CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-649

PHARMACOLOGY REVIEW(S)

October 4, 1996

NDA 20-649

DRUG: Alprostadil Alphadex (PGE_1·α-Cyclodextrin)

Sponsor: Schwarz Pharma, Inc.
Milwaukee, WI 53201

Recommendation: Based on the preclinical safety data, this new drug application for alprostadil alphadex (SPM691) is approvable. See page 10 for labeling revisions.

Jeni El-Hage 10/4/96

Jeni El-Hage, Ph.D.
Pharmacologist, HFD-580

A Jordan 10/8

cc: Original NDA 20-649
HFD-580 NDA, HFD-345
HFD-580/ A Jordan/ J El-Hage
20649.rev

Sponsor: Schwarz Pharma, Inc., Milwaukee, WI 53201

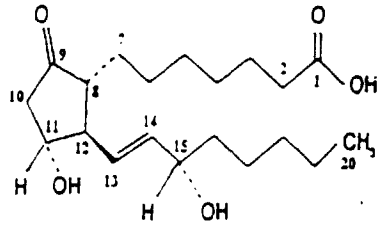
Submission Date: November 8, 1996

NDA REVIEW
EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

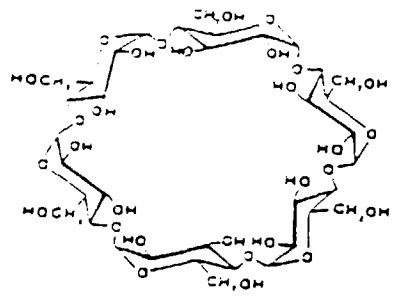
Drug: Alprostadil Alphadex, (Prostaglandin E_1-Alpha-cyclodextrin inclusion complex), SPM 691

Chemical Name: (1R,2R,3R)-3-Hydroxy-2-[(9E)-(3S)-3-hydroxy-1-octenyl]-5-oxocyclopentane heptanoic acid
CAS # 93591-00-5

Structure:



PGE_1



Alpha-cyclodextrin

Molecular Formula: $C_{20}H_{34}O_5$ (PGE_1) and $C_{36}H_{60}O_{30}$ (alpha-cyclodextrin)

Molecular weight: PGE_1 M.W. = 354.5; α-CD M.W. = 972.9

Formulation: 5, 10, 20 or 40 micrograms (ug) PGE_1 with alpha-cyclodextrin and lactose to be dissolved in 1 ml sterile water for injection.

Component	5 ug	10 ug	20 ug	40 ug
Alprostadil (ug)				
Alfadex (ug)				
Lactose Anhydrous NF (mg)				

Category: Vasodilator

Indication: Erectile Dysfunction (ED)

Related INDs/NDAs:
IND
IND
NDA 20-379 Upjohn/Pharmacia; PGE (intracavernosal) for erectile dysfunction
NDA 20-700 Vivus; PGE intra-urethral for erectile dysfunction

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STUDIES PREVIOUSLY REVIEWED

I. IND

* Studies with an Ono # were conducted by
Studies with an LPT # were conducted by the
Studies with an
HLD # were conducted by

II. IND

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III. Contents of NDA Review

PHARMACOLOGY

Prostaglandin E_1 (alprostadil) is one of the best characterized prostaglandins. PGE_1 is marketed for use in neonates with heart defects to maintain patency of the ductus arteriosus (Prostin VR; Upjohn). PGE_1 has also been approved for intracavernosal injection for the treatment of erectile dysfunction (Caverject NDA 20-379; Upjohn/Pharmacia). Schwarz Pharma markets Prostavasin (PGE_1-α-CD) in some countries for peripheral arterial occlusive disease (PAOD). Schwarz Pharma's NDA 20-546 for the indication of PAOD was not approved by the FDA due to inability to demonstrate clinical efficacy.

SPM 691 consists of alprostadil (PGE_1) in an α-cyclodextrin (α-CD) inclusion complex. The α-cyclodextrin inclusion complex improves the stability of the PGE_1. After reconstitution, the alprostadil immediately dissociates from the α-CD inclusion complex.

The prostaglandins (eicosanoids) are cyclic derivatives of certain unsaturated fatty acids having 20 carbon atoms. Alprostadil and the other monoeinoic acids are derived from dihomo-gamma-linoleic acid (DHLA), whereas dienoic eicosanoids (including PGE_2)are derived from arachidonic acid by interaction with prostaglandin synthetase in the tissues. In man, most tissues can synthesize alprostadil from DHLA. Prostaglandins act close to their site of biosynthesis and modulate the activity of nearby cells.

Pharmacodynamic effects related to the proposed indication are discussed below.

<u>In vitro Relaxation of Penile Erectile Muscle</u>

The relaxant effect of alprostadil on penile smooth muscle has been demonstrated in numerous in vitro studies. Relaxation of penile retractor muscle by alprostadil (2 to 300nM) has been demonstrated in tissue from the dog, cat, horse, ram and bull. In addition, relaxation of the corpus cavernosum urethra from macaque, rabbit, guinea pig, dog, cat and horse is produced in vitro by alprostadil within this concentration range (Acta Physiol Scand 100: 354, 1977). Preparations of human corpus cavernosum, corpus spongiosum and cavernous artery are also relaxed by alprostadil (J.Urol. 131:273, 1984).

<u>In vivo Intracavernosal Studies</u>

In vivo relaxant effects of alprostadil (5, 10 or 20 ug) on cavernous smooth muscle have been demonstrated in anesthetized pigtail monkeys. Intracavernous injections of 5, 10 or 20 ug PGE_1 produced a decrease in intracavernous pressure and an increase in intracavernosal blood flow. The return of intracavernosal pressures to pre-alprostadil levels was monitored as a indicator of alprostadil elimination. Intracavernosal

pressures returned to baseline values 13, 20 and 20 minutes after the 5, 10, and 15 ug PGE_1 dose, respectively. ((Int J Impotence Res 1: 211, 1989). Intracavernosal injection of alprostadil (1.25, 2.5, 5 ug) to cynomolgus monkeys (n =3) twice a week for 6 months resulted in penile elongation or tumescence following dosing (Eur Urol 20: 301, 1991).

Numerous clinical studies have established the efficacy of intracavernosal injection of alprostadil (2.5 -40 ug) in the treatment of male erectile dysfunction. Upjohn/Pharmacia has an approved NDA 20-379 for intracavernosal PGE_1 for use in erectile dysfunction. Doses of 10 to 20 ug of PGE_1 produce full erections in 70 to 80 % of men with erectile dysfunction.

Mechanism of Action

Relaxation of corporal smooth muscle is the key event in penile erection. In the non-erect penis, the corporal smooth muscle is in a state of tonic contraction maintained by underlying sympathetic tone. Cavernosal smooth muscle relaxation allows engorgement of the sinusoidal spaces while simultaneous arterial vascular smooth muscle relaxation results in increased penile arterial inflow. The penile veins between the sinusoids and tunica albuginea are compressed, retarding venous outflow from the corporal bodies. Penile tumescence progressing to a rigid erection results as inflow exceeds outflow in the penis. Alprostadil binds to PGE_1 receptors on smooth muscle modifies adenylyl cyclase activity and initiates a cascade of intracellular events that lead to vascular smooth muscle relaxation.

Other Pharmacologic Effects of PGE_1

Alprostadil is a potent vasodilator in most vascular beds of animals and man. Systemic blood pressure generally falls in response to systemic alprostadil administration and blood flow is increased to most organs. PGE_1 increases cardiac output. PGE_1 is also a mediator of the vascular symptoms of acute inflammation.

Alprostadil is a potent inhibitor of platelet aggregation. Alprostadil has been shown to stimulate bicarbonate and mucous production in the stomach of laboratory animals and can have 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 nonpregnant human uterus, and uterine contraction in pregnant women.
For further discussion of the general pharmacology of alprostadil see the original pharmacology review for IND 31,660 (appended).

PHARMACOKINETICS

Endogenous levels of alprostadil (PGE_1) are low in both mammalian tissues and plasma. Alprostadil is not biologically active after oral administration. Systemic absorption, distribution, metabolism and excretion(ADME) data for alprostadil in animals and man have been determined primarily after intravenous administration of alprostadil. Intravenous ADME data for the rat are reviewed under IND 31,660 (Review #1, appended). Systemically administered prostaglandins are rapidly metabolized in the lungs of most species including man (95% of administered dose metabolized during first pass through lungs).

PGE_1 and α-cyclodextrin rapidly dissociate upon reconstitution and the two moities exhibit their own specific pharmacokinetic characteristics. The main metabolite of PGE_1 in the serum of mice or rats after intravenous or intraperitoneal dosing is 13,14-dihydro-15-ketoPGE_1. No studies have been performed in animals to investigate the pharmacokinetics of PGE_1 or SPM 691 after intracavernous dosing in animals. The distribution of α-cyclodextrin after intracavernous dosing was studied in cynomolgus monkeys. The study is reviewed below.

The Tissue Distribution of Total Radioactivity in the Cynomolgus Monkey Following Intracavernous Administration of [^{14}C]-α-Cyclodextrin
(Study IRI 154346)

The study was conducted according to GLP at Inveresk Research International, Tranent, Scotland.

Male cynomolgus monkeys (n = 4) received a single intracavernosal injection of 650 ug ^{14}C-α-cyclodextrin. One animal was killed at 1, 6, 24, and 168 hours post dose and the tissue distribution of radioactivity was determined. (Tissues were combusted and radioactivity was measured by liquid scintillation counting). Levels of total radioactivity were also measured in urine and feces.

Radioactivity was excreted primarily in the urine (86-91%) for all monkeys. Radioactivity retained in the carcass ranged from 6% at 6 hours to 1% at 168 hours. Tissue levels of radioactivity are summarized in Table 2 on the next page.

1 Hour: 40% of radioactivity was recovered in the carcass and 16% in the excreta (Remainder of radioactivity presumed to be in urine which was not retained). Radioactivity was rapidly distributed with less that 0.1% of the dose recovered in the penis at 1 hour post dose. The highest levels of radioactivity were observed in the genitourinary tract (prostate > bladder, kidney > penis), consistent with the site of administration and route of excretion.

6 Hours: Highest tissue levels were present in the kidney and penis.

Tissue levels of total radioactivity continued to decrease at subsequent measurement times and were less than plasma levels in all tissues except the kidney and injection site.

TABLE 2

Tissue Levels of Total Radioactivity
Following Single Intracavernous Administration of [14C]-α-Cyclodextrin to Monkeys
Target Dose Level 650 μg per animal

Results expressed as μg equiv.g [1]

Tissue	Animal (Sacrifice Time)			
	1σ (1 h)	2σ (6 h)	3σ (24 h)	4σ (168 h)
CARCASS	0.081	0.011	0.003	0.002
ADRENALS	0.092	0.024	0.010	0.006
BLADDER	0.883	0.029	0.007	0.004
BONE MARR	0.055	0.014	0.008	0.002
BONE MIN	0.009	0.002	0.002	*0.000
BRAIN	0.025	0.012	0.004	0.003
EPIDIDYMUS	0.138	0.015	0.006	0.002
EYE 1	0.027	0.006	0.002	0.001
EYE 2	0.028	0.005	0.001	0.001
FAT WHITE	0.749	0.009	0.003	0.004
GALL BLADD	0.099	0.021	0.008	0.003
HEART	0.072	0.019	0.004	0.002
KIDNEYS	0.732	0.312	0.203	0.071
LIVER	0.078	0.020	0.016	0.007
LUNGS	0.128	0.017	0.005	0.003
LYMPH NES	0.229	0.020	0.013	0.012
MUSCLE	0.037	0.005	0.007	0.001
PANCREAS	0.056	0.014	0.004	0.003
PITUITARY	0.065	0.030	0.016	0.003
PLASMA	0.262	0.016	0.003	0.002
PENIS	0.377	0.127	0.050	0.046
PROSTATE	1.170	0.044	0.005	0.002
SALIV GLAN	0.065	0.021	0.007	0.003
SKIN	0.179	0.014	0.006	0.005
SPINAL COR	0.018	0.008	0.003	0.002
SPLEEN	0.057	0.017	0.012	0.005
TESTES	0.065	0.016	0.007	0.004
THYMUS	0.052	0.015	0.008	0.005
THYROID	0.044	0.008	0.002	0.004
TONGUE	0.119	0.025	0.008	0.003
WH BLOOD	0.152	0.010	0.002	0.001

[1] C03
* = Mean includes results calculated from data less than 30 d.p.m.

Conclusion: Radioactivity was rapidly distributed after intracavernosal dosing with less than 1.1% of the dose present in the penis one hour after dosing. The highest levels of radioactivity at each time point were observed in the genitourinary tract (prostate, kidney, bladder) consistent with the routes of elimination and excretion. Radioactivity was excreted almost exclusively in the urine (86-91% by 6 hrs post dose).

TOXICOLOGIC EFFECTS

The majority of the toxicology studies were performed to support the safety of systemic use of PGE_1 for peripheral arterial occlusive disease. Small, short-lived increases in PGE_1 and α-cyclodextrin are observed after intracavernosal administration of the low dose levels of SPM 691 utilized for impotence, therefore, no systemic toxicity would be expected . No systemic toxicity has been observed in the monkey intracavernosal toxicity studies with PGE_1 alone or PGE_1-α-CD. Toxic effects observed in the multidose systemic toxicity studies are summarized in Appendix I, pages 49-53.

Intracavernosal Toxicity

The effects of repeated intracavernosal administration of SPM 691 (PGE_1-αCD) were assessed in 14-Day and 26-Week studies in cynomolgus monkeys. See Appendix II for the complete reviews of these studies.

In the 14-day study, male monkeys (n = 2/dose) were administered 20, 40 and 80 ug SPM 691 daily for 14 days. There were no clinical signs or changes in body weight, food consumption or organ weights indicative of systemic toxicity. Histopathologic evaluation of the penis revealed inflammatory reactions in the cavernous body and subcutis and minimal inflammation of the urethra in all animals. Since there was no control group (vehicle or α-CD), it is impossible to determine if these observations were due to drug or simply the daily injection procedure. Mild inflammation and fibrosis have been observed with comparable frequency in control and treated monkeys secondary to the injection procedure in other monkey intrapenile toxicity studies.

In the 26-Week intracavernous toxicity study, male monkeys (n =6/dose) were administered 0, 20, and 40 ug PGE_1 (as the α-CD inclusion complex) daily for 6 months. Four animals per dose were killed after 26 weeks, 2/dose were killed after an 8 week recovery period. There were no drug-related signs, or effects on body weight, blood pressure, hematology, clinical chemistry, urinalysis or organ weights. A complete histologic evaluation was performed on all animals. There were no drug-related gross or microscopic findings except in the penis. Slight inflammation of the urethral mucosa and mucosa of the glans penis were observed in all monkeys including controls and was believed to be secondary to the daily injection procedure. Granulomatous inflammation was observed with increased incidence in PGE_1-treated monkeys (0% C, 30% LD, 60% MD, 30 % HD). The inflammation was still present in monkeys treated with 40 ug after the 8 week recovery period. No fibrosis was observed in any monkey. The results of this study with SPM 691 are not significantly different from those obtained in monkeys treated for 6 months or one year with PGE_1 alone, despite dosing only 3 times per week in Upjohn's toxicity studies.

The results from the monkey studies support the safety of SPM 691 for

human use since no significant pathology was observed despite frequent administration in the toxicity study (daily vs typical once per week use in impotent men). In addition, human experience in over 10,000 subjects supports the safety of intracavernosal administration of PGE_1 in impotent men.

Genotoxicity

PGE_1·α-cyclodextrin was tested in 3 in vitro and one in vivo genotoxicity assays. SPM 691 was not mutagenic in the Ames test or the in vivo rat micronucleus test. SPM 691 was not clastogenic in chromosome aberration assays conducted with human peripheral lymphocytes or Chinese hamster ovary cells.

Reproductive Toxicity

Two Segment I fertility and reproductive performance studies were conducted. These studies Ono 81/13 and LPT 5021/1/88 are reviewed under IND 31,660 (Appendix I). In study 81/13 two experiments were performed as follows:

I- females were treated with 0, 2, 20 and 200 ug PGE_1-αCD/kg/day,ip for 2 weeks prior to mating, during the mating period , and during the first seven days of gestation and mated with untreated males.

II- males were treated for 60 days prior to and during mating with 0, 2, 20 and 200 ug SPM-691/kg/day, ip and mated with untreated females.

In experiment I, female rats in the highest dose group of 200 ug/kg/day had significant decreases in the number of implantation sites ad the number of live fetuses. There were no other drug-related effects. In experiment II, doses of SPM 691 up to 200 ug/kg/day (6 ug/kg/day PGE_1) had no effects on male fertility or reproductive performance. In addition, no histologic changes were observed in the testes or epididymes of SPM 691 treated rats.

In the fertility and reproductive performance study conducted by LPT (#5021/1/88), female rats were treated with 0, 40, 400 and 4000 ug/kg/day SPM 691, iv for 2 weeks prior to and during mating, gestation and lactation. Females were mated with untreated males. Females administered the high dose of 4000 ug SPM 691/kg, iv (120 ug PGE_1) had decreased body weight gain (11-13%), an increased rate of resorptions (13.5%), and decreased fetal birth weights (13%). As a result of the increased resorption rate, there was also a decrease in the number of live fetuses in the litters of HD dams. Drug treatment had no effect on the fertility, gestation, viability, or lactation indices.

Teratology studies were performed in rats and rabbits (see Appendix I for complete reviews . In the rat teratology study, dose levels of 0.02, 0.2, 2 and 5 mg kg day, iv were administered on gestation days 7

through 17 (Note: SPM 691 is only 3% PGE_1, therefore, dose levels of PGE_1 were 0.6, 6, 60 and 150 ug/kg/day). The highest dose of 5 mg/kg SPM 691 decreased maternal weights and food consumption (11-12%) and decreased fetal weights. SPM 691 was not teratogenic in rats.

In the rabbit teratology study, dose levels of 0.02, 0.2, 2 and 5 mg/kg/day SPM 691, iv were administered on gestation days 6 through 18. (Again dose levels of PGE_1 were 0.6, 6, 60 and 150 ug/kg/day). Drug treatment had no effect on the number of corpora lutea or implantations but the highest dose of 5 mg/kg produced a 2-fold increase in fetal mortality. There were no drug-related effects on the rate of visceral or skeletal malformations. SPM 691 at dose levels up to 5 mg/kg (150 ug/kg PGE_1)was not teratogenic in rabbits.

In the peri- and postnatal toxicity study, female rats were treated with 0.02, 0.2, 2 and 5 mg/kg/day SPM 691, iv from day 17 of gestation through day 20 of lactation. Body weight and food consumption were reduced in dams receiving the two highest dose levels. The index of live pups was slightly reduced in the litters of high dose dams. There were no significant effects on the behavior, growth, fertility or reproductive function in the F_1 offspring of SPM-treated females rats.

LABELING REVIEW

The current labeling misrepresents the exposure comparisons between the dose levels utilized in the rodent Segment I studies and exposures with therapeutic dose levels. The labeling should be revised as follows:

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies have not been conducted. SPM 691 showed no evidence of mutagenicity in three in vitro assays including the Ames bacterial reverse mutation assay, Chinese hamster ovary forward gene mutation assay, and a chromosome aberrations assay in Chines hamster lung (V79) cells. SPM 691 did not produce damage to chromosomes or the mitotic apparatus in the in vivo rat micronucleus test.

SPM 691 did not cause any adverse effects on fertility or general reproductive performance when administered intra peritoneally to male or female rats at dose levels from 40 to 200 mcg/kg/day (2 to 10 times the maximum recommended human dose of 40 mcg PGE on a body weight basis.

The following comment should be communicated to the sponsor to support the revision of the exposure comparisons -

The high dose of 200 ug SPM 691 as may contains 11 PGE equivalent to a

6 mcg/kg/day dose of PGE_1. The maximum recommended human dose(MRHD) contains 40 mcg of PGE_1 or approximately 0.6 mcg/kg/day (MRHD is 40 mcg and the calculation assumes a mean human body weight of 60 kg). Therefore, the high dose of 200 ug SPM 691/kg/day (6 ug ~~PGE1~~) is about ~~10 times~~ the maximum human dose on a body weight basis.

[illegible] 200 ug SPM691 refers to the Concentration of the active ingredient PGE and not the PGE-cyclodextrin complex. Therefore, the exposure multiples expressed by the sponsor in the labeling are correct.

CE
1/5/1997