study 71PT015)

Beagle dogs (n = 1/sex for controls, 2/sex for treated) were infused with 0.04 ml/kg/min PGA1 via the renal artery for 4 hours for a total dose of 480 ug/kg.
There was no mortality or signs. All dogs (controls and treated) lost weight. There were no drug-related changes in hematology, clinical chemistry, urinalysis, organ weights or histopathology.

OVERALL SUMMARY AND CONCLUSIONS

This NDA is for a new formulation of Caverject as an aqueous solution for injection. A two week intrapenile irritation study was conducted in monkeys to compare the irritant potential of the new aqueous solution with the approved product, Caverject sterile powder. The results of this two week bridging toxicity study suggest the irritant potential of the aqueous solution is comparable to the approved product. Complete preclinical safety testing for PGE1 was conducted for the original NDA 20-371 for Caverject.

PGE1 in aqueous solution degrades to PGA1. A specification of not more than 5% PGA1 present at product expiry has been established. This specification would result in administration of not more than 2 ug PGA1 (40 ug PGE1 x .05 = 2 ug PGA1). The sponsor submitted reports for several acute and subchronic toxicity studies conducted with PGA1 to establish the safety of the degradation product. Administration of intravenous doses of 200 ug/kg PGA1 in rats or 500 ug/kg/day PGA1 in dogs for 28 days were well-tolerated. These studies demonstrate a large margin of safety for the PGA1 degradation product.

LABELING

No changes in the pharmacology/toxicology section of the labeling are required.

7/17/97

Jeri El-Hage, Ph.D.

CC: NDA 20-755, HFD-580 NDA
HFD-580/ A Jordan/ T Rumble/ J El-Hage
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