CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-649

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JUN -9 1997

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

Division of Pharmaceutical Evaluation II

NDA 20-649
Amendment (Serial No. 028)

SUBMISSION DATE: June 4, 1997

EDEX (Alprostadil for Injection)
Schwarz Pharma
Milwaukee, WI

REVIEWER: Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: Revised Labeling

Code: 3S

SYNOPSIS

EDEX (alprostadil for injection) indicated for the treatment of erectile dysfunction was approved by the Agency on November 8, 1996. In the action letter several comments and requests for additional information were communicated to the sponsor. On June 4, 1997, the sponsor submitted an Amendment (Serial No. 028) to NDA 20-649 for EDEX which includes Chemistry, Manufacturing and Controls data and a revised version of the Labeling.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed the Amendment (Serial No. 028) to NDA 20-649 which was submitted by Schwarz Pharma on June 4, 1997 for EDEX. OCPB/DPEII recommends that the following changes be incorporated in the revised version of EDEX's labeling dated June 6, 1997.

1. The "*Drug-Drug Interactions*" subsection included in the "***Pharmacokinetics***" section of the labeling be modified as follows:

JAN 7 1997

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

Division of Pharmaceutical Evaluation II

NDA 20-649 **SUBMISSION DATE:** December 17, 1996
Amendment (Serial No. 022)

EDEX (Alprostadil for Injection)
Schwarz Pharma
Milwaukee, WI **REVIEWER:** Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: Sponsor's Response **Code: 3S**

SYNOPSIS

EDEX (alprostadil for injection) indicated for the treatment of erectile dysfunction was approved by the Agency on November 8, 1996 In the action letter several comments and requests for additional information were communicated to the sponsor. On December 17, 1996, the sponsor submitted an Amendment (Serial No. 022) to NDA 20-649 for EDEX which includes their responses to the aforementioned comments regarding Biopharmaceutics Chemistry, Manufacturing and Controls, and Labeling

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed the Amendment (Serial No. 022) to NDA 20-649 which was submitted by Schwarz Pharma on December 17, 1996 for EDEX. OCPB/DPEII is of the opinion that the sponsor's response to the Agency's comment included in the "Biopharmaceutics" section of the action letter and the proposed revised labeling dated December 3, 1996, are appropriate and acceptable.

With respect to the Chemistry, Manufacturing and Controls information included in this Amendment, it should be directed to the reviewing chemist of HFD-580 for review.

Please convey the Recommendation as appropriate to the sponsor.

NOTE: Attachments I to III are being retained in OCPB and may be obtained under request.

Dorantes 1/6/97
Angelica Dorantes, Ph.D.
Pharmacokinetic Evaluation Branch II

RD Initialed by John Hunt. JPH 1/2/97
FT Initialed by John Hunt. 1/7/97

cc: NDA 20-649 HFD-580 (Fourcroy, Rumble), HFD-870 (Mei-Ling Chen, Dorantes, and C. Bott [for Drug]).

OCT 17 1996

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-649

Alprostadil (Prostaglandin E_1) for injection 5, 10, 20, and 40 μg/vial

BRAND NAME: Edex

SUBMISSION DATES:
11/07/95 (Amendment No. 000)
04/29/96 (Amendment No. 000BZ)
05/13/96 (Amendment No. 000BB)
06/19/96 (Amendment No. 010)
07/12/96 (Amendment No. 000BI)
09/16/96 (Amendment No. 014)
10/02/96 (Facsimile)
10/14/96 (Amendment No. 019)

SPONSOR: Schwarz Pharma

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: Original New Drug Application

Code: 3S

TITLE: "Review of Human Pharmacokinetic and Bioavailability Studies For Alprostadil"

SYNOPSIS:

On 11/07/95, Schwarz Pharma submitted NDA 20-649 to the Agency for Edex (alprostadil for Injection). It is a sterile, pyrogen-free, lyophilized powder for intracavernosal (IC) administration after reconstitution with 1 ml of sterile isotonic saline. It is supplied in a single-dose vial containing either 5, 10, 20 or 40 μg of alprostadil in an alfadex (α-cyclodextrin) inclusion complex (a clathrate complex).

Alprostadil is also known as prostaglandin E_1 (PGE_1), an endogenous substance which is a potent smooth muscle relaxant. By IC injection, it is to be indicated for 1) the diagnosis of male erectile dysfunction (ED) regardless of origin and 2) the treatment of ED. The dose range to be used is 1-40 μg. The dose should be individualized for each patient by careful titration under supervision by a physician. The recommended frequency of injection is no more than 3 times weekly, with at least 24 hr between each dose. For more information, please see the package insert (PI) for details.

Submitted to the human pharmacokinetic (PK)/ Bioavailability (Bio) section of this NDA were one analytical study for the new method used to determine plasma levels of PGE_1 and its two major metabolites, PGE_0 (13,14-dihydro-PGE) and 15-keto-PGE_0, and eleven PK studies that were all conducted in Germany using alprostadil-α-cyclodextrin complex. Only one of the 3 PK studies conducted for IC injection was considered to be pivotal (study No. PHAKI-848) in which 1) patients with ED were employed, 2) a single dose of 20 μg alprostadil was investigated in a crossover study for IC injection and 30-min intravenous (IV) infusion, 3) plasma levels of PGE_1 and its two major metabolites were analyzed.

Studies conducted in healthy volunteers following IV infusion were; one dose proportionality (30-120 μg alprostadil), two single-dose PK studies, and 4 Drug-Drug (D-D) interaction studies for concomitant administration of digoxin, glibenclamide, warfarin, and acetylsalicylic acid. The above IV infusion studies were cross-referenced to NDA 20-546 (Vasoprost®; 60 μg alprostadil by IV injection for treating severe peripheral arterial occlusive disease) and they were previously reviewed and found acceptable by OCPB/DPE II on 10/05/95. A new D-D study was conducted for heparin, but plasma levels of PGE_1 and its metabolites were not measured. On 05/13/96, submitted further were **1)** two pivotal studies for alprostadil PK in hepatically and renally impaired subjects after a 2-hr IV infusion of 120 μg alprostadil and **2)** two supportive PK studies for [^{14}C]-α-cyclodextrin in healthy volunteers.

The compositions of the clinically tested alprostadil formulation (in ampoule) is the same as the to-be-marketed one (in vial) for IC injection. Therefore, there are no bioequivalence or dissolution issues. Furthermore, since the four to-be-marketed strengths are compositionally the same but not proportionally similar, no issues are expected on alprostadil's bioavailability after reconstitution and/or after IC injection of the other three strengths (5, 10, and 40 μg/vial).

Based on baseline-corrected systemic PGE_1 plasma data, **1)** mean total body clearance (CL_T) of PGE_1 was calculated to be 115 l/min and **2)** the mean absolute bioavailability (F_{abs}) for IC injection was estimated to be 98 % as compared to an IV infusion. The large CL_T value which exceeded the cardiac output is consistent with the report that PGE_1 is rapidly and extensively metabolized mainly in the lungs (63-87%). Dose proportionality between 30 to 120 μg of PGE_1 was previously demonstrated after IV infusion.

Additional information on PGE_1 was summarized from literature, **1)** the protein binding for alprostadil is 92.6% (81.4% for albumin), **2)** in human, PGE_0 and 15-keto-PGE_0 are two major metabolites found in plasma and in urine, **3)** mean terminal half-life ($T_{1/2}$) of PGE_1 is around 8 min post 2-hr IV infusion, and **4)** by using animal isolated organs, metabolite PGE_0 was found to possess comparable biological activity as that of PGE_1 while metabolite 15-keto-PGE_0 possessed no significant activity.

No significant D-D interactions were reported previously for alprostadil with digoxin, glibenclamide, warfarin, or acetylsalicylic acid, but a significant effect of alprostadil on heparin in prolonging the thrombin time was observed. Furthermore, significant differences in PK parameters were observed in hepatically or renally impaired subjects for PGE_1, 15-keto-PGE_0 and PGE_0 as compared to those in healthy volunteers. However, these significant differences in the PK of PGE_1 and those for its metabolites did not correlate with subjects' plasma albumin binding nor could be rationalized kinetically by their hepatic or renal function. The mechanism(s) responsible for the observed discrepancies in the renal and hepatic studies is not known. Therefore, the reviewing medical officer should be aware of the significant changes in **1)** alprostadil PK in patients with ED who have hepatic or renal impairment or **2)** thrombin time in patients with ED whom are also under heparin acute and/or chronic treatment.

Previously, alprostadil-α-cyclodextrin complex has been shown to dissociate near completely once after IC injection of alfadex. The results of the newly submitted PK studies using radiolabeled [^{14}C]-α-cyclodextrin (without alprostadil) showed that 1) plasma radioactivity up to 6 hr postdose corresponded to unchanged component, 2) mean $T_{1/2}$ of radioactivity calculated from plasma data was around 2.2 to 2.5 hr, 3) elimination of radioactivity was rapid and complete with a mean 24-hr urinary recovery of around 81-83%, and 4) no significant changes in PK of radioactivity were observed after repeated IV infusion for 7 days.

Finally, the new analytical method (GC/MS/MS) used in the newly conducted studies and its validation report were reviewed and found acceptable. No dose proportionality nor multiple dose studies for alprostadil after IC injection were conducted. The influence of age on the PK of alprostadil was not analyzed nor was modeling and/or analyses of a pharmacokinetic/pharmacodynamic (PK/PD) relationship for alprostadil submitted. Alprostadil is not intended for female or pediatric population according to the proposed labeling of this NDA.

RECOMMENDATION:

NDA 20-649 that was submitted by Schwarz Pharma on 11/07/95 has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II). OCPB/DPE II is of the opinion that the sponsor has provided appropriate PK/Bio information to satisfy the clinical pharmacology and biopharmaceutic requirements and this NDA is acceptable.

Please convey General Comment No. 4 (page 19) and Labeling Comments (pages 19-23) as appropriate to the sponsor.

Tien-Mien Chen

09/10/96

Tien-Mien Chen, Ph.D.
Division of Pharmaceutical Evaluation II

CPB Briefing on 09/26/96 [Drs. M.L. Chen, A. Dorantes, N. Fleischer, J. Fourcroy (MO), S.M. Huang, M. Mehta, and J. Strong.]

RD initialed by Angelica Dorantes, Ph.D. AD 09/17/96

FT initialed by Angelica Dorantes, Ph.D. Dorantes 10/8/96

cc: NDA 20-649, HFD-580 (Fourcroy, Rumble), HFD-870 (M.L. Chen, A. Dorantes, T.M. Chen), HFD-850 for C. Bott (Drug, Reviewer, Chron), HFD-340 (Viswanathan).

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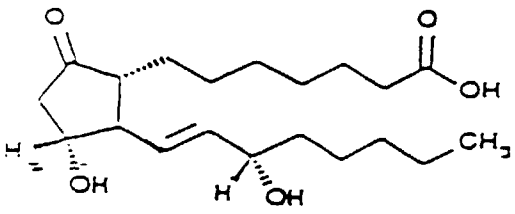
The above Appendices are being retained in OCPB/DPE II and can be obtained upon request. In addition, the raw data of the above PK studies reviewed are available in ASCII format on diskettes and they are also being retained in OCPB/DPE II and can be obtained upon request.

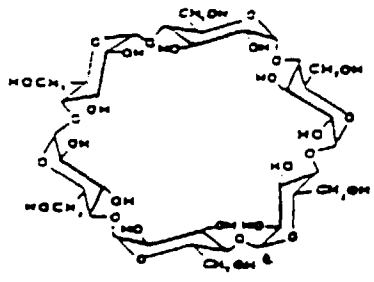
I. BACKGROUND:

The chemical structures for alprostadil and α-Cyclodextrin are shown below:

Alprostadil (MW. 354.49)



α-Cyclodextrin (MW. 972.85)



For physical and chemical properties of alprostadil and alprostadil-α-cyclodextrin complex, please see bioreview for NDA 20-546 dated 10/05/95 for details.

II. SUMMARY OF PHARMACOKINETICS, BIOEQUIVALENCE, PHARMACODYNAMICS, ETC.:

For the PK studies submitted under this NDA, please see study summary in Table 1 for details.

Table 1

Study #	Study Design	Subjects	Age (Range)	Dosing Regimen
#2 (PHAKI-848)[a] Bioavailability PK Study	open-label, randomized, crossover	patients with ED (n = 24)	38-64	20 μg PGE, by 30min IV infusion 20 μg PGE, by IC injection
#3 (F-8495)[b] Pilot PK Study	open-label, crossover	patients with ED (n = 12)	23-61	20 μg PGE, + 80 mg papaverine and 3 mg phentolamine by IC injection 20 μg PGE, by IC injection
#4 (PHAKI- 847)[c] Pilot PK Study	Multicenter, open-label	patients with ED (n = 19)	26-65	20 μg PGE, by IC injection
#5 (PHAKI-725)[b] Infusion PK Study	single-blind, placebo-controlled, randomized, crossover	healthy volunteers (n = 13)	18-36	placebo (8 days) 60 μg PGE, by IV infusion (Day 9)
#6 (PHAKI- 729)[b] IV Dose Proportion-ality Study	controlled, randomized, crossover	healthy volunteers (n = 12)	20-35	30 μg PGE_1, 60 μg PGE1, or 120 μg PGE, by IV infusion
#7 (PHAKI-829)[c] Infusion PK Study	open-label, randomized, 4-way, crossover, pilot	healthy volunteers (n = 6)	21-38	IV infusion: 120 μg PGE, over 15 min, 30 min, 40 μg PGE, over 5 min, or 120 μg PGE, in buffered lipid emulsion over 15 min
#8 (PHAKI-824)[b] D-D Interaction Study	open-label, crossover	healthy volunteers (n = 12)	20-39	Day 1: 0.25 mg digoxin q8hr; Days 2-9: 0.25 mg digoxin qd Day 9: 90 μg PGE, by 3-hr IV infusion + 0.25 mg digoxin 15 min after infusion
#9 (PHAKI-825R)[b] D-D Interaction Study	open-label, randomized, crossover	subjects with diabetes mellitus (8M + 4F)	53-72	Days 1-4:1-3 tablets of 3.5 mg glibenclamide Day 5: 90 μg PGE, by 3-hr infusion + 1-3 tablets of 3.5 mg glibenclamide 15 min after infusion
#10 (PHAKI-826)[c] D-D Interaction Study	open-label, randomized, crossover	healthy volunteers (n = 12)	22-40	heparin 5,000 IU by IV bolus 90 μg PGE, by 3-hr infusion + heparin 5,000 IU by IV bolus 30 min after infusion

#11 (PHAKI-827)[b] D-D Interaction Study	open-label, crossover	healthy volunteers (n = 24)	20-40	Day 1: 50 mg warfarin p.o. Day 2: 90 μg PGE, by 3-hr infusion + 50 mg warfarin p.o. at beginning of infusion
#12 (PHAKI-828)[b] D-D Interaction Study	open-label, randomized, 3-way crossover	healthy volunteers (n = 12)	23-38	1.0 g acetylsalicylic acid (ASA) p.o. 90 μg PGE, by 3-hr infusion 1.0 g ASA p.o. + 90 μg PGE, by 3-hr infusion
#13 (PHAKI-830)[a] PK Study in Special population	open-label, single-dose	healthy volunteers (n = 12) subjects with hepatic impairment (n = 12)	46-74 39-71	120 μg PGE, by 2-hr infusion
#14 (PHAKI-841)[a] PK Study in Special population	open-label, single-dose	healthy volunteers (n = 12) subjects with renal impairment (n = 12)	18-64 22-54	120 μg PGE, by 2-hr infusion
#15 (PHAKI-941)[c] PK Study for α-cyclodextrin	open-label, 2-way crossover	healthy volunteers (n = 4)	31-40	0.33 mg [^{14}C]-α-cyclodextrin by IV bolus or 2-hr infusion
#16 (PHAKI-942)[c] PK Study for α-cyclodextrin	open-label, multiple-dose	healthy volunteers (n = 4)	30-43	Days 1 and 7: 0.65-0.68 mg [^{14}C]-α-cyclodextrin by 2-hr IV infusion Days 2-6: non-labeled α-cyclodextrin by 2-hr IV infusion

[a]. Pivotal studies (bolded).
[b]. Previously reviewed and referenced to NDA 20-546.
[c]. Supportive or non-pivotal studies.

1. PHARMACOKINETICS:

A. **Alprostadil:**

Baseline or endogenous levels of PGE_1, 15-keto-PGE_0, and PGE_0 were reported to be around 1.2 -1.8 pg/ml, 4.2-6.0 pg/ml, and 0.8-1.3 pg/ml, respectively and the mean $T_{1/2}$ for PGE_1 was 8.3 ±6.3 min (Cawello et al, Eur. J. Clin. Pharmacol. 1994; 46: 275-277). A single dose of 20 μg alprostadil was studied in the pivotal study (Study #2). Mean PK parameters obtained from baseline-corrected plasma levels of PGE_1 and its metabolites, 15-keto-PGE_0, and PGE_0 are summarized in Table 2 and their mean plasma levels are shown in Figure 1.

Table 2

PGE_1

Basuline-corrected[a]	IV[*]	IC[*]
C_{max} (pg/ml)	7.1(±3.1)[b]	16.8 (±18.9)
T_{max} (min)	25.5 (±4.8)	4.8 (±3.3)
AUC[c] (pg-min/ml)	174 (±101)	171 (±115)

15-keto-PGE_0

Baseline-corrected	IV	IC
C_{max} (pg/ml)	471 (±88)	421 (±337)
T_{max} (min)	29.9 (±1.2)	9.7 (±7.7)
AUC (pg-min/ml)	13705 (±2559)	10500 (±4101)
$T_{1/2}$ (min)	15.6 (±5.6)	40.9 (±16.5)

PGE_0

Baseline-corrected	IV	IC
C_{max} (pg/ml)	7.1 (±2.2)	3.9 (±2.3)
T_{max} (min)	32.2 (±2.4)	20.3 (±12.6)
AUC (pg-min/ml)	380. (±115)	251 (±134)
$T_{1/2}$ (min)	39.8 (±26.3)	63.2 (±31.1; n=17)

*. No terminal T1/2 was obtained.

a. Postdose minus predose (baseline) plasma levels for each individual.

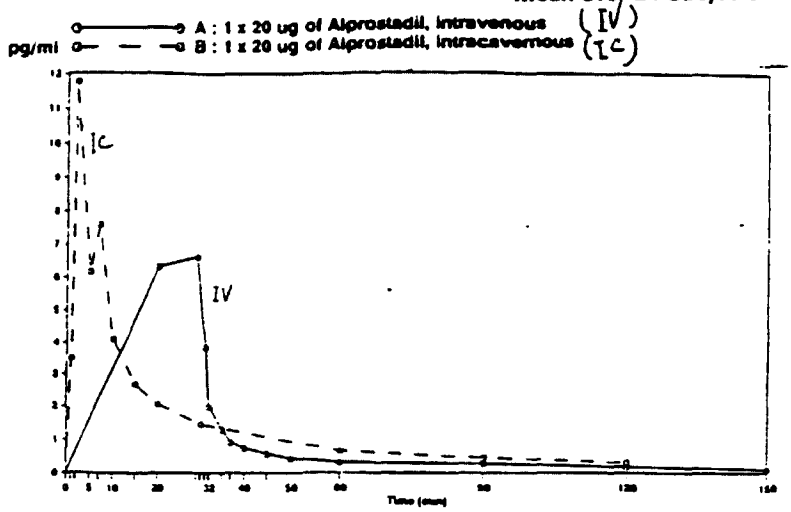
b. Mean (± standard deviation, SD).

c. $AUC_{0\text{-}150}$ and $AUC_{0\text{-}120}$ for IV and IC, respectively.

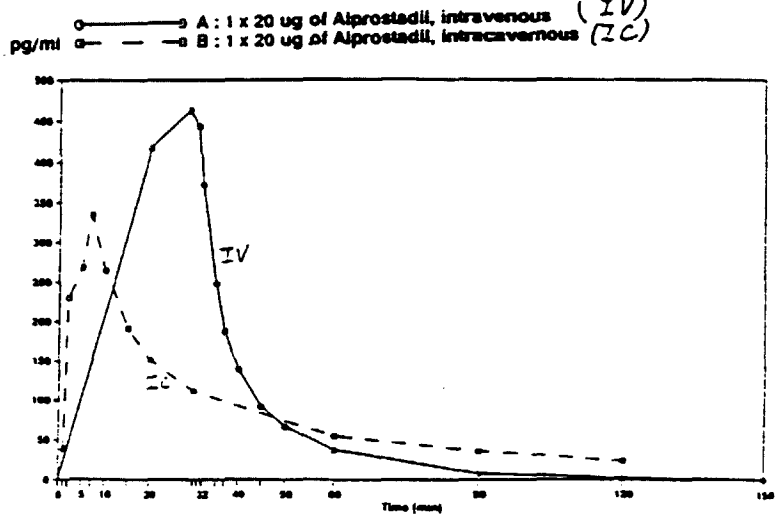
Based on the IV dose, 1) mean F_{abs} value for alprostadil after IC injection was calculated to be around 98% and 2) the mean CL_T value of alprostadil was estimated to be around 115 l/min which is much greater than cardiac output indicating a rapid and extensive pulmonary clearance for this drug. The above results are consistent with 1) the reported value (=104 to 135 l/min; Cawello et al, Eur. J. Clin. Pharmacol. 1994; 46: 275-277) and 2) the high pulmonary extraction of PGE_1, 63 to 87% (Gillis et al, Am. Rev. Respir. Dis. 1986; 134: 739-744.

Figure 1

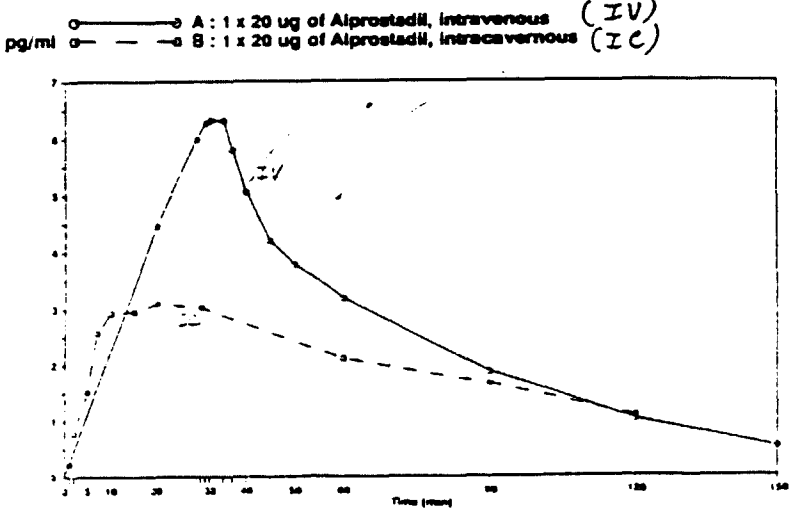
Plasma Levels of Prostaglandin E1 (baseline corrected)
Mean over 24 Subjects



Plasma Levels of 15-keto-prostaglandin E0 (baseline corrected)
Mean over 24 Subjects



Plasma Levels of Prostaglandin E0 (baseline corrected)
Mean over 24 Subjects



Note: Study #3 (an independent study) had been previously submitted by Upjohn under NDA 20-379 (Caverject®, alprostadil for injection) and it was reviewed and found acceptable by OCPB/DPE II on 04/28/95. NDA 20-379 was approved on 07/06/95 for the same indication, treating male patients with ED by IC injection. Finally, Upjohn's NDA 18-484 for alprostadil (Prostin VR Pediatric® Sterile Solution) was approved previously by the Agency for use in pediatric patients with cyanotic congenital heart disease.

No multiple-dose PK study for alprostadil after IC injection was provided in the human PK/Bio section of this NDA.

B. **Alpha-cyclodextrin:**

The PK of [^{14}C]-α-cyclodextrin was also investigated in two supportive studies (Study #15 and 16). The results of the single-dose PK study (#15) are summarized below in Table 3:

Table 3

[^{14}C]-α-cyclodextrin

Parameter	C_{max} (μg/ml)	$T_{1/2}$ (hr^{-1}, α phase)	$T_{1/2}$ (hr^{-1}, β phase)	AUC_{0-24} (μg-hr/ml)
IV Bolus	0.615	0.59	2.46	0.81
IV Infusion	0.21	NA	2.20	0.85

Radioactive components were found not to be associated with RBC. Plasma extracts (up to 6 hr postdose) co-chromatographed with unchanged α-cyclodextrin. The major route of elimination of radioactivity is excretion via urine. Up to 4 components in urine (0-6 hr postdose) were detected. The excretion is rapid and essentially complete by 24 hr postdose accounting for ≈83% and ≈81% (mean) of the dose after IV bolus and infusion, respectively. Around 0.1% of radioactivity was excreted via feces for both routes of administration.

After repeated 2-hr IV infusion of α-cyclodextrin for 7 days ([^{14}C]-α-cyclodextrin for Days 1 and 7 and non-radiolabeled α-cyclodextrin for Days 2 to 6), no changes in plasma PK of radioactivity at Day 7 were found except that urinary excretion (0-24 hr postdose) was slightly increase to 86.1% (Study #16). Single-dose IV or IC bolus injection of [^{14}C]-α-cyclodextrin was further performed in monkey (Study #17, not shown here) and the results are comparable to those obtained from human (Study #15).

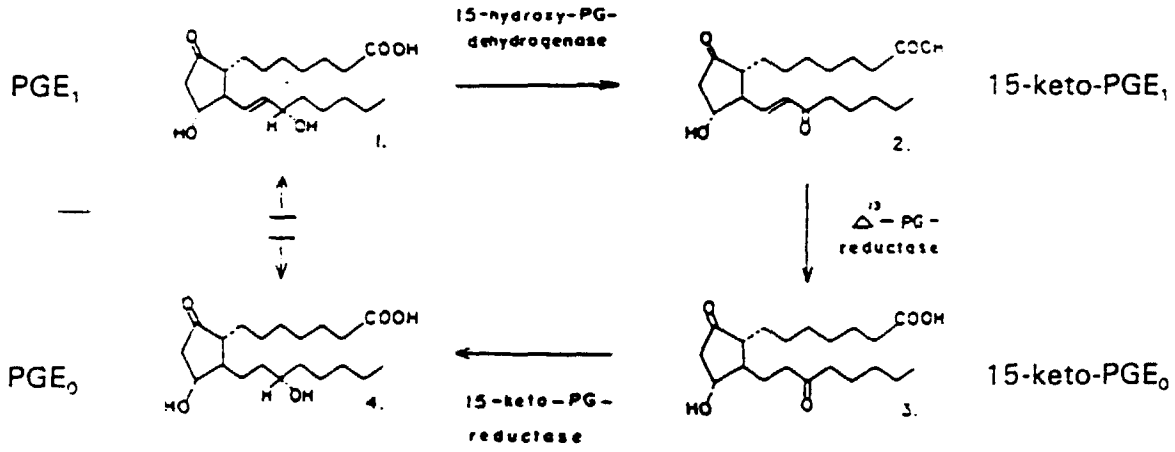
2. BIOEQUIVALENCE:

The alprostadil 20 μg ampoule that has been approved in several European countries for IV administration was used in the clinical and PK/Bio studies of

this NDA. It has exactly the same active and inactive ingredients as the to-be-marketed 20 μg vial product. There are no bio-issues and therefore, no bioequivalence study is needed.

3. METABOLISM:

The information on in vivo or in vitro metabolism of PGE_1 was obtained/ summarized from literature. The metabolism of PGE_1 was studied using supernatant fraction of homogenized animal organs and the proposed metabolic pathway and the responsible enzymes are summarized below in Scheme 1 (Änggard et al, Eur. J. Pharmacol. 1971;14: 66-70):



Lungs and blood were presumed to be the major sites for metabolism of PGE_1 in vivo. After IC injection of alprostadil-α-cyclodextrin complex, the metabolism of PGE_1 in penile corpora cavernosa was investigated (Study #3). The results showed that 1) PGE_1 was rapidly metabolized locally which is consistent with those reported in the literature, i.e., PGE_1 was metabolized in the homogenate of penile corpora cavernosal tissue in vitro (Roy et al, Brit. J. Urology 1989; 64: 180-1820).

In vivo metabolic disposition of PGE_1 in man was also reported using 17,18-^{3}H-PGE_1 (Rosenkranz et al, Biochem. Biophys. Acta 1983; 750: 231-236). The results showed that 1) radioactivity in plasma decline very rapidly and 2) 88% of radioactivity infused were recovered in urine and 12% in feces. Virtually no unchanged drug was found in urine after IV infusion of PGE_1.

The results of a study for the biological activities of PGE_1 and its metabolites using animal isolated organs showed that 1) PGE_0 possessed comparable activity of PGE_1, i.e., saturation of the double bond of PGE_1 between carbons 13 and 14 did not markedly alter its effects and 2) 15-keto-PGE_0 lost significantly its effects, i.e., oxidation of the alcohol group at carbon 15 to a ketone caused diminution of the biological activity (Änggard et al, Acta Physiol. Scand. 1966; 66: 509-510).

4. DOSE PROPORTIONALITY:

Dose proportionality between 30 to 120 μg of PGE_1 has been demonstrated in the previously reviewed study (Study #6). The results obtained from a non-pivotal IV infusion study (Study #7), however, showed that 1) the mean bioavailability of alprostadil in emulsion increased 220% as compared to that in aqueous solution and 2) some deviation from dose proportionality was observed. However, no dose proportionality study to cover the proposed IC dose range of 1 to 40 μg was provided in the human PK/Bio section. Nevertheless, it may be less of a concern since 1) the optimal IC dose should be obtained by careful titration, 2) no tissue accumulation of PGE_1 is expected, and 3) the PI does not recommend IC injection for more than 3 times per week.

5. SPECIAL POPULATION:

The influence of age on the PK of PGEs was not examined. The PK of alprostadil was investigated in subjects with hepatic or with an end-stage renal impairment as compared to healthy volunteers. It is noted that no baseline correction was performed for these two studies.

A. Study # 13 (PHAKI-830) for hepatically impaired subjects:

Hepatically impaired subjects were enrolled in the study based on three tests, i.e., aminopyrine breath test (normal range 0.6-1.0% dose), extrarenal sorbitol clearance test (normal range > 12 ml/min/kg), and caffeine clearance test (normal range > 0.8 ml/min/kg). These subjects had most of the test values below the normal ranges. Please see the individual study report in Appendix 2 for details.

In this study, alprostadil (120 μg) was given by a 2-hr IV infusion to 12 subjects (7M + 5F) with hepatic impairment and to 12 healthy volunteers (7M + 5F). The PK results of study are summarized in Table 4 and mean plasma profiles are shown in Figure 2.

For hepatically impaired subjects, 1) the CL_T for PGE_1 decreased by 50%, 2) the mean AUC value for 15-keto-PGE_0 increased by 67%, and 3) the mean AUC value for PGE_0 increased by 88% as compared to

those for healthy male volunteers. However, no significant changes in participants' plasma albumin levels were observed prior to and after the study. The above significant PK changes seemingly did not correlate with subjects' mean plasma albumin levels (42.1 ± 2.7 g/l for hepatically impaired subjects vs. 42.8 ± 2.1 g/l for healthy volunteers).

Table 4

PGE_1

	Healthy Volunteers (n=12)	Subjects With Hepatic Impairment (n=12)	P value
C_{max} (pg/ml)	8.9 (±3.1)	17.4 (±6.6)	0.0006*
AUC_{0-240} (pg-min/ml)	1040. (±308)	2080. (±864)	0.0061*
$T_{1/2}$ (min)	9.1 (±11.5)	13.8 (±22.4)	>0.05

15-Keto-PGE_0

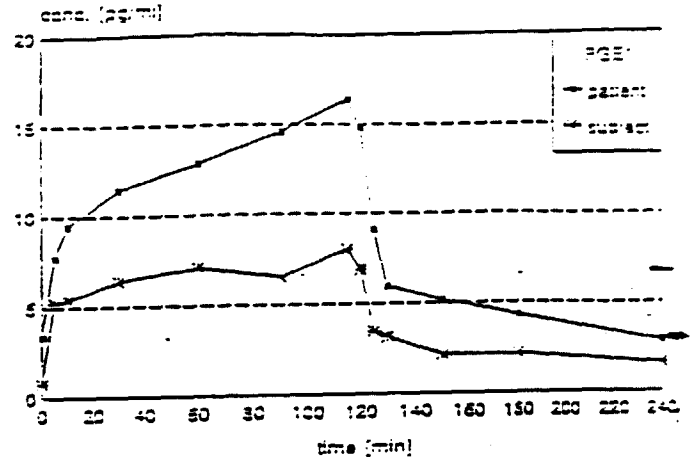
	Healthy Volunteers (n=12)	Subjects With Hepatic Impairment (n=12)	P value
C_{max} (pg/ml)	776 (±178)	1278 (±454)	0.003*
AUC_{0-240} (pg-min/ml)	82596 (±14531)	137587 (±45649)	0.0015*
$T_{1/2}$ (min)	7.5 (±2.7)	9.0 (±5.1)	>0.05

PGE_0

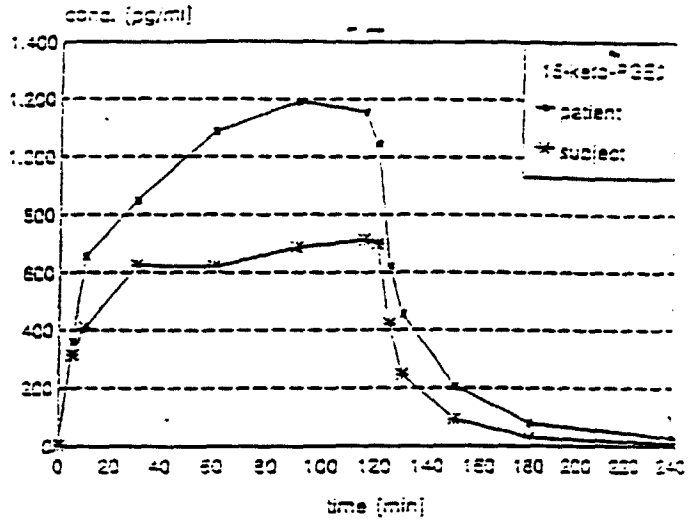
	Healthy Volunteers (n=12)	Subjects With Hepatic Impairment (n=12)	P value
C_{max} (pg/ml)	18.1 (±6.1)	29.8 (±10.3)	0.0027*
AUC_{0-240} (pg-min/ml)	1895 (±553)	3558 (±1322)	0.0012*
$T_{1/2}$ (min)	30.3 (±12.2)	40.0 (±17.0)	>0.05

A brief analysis was done on PK data obtained from the male and female subjects enrolled in this study. No gender issues were found. However, it could be due to the small numbers of subjects enrolled.

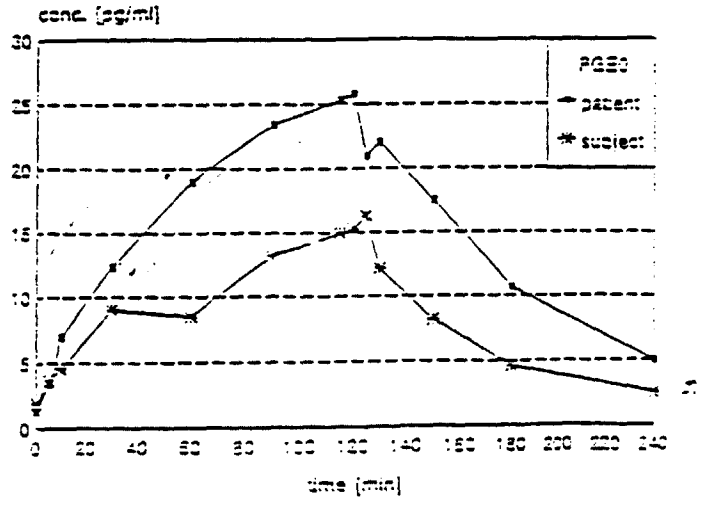
Figure 2



Mean PGE_1 plasma concentrations (n = 12)



Mean 15-keto-PGE_2 plasma concentrations (n = 12)



Mean PGE_2 plasma concentrations (n = 12)

B: Study # 14 (PHAKI-841) for renally impaired subjects:

In this study, alprostadil (120 μg) was given by a 2-hr IV infusion to 12 male subjects with an end-stage renal impairment and to 12 healthy male volunteers. The results of study are summarized in Table 5 and mean plasma profiles are shown in Figure 3. No results of statistical analysis are presented.

For renally impaired subjects, 1) the CL_T for PGE_1 increased by 45%, 2) the mean AUC value for 15-keto-PGE_0 increased by 106%, and 3) the mean AUC value for PGE_0 increased by 180% as compared to those for healthy male volunteers. Similar to Study #13, 1) no significant changes in participants' plasma albumin levels were observed prior to and after the study and 2) significant PK changes seemingly are not correlated with subjects' mean plasma albumin levels (40.4 ± 2.4 g/l for renally impaired subjects vs. 40.6 ± 2.4 g/l for the healthy volunteers).

Table 5

PGE_1

	Healthy Male Volunteers (n = 12)	Male Subjects With Renal Impairment (n = 12)
C_{max} (pg/ml)	58.2 (±12.0)	36.7 (±18.5)
$AUC_{0\text{-}360}$ (pg-min/ml)	7430. (±2085)	5111 (±2558)
$T_{1/2}$ (min)	11.4 (±10.6)	12.9 (±9.2; n = 11)

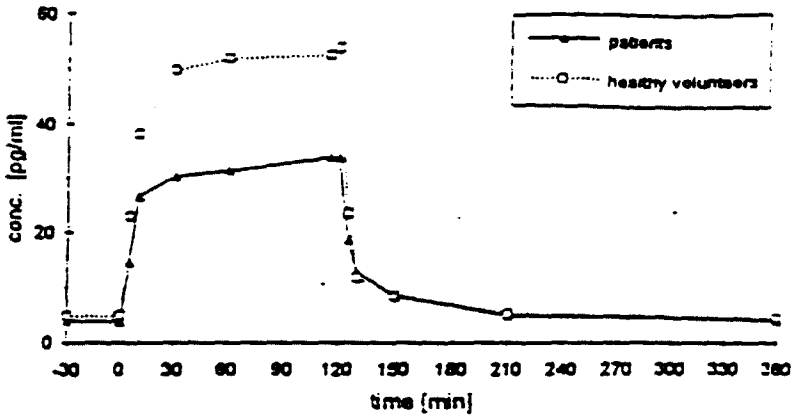
15-Keto-PGE_0

	Healthy Male Volunteers (n = 12)	Subjects With Renal Impairment (n = 12)
C_{max} (pg/ml)	193 (±42)	394 (±233)
$AUC_{0\text{-}360}$ (pg-min/ml)	23192 (±4931)	47822 (±34191)
$T_{1/2}$ (min)	13.3 (±14.8)	28.8 (±32.3)

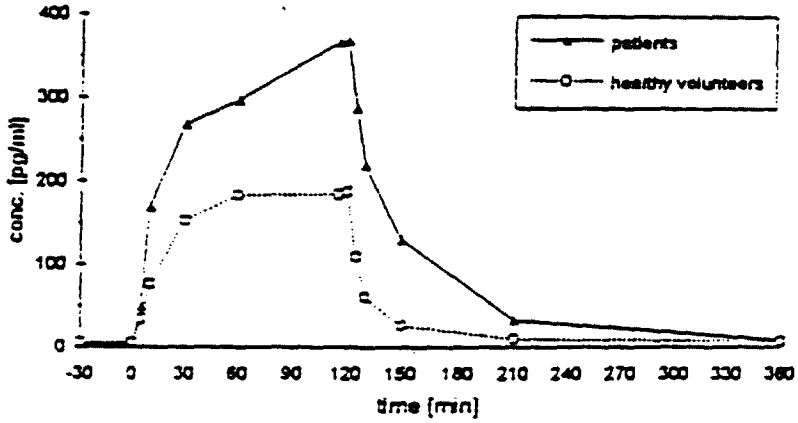
PGE_0

	Healthy Male Volunteers (n = 12)	Subjects With Renal Impairment (n = 12)
C_{max} (pg/ml)	23.8 (±7.3)	58.2 (±37.3)
$AUC_{0\text{-}360}$ (pg-min/ml)	3270. (±1272)	9115 (±7188)
$T_{1/2}$ (min)	29.1 (±15.0)	46.0 (±26.0; n = 11)

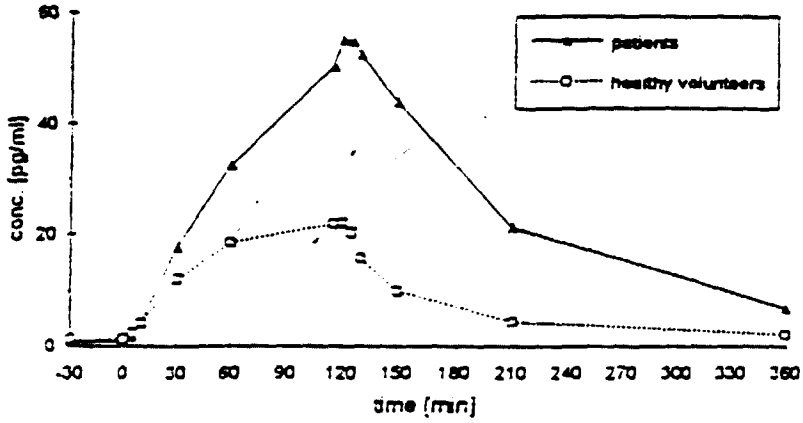
Figure 3



Mean PGE_1 plasma concentrations (n=12)



Mean 15-keto-PGE_0 plasma concentrations (n=12)



Mean PGE_0 plasma concentrations (n=12)

Interstudy comparison between Study #13 and 14 showed that under the same study conditions (120 μg alprostadil given by a 2-hr IV infusion), the mean AUC value of PGE_1 obtained from the healthy volunteers of Study #14 (7430 pg-min/ml) is about [redacted]-fold greater than that from Study #13 (1040 pg-min/ml). The discrepancies in mean AUC values and in mean C_{max} as well, however, could not be explained merely by the minor difference in AUCs, i.e., AUC_{0-240} (Study #13) vs. AUC_{0-360} (Study #14).

6. GENDER:

Gender differences were not evaluated in the human PK/Bio section since this drug is for use in male adults only.

7. PEDIATRICS:

The product is not intended for pediatric use.

8. FOOD EFFECT:

Food effect study was not conducted, however, food may not have impact on the PK of alprostadil after IC injection.

9. DRUG-DRUG INTERACTION:

Four D-D interaction for alprostadil with digoxin (Study #8), glibenclamide (Study #9), warfarin (Study #11), or acetylsalicylic acid (Study #12) were previously submitted under NDA and reviewed by OCPB/DPE II on 10/05/95. These studies were found acceptable and no significant D-D interactions were reported.

One new D-D interaction study with heparin (Study #10) using 12 healthy male volunteers was included in this NDA. Only the plasma levels of heparin, and its partial thromboplastin time (PTT) and thrombin time (TT) were measured. No PK data for PGEs were obtained. The study results showed that the significant net (baseline-corrected) increases in median PTT from 53.4 (heparin alone) to 65.2 seconds (combination) and median PT from 4.08 (heparin alone) to 6.30 seconds (combination) are consistent with a 16% increase in heparin mean AUC value for combination therapy as compared to that for heparin alone. The sponsor concluded that a possible interaction between alprostadil and heparin could not be excluded, but it is not considered to be clinically relevant. The D-D interaction between the treatment dose of alprostadil and acute/chronic administration of an anticoagulant, however, is not known. Therefore, the reviewing medical officer should be aware of the above changes.

10. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS:

No modeling nor analyses for the PK/PD relationship of PGEs were conducted.

11. FORMULATIONS, DOSAGE, AND DRUG ADMINISTRATION:

The alprostadil 20 μg ampoules used throughout the major clinical trials and the PK/Bio studies were all manufactured by The batch Nos./sizes used in PK/Bio studies are summarized in Appendix 3. The sponsor indicated that no experimental or pilot batches/formulations were employed. The to-be-marketed alprostadil formulation is shown below in Table 6:

Table 6: Compositions of Edex Lyophilized powder*:

Alprostadil (Used as alprostadil-alfadex)	5 μg	10 μg	20 μg	40 μg
Alfadex	mg	mg	mg	mg
Lactose	mg	mg	mg	mg

*: Nitrogen is used to purge chamber at the end of the lyophilization cycle and water is removed during lyophilization and is not present in the finished product.

The above 4 strengths are compositionally but not proportionally the same. They are to be manufactured and packaged by

One ml of normal saline (0.9% Sodium Chloride Injection, USP) is for reconstitution.

Only one IC dose level of 20 μg was investigated in human PK/Bio studies. For dosage administration, please see the individual study reports in Appendix 2 for details.

12. DISSOLUTION AND CONTENT UNIFORMITY:

No dissolution testing is required for this products, since it is a lyophilized, sterile product for IC injection after reconstitution with 1 ml of sterile isotonic NaCL solution. The content uniformity (with a % overage) ranged from %.

13. SAMPLE COLLECTION:

Prior to blood sample collection, polypropylene tubes which contained 1-1.2 ml of Biostabil (50-60 μg of indomethacin) were pre-cooled in an ice-bath. Upon collection, blood dripped into the tube without a major stasis. The tube was cooled in the ice-bath immediately and the blood sample was then centrifuged for 10 min at +4°C and 2500 g (3600 rpm) in a controlled temperature centrifuge. The sponsor indicated that the samples were stable

during the preparation and handling procedures. Please see blood sample collection and treatment in the individual study reports in Appendix 2 for details.

14. ASSAY:

15.

III. GENERAL COMMENTS: (No. 4 needs to be sent to the sponsor)

1. Only 20-μg ampoules of alprostadil were tested in clinical trials and PK/Bio studies. No other studies were submitted to investigate 1) the bioavailability of 5, 10 and 40 μg/vial and 2) the effects of different concentrations (5, 10, and 40 μg/ml after reconstitution) on the PK performance of PGE_1.

   Since for alprostadil, 1) it will form a clear solution after reconstitution with diluent, 2) it is for IC injection directly to the acting site, and 3) its dose proportionality had been demonstrated between 30 to 120 μg after IV infusion, no bio-issues would be expected.

2. In Study #13, 120 μg alprostadil was given by 2-hr infusion to 12 healthy volunteers and 12 subjects with hepatic impairment. The study results showed significant changes in PK of PGEs in subjects with hepatic impairment as compared to those from healthy volunteers. The results of Study #14 for subjects with renal impairment also showed significant changes in PK of PGEs as compared to those from healthy volunteers. The mechanisms are not known. Therefore, the reviewing medical officer should be aware of the above significant changes when treating patients with ED who also have hepatic or renal impairment.

3. The reviewing medical officer also should be aware of the significant changes in partial thromboplastin time and in thrombin time for acute and/or chronic administration of heparin with alprostadil.

4. An inter-study comparison was carried out for the pharmacokinetic data obtained in studies PHAKI 830 and PHAKI 841 which were conducted using the same dose, IV-infusion rate, and assay methodology. Since there was a 7-fold difference between these studies in mean AUC values for PGE_1 in healthy volunteers, the sponsor is asked to explain the above discrepancy. Possible sources of differences such as pharmacokinetic calculations, analytical site, and analytical operating procedures should be further investigated by the firm.

   Therefore, it is recommended that the sponsor 1) verify the pharmacokinetic calculations of the submitted data, 2) conduct an internal audit of the analytical sites and inform the Agency of the audit results, and 3) recalculate and submit the pharmacokinetic parameters for review, if discrepancies in the assay results are found.

IV. LABELING COMMENTS: (Need to be sent to the sponsor)

The sponsor's revised PI (version of June 14 1996) included in Appendix 1 needs further revision.

1. The PK information on the intravenous infusion is irrelevant to the indication for this NDA, therefore, it has been deleted from the pharmacokinetics subsection.

2. For information obtained from literature, e.g., study results of In Vivo or In Vitro metabolism of PGE_1, the reference should be provided accordingly.

3. The Agency's version of draft labeling was sent to the sponsor by fax on 10/10/96. The proposed package insert was revised and submitted to the Agency for review by the sponsor on 10/19/96.

   After reviewing the sponsor's revised labeling (10/19/96 version), there are some minor changes that need to be made. The updated FDA's version of the pharmacokinetics subsection under CLINICAL PHARMACOLOGY section is attached (page Nos. 20-23). It is recommended that the updated FDA's version of the pharmacokinetics subsection be incorporated in the final labeling accordingly.

FDA's recommended version of the pharmacokinetic subsection of the labeling:

PHARMACOKINETICS

I. ALPHA-CYCLODEXTRIN

After reconstitution, PGE_1 immediately dissociates from α-cyclodextrin inclusion complex; the *in vivo* disposition of both components occurs independently after administration. After intravenous infusion of radiolabeled α-cyclodextrin to healthy volunteers, the radiolabeled components were rapidly eliminated within 24-hours; urine accounting for 81-83% of radioactivity and feces for 0.1%. There was no evidence of significant accumulation of radiolabeled α-cyclodextrin in the body even after 7 days of repeated intravenous injection. After intracavernous administration in monkeys, radiolabeled α-cyclodextrin was rapidly distributed from the injection site with less than 0.1% of the dose remaining in the penis 1 hour after administration. There was no evidence of tissue retention of radiolabeled α-cyclodextrin in monkeys.

II. ALPROSTADIL

Absorption: After intracavernous injection of 20 mcg of EDEX in 24 patients with erectile dysfunction, mean systemic plasma concentrations of PGE_1 increased from baseline of 0.8 ±0.6 pg/mL to a peak (C_{max}) of 16.8± 18.9 pg/mL (corrected for baseline) within 2 to 5 minutes and dropped to endogenous plasma levels within 2 hours (Table 1). The absolute bioavailability of alprostadil estimated from systemic exposure was about 98% as compared to the same dose given by a short-term intravenous infusion.

Distribution: The volume of distribution for PGE_1 was not estimated. Approximately 93% of PGE_1 found in plasma is protein-bound.

Metabolism: PGE_1 is metabolized in the corpus cavernosum after intracavernous administration. PGE_1 entering the systemic circulation is rapidly and extensively metabolized in the lungs with a first-pass pulmonary elimination of 60 to 90% of PGE_1. Enzymatic oxidation of the C15-hydroxy group followed by reduction of the C13,14-double bond produces the primary metabolites, 15-keto-PGE_1, 15-keto-PGE_0, and PGE_0. 15-keto-PGE_1 has only been detected *in vitro* in homogenized lung preparations, whereas 15-keto-PGE_0 and PGE_0 have been measured in plasma. Unlike the 15-keto metabolites which are less pharmacologically active than the parent compound, PGE_0 is similar in potency to PGE_1 *in vivo*.

After intracavernous injection of 20 mcg alprostadil to 24 patients with erectile dysfunction, mean systemic plasma 15-keto-PGE_0 levels increased within 7 minutes from endogenous levels of 12.9 ± 11.8 pg/mL to a C_{max} of 421 ± 337 pg/mL (corrected for baseline) followed by a decrease to baseline levels in several hours. Mean systemic plasma PGE_0 levels increased within 20 minutes from endogenous levels of 0.6 ± 0.5 pg/mL to a C_{max} of 3.9 ± 2.3 pg/mL (corrected for baseline) followed by a decrease to baseline levels in several hours.

Excretion: After further degradation of PGE_1 by beta and omega oxidation, the main metabolites are excreted primarily in urine (88%) and feces (12%) over 72 hours, and total excretion is essentially complete (92%) within 24 hours after administration. No unchanged PGE_1 has been found in the urine and there is no evidence of tissue retention of PGE_1 and its metabolites. After intracavernous injection of 20 mcg of EDEX in patients with erectile dysfunction, the terminal half-lives ($T_{1/2}$) of 15-keto PGE_0 and PGE_0 were calculated to be 40.9 ± 16.5 minutes and 63.2 ± 31.1 minutes, respectively. The terminal half-life of PGE_1 in healthy volunteers was calculated to be around 9-11 minutes which is consistent with that reported in the literature (8 minutes).

Mean total body clearance of PGE_1 in patients with erectile dysfunction was calculated to be around 115 L/min after an intravenous infusion of 20 mcg alprostadil. The above value exceeded cardiac output indicating extensive and rapid elimination of PGE_1 in the lungs and/or blood. .

SPECIAL POPULATIONS:

Geriatrics: The potential effect of age on the pharmacokinetics of alprostadil has not been formally evaluated.

Race: The potential influence of race on the pharmacokinetics of alprostadil has not been formally evaluated.

Hepatic Insufficiency: In a study in symptomatic subjects with impaired hepatic function and age/weight/sex-matched healthy volunteers, 120 mcg of alprostadil was administered by intravenous infusion over 2 hours. Mean C_{max} value of PGE_1 in hepatically impaired patients was 96% higher than that in healthy volunteers. Similarly, mean C_{max} values of both 15-keto-PGE_0 and PGE_0 increased 65% as compared to those in healthy volunteers. The terminal half-lives of PGE_1, PGE_0, and 15-keto-PGE_0 and plasma albumin levels were similar in hepatically impaired subjects compared to healthy volunteers. The mechanism responsible for the observed discrepancies between hepatically impaired subjects and healthy volunteers is not known.

Renal Insufficiency: In a study in symptomatic subjects with end-stage renal disease undergoing hemodialysis and age/weight/sex-matched healthy volunteers, 120 mcg of alprostadil was administered by intravenous infusion over 2 hours. The mean C_{max} value of PGE_1 in patients was 37% lower as compared to that in healthy volunteers whereas mean C_{max} values of 15-keto-PGE_0 and PGE_0 in patients increased 104% and 145%, respectively as compared to those in healthy volunteers. The terminal half-lives of PGE_1, PGE_0, and 15-keto-PGE_0 and plasma albumin levels were similar in renally impaired subjects compared to healthy volunteers. The mechanism responsible for the observed discrepancies between renally impaired subjects and healthy volunteers is not known.

Pulmonary Disease: The pulmonary extraction of alprostadil following intravascular administration was reduced by 15% (66 ± 3.6% vs. 78 ± 2.3%) in patients with acute respiratory distress syndrome (ARDS) compared with a group of patients with normal

respiratory function who were undergoing cardiopulmonary bypass surgery. Pulmonary clearance was found to vary as a etc...

Drug-Drug Interaction: In clinical trials, concomitant use of agents such as antihypertensive drugs, diuretics, antidiabetic agents (including insulin), or nonsteroidal anti-inflammatory drugs had no apparent effect on the efficacy or safety of EDEX. Several drug-drug interaction studies have been conducted with alprostadil alone or in combination with aspirin, digoxin, heparin or warfarin in healthy volunteers and with glyburide in subjects with stable, non-insulin dependent diabetic mellitus. The pharmacokinetic profiles of aspirin, warfarin, digoxin, and glyburide were not affected by concomitant administration of alprostadil. There were no clinically important changes or trends in pharmacodynamic parameters for these drugs. Concomitant administration of alprostadil intravenous infusion 90 mcg over 3 hours and heparin (5,000 IU), resulted in a 140% increase in partial thromboplastin time and a 120% increase in thrombin time.

TABLE 1:

Study No.	Participants	Route and Dose Administration	Drug/ Metabolites	C_{max}[1] (pg/ml)	T_{max} (min)	AUC_{0-t}[2] (pg-min/ml)	Total Clearance[3] (Liters/min)	$T_{1/2}$[4] (min)
PHAKI 848	Erectile Dysfunction Patients	20mcg/0.5 hr IV	PGE_1	7.09 ±3.12	25.5 ±4.8	174 ±101	115	-----
			15-keto- PGE_0	7.10 ±2.19	29.9 ±1.2	13705 ±2659	-----	15.6 ±5.6
			PGE_0	471 ±88	32.2 ±2.4	380. ±115	-----	39.8 ±26.3
		20 mcg/IC	PGE_1	16.8 ±18.9	4.8 ±3.3	171 ±115	-----	-----
			15-keto-PGE_0	3.9 ±2.3	9.7 ±7.7	10500 ±4101	-----	40.9 ±16.5
			PGE_0	421 ±337	20.3 ±12.6	251 ±134	-----	63.2 ±31.1

1. Baseline-corrected data.
2. AUC_{0-150} for IV infusion and AUC_{0-120} for IC injection.
3. Calculated as IV dose/AUC_{0-150} (IV).
4. Apparent terminal half-life.

DEC 1 3 1995

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
DIVISION OF PHARMACEUTICAL EVALUATION II

Date: Dec. 12, 1995

To: Division Director, Mei-Ling Chen, Ph.D.
Deputy Director, Mr. John Hunt
Team Leader, Angelica Dorantes, Ph.D.

From: Tien-Mien Chen, Ph.D.

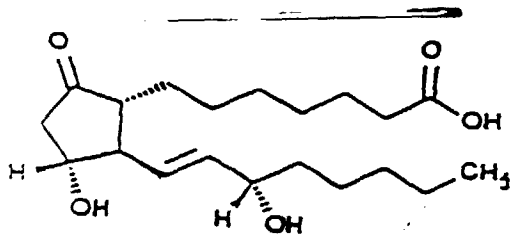
RE: NDA 20-649 (Schwarz Pharma's alprostadil for injection)

Prefiling Meeting: Dec. 11, 1995 at 1:30pm in Mei-Ling's Office

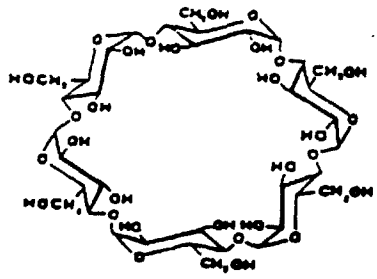
SYNOPSIS:

On 11/07/95, Schwarz Pharma submitted NDA 20-649 for Alprostadil for Injection. Alprostadil is also known as prostaglandin E_1 (PGE_1), an endogenous substance. It is a sterile, pyrogen-free, lyophilized powder for intracavernous (IC) administration after reconstitution with 1 ml of sterile isotonic saline. It is supplied in single-dose vials containing either 5, 10, 20 or 40 μg of alprostadil in an alfadex (α-cyclodextrin) inclusion complex (a 1:1 clathrate complex). Their chemical formula are shown below:

Alprostadil (MW. 354.49)



α-Cyclodextrin (MW. 972.85)



The formulations for the four to-be-marketed strengths are summarized below:

Component	5 μg/vial	10 μg/vial	20 μg/vial	40 μg/vial
Alprostadil	μg	μg	μg	μg
Alfadex (used as alprostadil-alfadex)	μg	μg	μg	μg
Lactose Anhydrase, NF	mg	mg	mg	mg
Nitrogen*, NF				
Water for Injection#, USP				

*. Used to purge chamber pressure at the end of the lyophilization cycle.
#. Removed during lyophilization and not present in the finished product.

Alprostadil 20 μg ampoule that has been approved in several European countries has exactly the same active and inactive ingredients as the to-be-marketed 20 μg vial product and the 20 μg ampoules were used in the clinical and pharmacokinetic (PK) studies of this NDA.

Alprostadil is a potent smooth muscle relaxant. By IC injection, it is to be indicated for I) the diagnosis of male's erectile dysfunction regardless of origin and ii) the treatment of erectile dysfunction. In the package insert (PI; Attachment 1), I) an initial dose of 2.5-40 μg of alprostadil is recommended for the simplest diagnosis of erectile dysfunction, however, for patients with a suspected psychogenic or neurogenic origin, the first dose should be 2.5-5 μg and for patients with a suspected vasculogenic erectile dysfunction, the first dose should be 5-10 μg and ii) the dosage range of alprostadil for the treatment of erectile dysfunction is 1-40 μg. The dose should be individualized for each patient by careful titration under supervision by the physician. The IC injection should be given over a 5-10 second interval. The recommended frequency of injection is no more than 3 times weekly, with at least 24 hr between each dose. It is also recommended that three, in-office dose-titration be given in order to establish the patient's individual optimum dose for at-home (maintenance) self-injection therapy.

Submitted under NDA 20-649 were one background validation study for the assay method, GC/MS/MS, used (Study #1) and eleven PK studies that were all conducted in Germany. Three studies (Study # 2 to 4) that employed patients used only one dose level of 20 μg alprostadil for IC injection. In Study #2, the same dose was also given intravenously (IV) by 30-min infusion in a crossover fashion. In Study #4, 20 μg alprostadil was given IC to patients and plasma levels of PGE_1 and its two major metabolites, PGE_0, (13, 14-dihydro PGE_1) and 15-keto-PGE_0 were analyzed. Mean PK parameters for PGE_1, PGE_0, and 15-keto-PGE_0 are summarized in Table 1.

For other route of administration, 30-120 μg alprostadil was given IV in Study # 5 to 7 employing healthy volunteers for single-dose PK and dose proportionality studies. Finally, Drug-Drug (D-D) interaction kinetics were evaluated in 5 studies for concomitant administration of digoxin (Study #8), glibenclamide (Study #9), heparin (Study #10), warfarin (Study #11), and acetylsalicylic acid (Study #12). For the D-D interaction studies, an IV infusion of alprostadil in either patients or healthy volunteers was used. Please see Attachment 2 for details.

Four female subjects with Type II Diabetes Mellitus were used in Study #9 but alprostadil is not intended for female or pediatric population. The influence of age on the PK of alprostadil was not investigated. Furthermore, for this NDA, no analyses and/or modeling for PK/pharmacodynamic (PD) relationship for alprostadil were submitted.

Note 1: Alprostadil (Prostin VR Pediatric® Sterile Solution; The Upjohn Company's NDA 18-484) had been approved previously by the Agency for use in pediatric patients with cyanotic congenital heart disease.

Note 2: Study #3 that was submitted in the current NDA 20-649 was an independent study using ampoules of alprostadil 20 μg (in alfadex complex) for IC administration and the study had been previously submitted under NDA 20-379 (Caverject®, alprostadil for injection) on 02/11/94 by the Upjohn Company for treating male erectile dysfunction. It was the only one PK study submitted under NDA 20-379. However, NDA 20-379 was filed based on clinical safety and efficacy information. Study #3 was reviewed by HFD-870 on 12/22/94 and it was found acceptable. NDA 20-379 was approved later on 07/06/95.

Note 3: Study # 5, 6, 8, 9, 11, and 12 were cross-referenced to NDA

On 11/28/95 and 12/04/95, telecons were made between the Agency and the sponsor. They are summarized below:

1. No absolute bioavailability (F_{abs}) was reported in this NDA. The sponsor, however, indicated that PGE_1 is 100% bioavailable at the acting site (cavernous body) after IC injection, although it is rapidly metabolized locally. The conventional estimation of F_{abs} by comparing plasma AUC values of PGE_1 after IC injection to that after IV injection may be less of a concern for the IC administration of this drug.

2. No information on the dose proportionality after IC administration of alprostadil was submitted, although it is desirable. Only one dose level of 20 μg after IC injection was tested, while the to be recommended dosage range is 1 to 40 μg.

3. The sponsor indicated that no information on the PK of PGE_1 after long-term treatment was included nor was PK information from clinical trials available.

4. As indicated by the sponsor, information on the enzyme(s) responsible for the metabolism of PGE_1 in vivo and/or in vitro is available from the literature. In addition, the sponsor indicated that the PK studies on the patients with hepatic/renal impairment after IV administration of alprostadil are ongoing and will be available in early 1996.

5. The sponsor indicated that I) no other changes in manufacturing process for alprostadil products in addition to the change in manufacturing site and the change from ampoules to the final vial products were made, ii) only the alprostadil ampoules that were manufactured in Europe were used in the clinical and PK/Bio studies, and iii) the vial products that were manufactured at new site will be used in the ongoing clinical trial # KU-620-001, KU-620-002, KU-620-003.

RECOMMENDATION:

The Division of Pharmaceutical Evaluation II (HFD-870) has briefly reviewed the PK/Bio studies for NDA 20-649 that was submitted on 11/07/95. HFD-870 is of the opinion that the NDA is acceptable for filing. The following comment needs to be communicated to the sponsor, if the NDA is filed.

COMMENT: (Needs to be sent to the sponsor)

You indicated that the pharmacokinetic studies for alprostadil on patients with hepatic/renal impairment after intravenous administration are currently ongoing and they will be available in early 1996. It is recommended that the study results be submitted to the Agency for review, once they become available.

Tien-Mien Chen, Ph.D.

Division of Pharmaceutical Evaluation II

cc: HFD-510, HFD-850 (Lesko, Drug), HFD-870 (M. Chen, J. Hunt, A. Dorantes, T. Chen)

Table 1
Pharmacokinetics of PGE_1 and its Metabolites After Intracavernosal Injection of PGE_1 in Patients With Erectile Dysfunction
Study KU-620-004

Parameter[a]		PGE_1			PGE_0			15-keto-PGE_0		
		All Patients	Responders	Non-responders	All Patients	Responders	Non-responders	All Patients	Responders	Non-responders
Endogenous Concentration (pg/mL)	Range Mean ± SD Median	4.1 - 17.8 7.3 ± 4.1 6.3	4.5 - 6.6 5.4 ± 0.9 5.1	4.1 - 17.8 8.4 ± 4.8 7.5	0.1 - 14.0 2.6 ± 3.2 1.5	0.1 - 2.7 1.6 ± 1.1 1.6	0.4 - 14.0 3.2 ± 3.8 1.5	3.4 - 121 21.7 ± 27.0 14.0	3.4 ± 16.5 9.7 ± 5.2 11.4	4 8 - 121 26.4 ± 32 8 15 0
C_{max} (pg/mL)	Range Mean ± SD Median	27.4 - 411.6 118.7 ± 104.2 80.0	27.4 ± 246.3 93.7 ± 80.0 65.5	34.1 - 411.6 132.3 ± 116.6 85.0	3.8 - 36.9 16.0 ± 8.5 14.5	3.8 - 17.5 10.5 ± 4.4 10.5	5.7 - 36.9 19.0 ± 8.8 16.9	216.2 - 1960.8 893.9 ± 488.1 871.8	216.2 - 1097.5 762.4 ± 329.8 810.3	295.1 - 1960 8 965.6 ± 557 4 993
t_{max} (min)	Range Mean ± SD Median	1 - 15 3.2 ± 3.6 2.0	1 - 7 2.7 ± 2.2 2.0	1 - 15 3.5 ± 4.3 2.0	2 - 20 10.7 ± 6.5 7.0	5 - 15 7.7 ± 3.7 7.0	2 - 20 12.4 ± 7.2 15.0	1 - 15 6.7 ± 4.1 5.0	1 - 10 5.2 ± 2.9 5.0	2 - 15 7.5 ± 4 5 7.0
AUC_{0-120} (pg/mL·min)	Range Mean ± SD Median	966 - 4881 2537 ± 1339 2335	991 - 4153 2364 ± 1019 2270	966 - 4881 2631 ± 1523 2465	189 - 2041 846 ± 430 840	189 - 1018 673 ± 280 736	251 - 2041 941 ± 478 952	6258 - 35167 20952 ± 8216 20118	6258 - 27977 18437 ± 8047 19870	8961 - 35167 22282 ± 8360 23982

[a] Values of pharmacokinetic parameters represent the two-minute timepoint (two minutes after alprostadil injection). Endogenous plasma concentrations of PGE_1, PGE_0, and 15-keto-PGE_0 were taken from timepoint -10 (10 minutes before injection).

Data Source: Individual Clinical Trial Report

000340

19 pages (1-19)

Deleted

Attachment 1

Annotated Proposed

Labeling

Attachment 2

Table A
Table of All Studies

Name of company: Schwarz Pharma AG Name of finished product: Alprostadil for Injection or PGE_1•α-CD Name of active ingredient(s): Prostaglandin E_1 (PGE_1) or Alprostadil		SUMMARY OF CLINICAL TRIALS HUMAN PHARMACOKINETICS & BIOAVAILABILITY STUDIES (STUDIES)							
Study No. Investigator Dates	Study Design	Diagnosis + Criteria for Inclusion	Subjects/Patients N (W/B/H/O)	Subjects/Patients Age Range (yrs)	Subjects/Patients Per R_x Group	Drug Regimen	Duration of Treatment	Results	Safety Results
Background Validation Study									
PHAK1-849 Schweer (Germany) January 1995	analytical validation study for the determination of PGE_1 and metabolites PGE_0 and 15-keto-PGE_0 by gas chromatography/negative ion chemical ionization triple stage quadrupole mass spectrometry	not applicable	not applicable	not applicable	not appl.	not applicable	not applicable	Specificity of GC/MS/MS method for the quantitation of PGE_1 and metabolites PGE_0 and 15-keto-PGE_0 was much higher than previously developed methods (e.g., radioimmunoassay, enzyme immunoassay, and GC/MS).	not applicable

#1

000318

ED = erectile dysfunction; W = white; B = black; H = hispanic; O = other; M = male; I.C. = intracavernosal; I.A. = intraarterial; I.V. = intravenous; Per R_x Grp. = number of patients or subjects/treatment group.

Table A
Table of All Studies

Name of company: Schwarz Pharma AG Name of finished product: Alprostadil for Injection or PGE_1•α-CD Name of active ingredient(s): Prostaglandin E_1 (PGE_1) or Alprostadil		SUMMARY OF CLINICAL TRIALS HUMAN PHARMACOKINETICS & BIOAVAILABILITY STUDIES (STUDIES)							
Study No. Investigator Dates	Study Design	Diagnosis + Criteria for Inclusion	Subjects/Patients N (W/B/H/O)	Age Range (yrs)	Per R_x Group	Drug Regimen	Duration of Treatment	Results	Safety Results
Intracavernosal Pharmacokinetic Studies									
DA-229 (PHAKI-848; KU-620-008) Dietrich (Germany) 29 Oct. 1994 - 1 Nov. 1994	open-label, randomized, crossover	volunteers with a confirmed diagnosis of ED existing at least six months	24 (race not collected)	38-64	24 24	20 µg PGE_1 30-minute I.V. infusion (5-hour washout) 20 µg PGE_1 intracavernous injection	1 day	Concentration-time profiles differed between routes of administration, which was most likely due to the different speeds of administration. Plasma levels of PGE_1 demonstrated a rapid decrease after the end of intravenous administration or following intracavernous administration. C_{max} of PGE_1 after intracavernous injection was approximately twice that following intravenous infusion.	7 (29%) patients reported adverse experiences. No deaths, serious adverse experiences, or discontinuations were reported.

#2

000319

ED = erectile dysfunction; W = white; B = black; H = hispanic; O = other; M = male; I.C. = intracavernosal; I.A. = intraarterial; I.V. = intravenous; Per R_x Grp. = number of patients or subjects/treatment group.

Table A
Table of All Studies

Name of company: Schwarz Pharma AG Name of finished product: Alprostadil for Injection or PGE_1•α-CD Name of active ingredient(s): Prostaglandin E_1 (PGE_1) or Alprostadil		SUMMARY OF CLINICAL TRIALS HUMAN PHARMACOKINETICS & BIOAVAILABILITY STUDIES (STUDIES)							
Study No. Investigator Dates	Study Design	Diagnosis + Criteria for Inclusion	Subjects/Patients N (W/B/H/O)	Subjects/Patients Age Range (yrs)	Subjects/Patients Per R_x Group	Drug Regimen	Duration of Treatment	Results	Safety Results
F-8495 van Ahlen (Germany) March 1989 - September 1989	open-label, crossover	6 patients with ED of diabetogenic origin, 6 patients with normal erectile potency and penile deviation	12 (race not collected)	23-61	12 12	20 µg PGE_1 80 mg papaverine + 3 mg phentolamine I.C. injection	1 day	Locally, PGE_1 concentration rose to an average of 32,000 pg/mL and fell rapidly due to metabolism. A significant rise of PGE_1 in peripheral-venous blood was not demonstrated. PGE_1 seldom induced an hemolysis and only a slight activation of fibrinolysis in contrast to results with papaverine/ phentolamine. Plasminogen and AP were not significantly lowered. Following administration, C_{max} for PGE_1 was 119 ± 104 (pg/mL).	No adverse experiences were reported.

#3

000320

ED = erectile dysfunction; W = white; B = black; H = hispanic; O = other; M = male; I.C. = intracavernosal; I.A. = intraarterial; I.V. = intravenous; Per R_x Grp. = number of patients or subjects/treatment group.

Table A
Table of All Studies

Name of company: Schwarz Pharma AG Name of finished product: Alprostadil for Injection or PGE_1•α-CD Name of active ingredient(s): Prostaglandin E_1 (PGE_1) or Alprostadil		SUMMARY OF CLINICAL TRIALS HUMAN PHARMACOKINETICS & BIOAVAILABILITY STUDIES (STUDIES)							
Study No. Investigator Dates	Study Design	Diagnosis + Criteria for Inclusion	Subjects/Patients N (W/B/H/O)	Age Range (yrs)	Per R_x Group	Drug Regimen	Duration of Treatment	Results	Safety Results
KU-620-004 (PHAKI-847/1994; F-8878) Jünemann, Hatzinger, and Wetterauer (Germany) January 1994 - October 1994	multicenter, open-label, pilot study	ED of various etiologies including arterial, venous/ cavernous, neurogenic, and mixed	19 (race not collected)	26-65	19 17	20 μg PGE_1 screening injection 20 μg PGE_1 I.C. injection	2 days	Plasma concentrations of PGE_1, PGE_0, and 15-keto-PGE_0 increased to more than 10 times endogenous concentrations following intracavernosal injection of PGE_1. No differences were seen in the pharmacokinetics of these compounds in patients with an optimum erectile response compared to patients without an optimum erectile response. Following administration, C_{max} for PGE_1 was 119 ± 104 (pg/mL).	6 (35%) patients reported adverse experiences. No deaths, serious adverse experiences, or discontinuations were reported.

#4

163000

ED = erectile dysfunction; W = white; B = black; H = hispanic; O = other; M = male; I.C. = intracavernosal; I.A. = intraarterial; I.V. = intravenous; Per R_x Grp. = number of patients or subjects/treatment group.

Table A
Table of All Studies

Name of company: Schwarz Pharma AG Name of finished product: Alprostadil for Injection or PGE_1•α-CD Name of active ingredient(s): Prostaglandin E_1 (PGE_1) or Alprostadil		SUMMARY OF CLINICAL TRIALS HUMAN PHARMACOKINETICS & BIOAVAILABILITY STUDIES (STUDIES)							
Study No. Investigator Dates	Study Design	Diagnosis + Criteria for Inclusion	Subjects/Patients N (W/B/H/O)	Age Range (yrs)	Per R_x Group	Drug Regimen	Duration of Treatment	Results	Safety Results
Pharmacokinetic Studies - Other Routes of Administration									
PHAKI-725 Strobel (Germany) May 1991 - June 1991	single-blind, placebo-controlled, randomized, crossover	healthy volunteers	13 (race not collected)	18-36	13 13	Placebo (647 μg α-cyclodextrin) 60 μg PGE_1 I.V. infusion	9 days (1 day of PGE_1)	Interindividual variability in plasma concentrations of PGE_1 and of PGE_1 metabolites during I.V. infusion.	7 (54%) PGE_1 volunteers reported adverse experiences. No deaths, discontinuations, or serious adverse experiences were reported.
PHAKI-729 Strobel (Germany) Mar. 1992 - Apr. 1992	controlled, randomized, crossover	healthy volunteers	12 (race not collected)	20-35	12 12 12	30 μg PGE_1 60 μg PGE_1 120 μg PGE_1 I.V. infusion	3 days with wash-out period	interindividual variability in plasma concentrations of PGE_1 and its metabolites; dose-dependent increases in C_{max} and AUC; exact linearity of pharmacokinetics of PGE_1 and its metabolites observed within dose range of 30 to 120 μg/2-hr I.V. infusion	8 (67%) volunteers reported adverse experiences. No deaths, discontinuations, or serious adverse experiences were reported.

#5

#6

000322

ED = erectile dysfunction; W = white; B = black; H = hispanic; O = other; M = male; I.C. = intracavernosal; I.A. = intraarterial; I.V. = intravenous; Per R_x Grp. = number of patients or subjects/treatment group.

Table A
Table of All Studies

Name of company: Schwarz Pharma AG Name of finished product: Alprostadil for Injection or PGE_1•α-CD Name of active ingredient(s): Prostaglandin E_1 (PGE_1) or Alprostadil		SUMMARY OF CLINICAL TRIALS HUMAN PHARMACOKINETICS & BIOAVAILABILITY STUDIES (STUDIES)							
Study No. Investigator Dates	Study Design	Diagnosis + Criteria for Inclusion	Subjects/Patients N (W/B/H/O)	Age Range (yrs)	Per R_x Group	Drug Regimen	Duration of Treatment	Results	Safety Results
PHAKI-829 Reh L.A.B. GmbH & Co. (Germany) 10 Dec. 1992 - 11 Dec. 1992	open-label, randomized, four-way crossover, pilot study	healthy volunteers	6 (race not collected)	21-38	 6 6 6	PGE, I.V.: 120 μg in isotonic saline over 30 min 120 μg in isotonic saline over 15 min 40 μg in isotonic saline over 5 min 120 μg in buffered lipid emulsion over 15 min	2 days	Administration as a lipid emulsion caused significantly higher levels of PGE_1, whereas the PGE_0 and 15-keto-PGE_0 concentrations remained unchanged in comparison with the analogous aqueous treatments. Within the three aqueous treatments, concentrations of PGE_1, PGE_0, and 15-keto-PGE_0 remained in the same range; there was no influence of the infusion time on the AUC of PGE_1, PGE_0, or 15-keto-PGE_0.	5 (83%) volunteers reported adverse experiences. No deaths, discontinuations, or serious adverse experiences were reported.

#7

000323

ED = erectile dysfunction; W = white; B = black; H = hispanic; O = other; M = male; I.C. = intracavernosal; I.A. = intraarterial; I.V. = intravenous; Per R_x Grp. = number of patients or subjects/treatment group.

Table A
Table of All Studies

Name of company: Schwarz Pharma AG Name of finished product: Alprostadil for Injection or PGE_1•α-CD Name of active ingredient(s): Prostaglandin E_1 (PGE_1) or Alprostadil		SUMMARY OF CLINICAL TRIALS HUMAN PHARMACOKINETICS & BIOAVAILABILITY STUDIES (STUDIES)							
Study No. Investigator Dates	Study Design	Diagnosis + Criteria for Inclusion	Subjects/Patients N (W/B/H/O)	Age Range (yrs)	Per R_x Group	Drug Regimen	Duration of Treatment	Results	Safety Results
Drug Interaction Studies - Other Routes of Administration									
PHAKI-824 Heuer (Germany) L.A.B. GmbH & Co. (Germany) November 1992	open-label, crossover	healthy volunteers	12 (race not collected)	20-39	12 12	Day 1: 1 tab (0.25 mg) digoxin q8h; Days 2 - 9: 1 tab (0.25 mg) digoxin qd (Treatment A) Day 9: 90 μg PGE_1 dissolved in 150 mL of 0.9% saline (Treatment B) + last dose of Treatment A 15 min. after start of I.V. infusion 3-hr I.V. infusion	9 days (1 day of PGE_1)	No difference in plasma concentration of digoxin between treatment groups was observed.	7 (58%) PGE_1 + digoxin volunteers and 8 (67%) digoxin volunteers reported adverse experiences. No deaths, discontinuations, or serious adverse experiences were reported.

#8

000324

ED = erectile dysfunction; W = white; B = black; H = hispanic; O = other; M = male; I.C. = intracavernosal; I.A. = intraarterial; I.V. = intravenous; Per R_x Grp. = number of patients or subjects/treatment group.

Table A
Table of All Studies

Name of company: Schwarz Pharma AG Name of finished product: Alprostadil for Injection or PGE_1•α-CD Name of active ingredient(s): Prostaglandin E_1 (PGE_1) or Alprostadil		SUMMARY OF CLINICAL TRIALS HUMAN PHARMACOKINETICS & BIOAVAILABILITY STUDIES (14 STUDIES)							
Study No. Investigator Dates	Study Design	Diagnosis + Criteria for Inclusion	Subjects/Patients N (W/B/H/O)	Subjects/Patients Age Range (yrs)	Subjects/Patients Per R_x Group	Drug Regimen	Duration of Treatment	Results	Safety Results
PHAKI-825R Baedeker (Germany) L.A.B. GmbH & Co. (Germany) May 1993 - June 1993	open-label, randomized, crossover	volunteers with type II diabetes mellitus	12 (12/0/0/0) 8 males 4 females	53-72	12	1-3 tabs (3.5 mg) glibenclamide (≥ 3.5 mg total dose) (Treatment A) 90 μg PGE_1 dissolved in 150 mL 0.9% saline + 1-3 tabs glibenclamide (Day 16 or 18 only) (Treatment B) 3-hr I.V. infusion	5 days (1 day of PGE_1)	C_{max} values of glibenclamide were different between treatment groups; AUC of glibenclamide equivalence between groups; no clinically relevant, between-group differences in plasma glucose levels.	6 (50%) PGE_1 + glibenclamide volunteers reported adverse experiences. No deaths, discontinuations, or serious adverse experiences were reported.

ED = erectile dysfunction; W = white; B = black; H = hispanic; O = other; M = male; I.C. = intracavernosal; I.A. = intraarterial; I.V. = intravenous; Per R_x Grp. = number of patients or subjects/treatment group.

Table A
Table of All Studies

Name of company: Schwarz Pharma AG Name of finished product: Alprostadil for Injection or PGE_1•α-CD Name of active ingredient(s): Prostaglandin E_1 (PGE_1) or Alprostadil		SUMMARY OF CLINICAL TRIALS HUMAN PHARMACOKINETICS & BIOAVAILABILITY STUDIES (STUDIES)							
Study No. Investigator Dates	Study Design	Diagnosis + Criteria for Inclusion	Subjects/Patients N (W/B/H/O)	Subjects/Patients Age Range (yrs)	Subjects/Patients Per R_x Group	Drug Regimen	Duration of Treatment	Results	Safety Results
PHAKI-826 Heuer I.A.B. GmbH & Co. (Germany) 29 June 1993 - 29 July 1993	open-label, randomized, crossover	healthy volunteers	12 (race not collected)	22-40	12 12	I.V. bolus injection of heparin 5000 I.U. PGE_1 90 µg infusion over 3 hours followed by an I.V. bolus injection of 5000 I.U. heparin	1 day (1-week washout) 1 day	Higher increases in the partial thromboplastin times and thrombin times were observed for the combination treatment of PGE_1 + heparin compared to heparin alone. Heparin concentrations were clearly higher from baseline for the combination treatment compared to heparin alone; results show possible interaction between PGE_1 and heparin.	9 (75%) PGE_1 + heparin volunteers reported adverse experiences. No deaths, discontinuations, or serious adverse experiences were reported.

10

000326

ED = erectile dysfunction; W = white; B = black; H = hispanic; O = other; M = male; I.C. = intracavernosal; I.A. = intraarterial; I.V. = intravenous; Per R_x Grp. = number of patients or subjects/treatment group.

Table A
Table of All Studies

Name of company: Schwarz Pharma AG Name of finished product: Alprostadil for Injection or PGE_1•α-CD Name of active ingredient(s): Prostaglandin E_1 (PGE_1) or Alprostadil	SUMMARY OF CLINICAL TRIALS HUMAN PHARMACOKINETICS & BIOAVAILABILITY STUDIES (STUDIES)							
Study No. Investigator Dates	Study Design	Diagnosis + Criteria for Inclusion	Subjects/Patients N (W/B/H/O)	Subjects/Patients Age Range (yrs)	Subjects/Patients Per R_x Group	Drug Regimen	Duration of Treatment	Results	Safety Results
PHAKI-827 Heuer (Germany) March 1993 - April 1993	open-label, crossover	healthy volunteers	24 (race not collected)	20-40	24 24	50 mg warfarin sodium orally (Treatment A) 90 µg PGE_1 dissolved in 150 mL 0.9% saline 3-hr I.V. infusion (6 days) + 50 mg warfarin sodium orally (Treatment B)	2 days	Pharmacokinetic parameters for R- and S-warfarin and effects on coagulation parameters (PT and PTT) were equivalent for both treatment groups.	6 (25%) warfarin volunteers and 24 (100%) PGE_1 + warfarin volunteers reported adverse experiences. No deaths, discontinuations, or serious adverse experiences were reported.

000327

ED = erectile dysfunction; W = white; B = black; H = hispanic; O = other; M = male; I.C. = intracavernosal; I.A. = intraarterial; I.V. = intravenous; Per R_x Grp. = number of patients or subjects/treatment group.

Table A
Table of All Studies

Name of company: Schwarz Pharma AG Name of finished product: Alprostadil for Injection or PGE_1•α-CD Name of active ingredient(s): Prostaglandin E_1 (PGE_1) or Alprostadil		SUMMARY OF CLINICAL TRIALS HUMAN PHARMACOKINETICS & BIOAVAILABILITY STUDIES (STUDIES)							
Study No. Investigator Dates	Study Design	Diagnosis + Criteria for Inclusion	Subjects/Patients N (W/B/H/O)	Subjects/Patients Age Range (yrs)	Subjects/Patients Per. R_x Group	Drug Regimen	Duration of Treatment	Results	Safety Results
PHAKI-828 Weber (Germany) 6 Dec. - 29 Dec. 1992	open-label, randomized, crossover	healthy volunteers	12 (12/0/0/0)	23-38	12 12 12	1.0 g acetylsalicylic acid (ASA) orally (Treatment A) 90 µg PGE_1 dissolved in 150 mL 0.9% saline 3-hr I.V. infusion (Treatment B) 1.0 g ASA + 90 µg PGE_1 dissolved in 150 mL 0.9% saline 3-hr I.V. infusion (Treatment C)	2 days each sequence (2 days of PGE_1)	AUC and C_{max} of PGE_1 and its metabolites influenced slightly by concomitant ASA; clinical relevance questionable due to inter- and intra-individual variability of PGE_1 concentrations.	1 (8%) ASA volunteer, 8 (67%) PGE_1 volunteers, and 5 (42%) PGE_1 + ASA volunteers reported adverse experiences. No deaths, discontinuations, or serious adverse experiences were reported.

-- = Not Available

000328

ED = erectile dysfunction; W = white; B = black; H = hispanic; O = other; M = male; I.C. = intracavernosal; I.A. = intraarterial; I.V. = intravenous; Per R_x Grp. = number of patients or subjects/treatment group.