CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Brand Name	Ventavis (proposed)
Generic Name	Iloprost
Formulation/Strength	Solution for inhalation/ 10 µg/mL
NDA	21-779
Applicant	CoTherix, Inc.
Submission Dates	June 30, 2004, September 8, 2004 and November 16, 2004
OCPB Division	DPE1
OND Division	Cardio-Renal Drug Products
Reviewer	Robert O. Kumi, Ph.D.
Team Leader	Patrick Marroum, Ph.D.

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I. EXECUTIVE SUMMARY

In NDA 21-779, Ventavis (iloprost) is proposed for the treatment of pulmonary arterial hypertension (PAH) in patients with New York Heart Association Class III or IV symptoms [redacted] Iloprost will be marketed as a 10 µg/mL solution (provided in ampule) for inhalation via a ProDose Nebulizer or similar nebulizer device. The proposed maintenance dosage is 5 µg, six to nine times per day during waking hours depending on individual need and tolerability. Four clinical studies were conducted with iloprost inhalation solution in patients with PAH; an additional inhalation study was conducted in healthy volunteers. Several other studies were conducted in healthy subjects and various patient groups, however, iloprost was administered intravenously or orally in these other studies.

A. Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed the information submitted to NDA 21-779. The clinical pharmacology and biopharmaceutics information provided in NDA 21-779 is acceptable provided that satisfactory agreement is reached between the applicant and the Agency regarding labeling language. Please refer to the Appendix (pg. 30) for OCPB revised labeling.

Comment to Medical Reviewer on Dosage Adjustment in Special Populations

Iloprost dosage adjustment is required in patients with moderately impaired hepatic (Child Pugh Class B) or impaired renal (CLcr ≤ 30 mL/min) function. The initial dose for these two classes of patients should be 1.25 µg iloprost; however, the applicant does not have a dose controlling disc for the 1.25 µg dose strength. The applicant only proposed a 2.5 and 5.0 µg dose controlling disc for iloprost delivery.

B. Phase IV Commitments

None

C. Summary of Clinical Pharmacology and Biopharmaceutic Findings

The clinical pharmacology and biopharmaceutics development program for the use of iloprost in pulmonary arterial hypertension included over 15 studies in which iloprost was administered by the oral, intravenous or inhaled route. Additionally, iloprost was evaluated in three *in vitro* studies. Studies included in NDA 21-779 are summarized in Table 1. In general studies involving oral administration were not reviewed because they are not relevant for evaluation of this NDA.

Table 1: Clinical Pharmacology and Biopharmaceutics Studies

Study Report	Evaluation Conducted	Iloprost Administered		Reviewed
		Route	Formulation	
	PK and PD studies with inhaled, oral or intravenous iloprost			
AX15	PK/PD in PAH Patients	Inhalation	Solution	Yes
6210/6496	PK	Oral and IV	Solution	Yes
7312	PK/PD	Oral and IV	Solution	Yes
9356	PK in PAOD patients	Oral and IV	Capsule and Solution	No
AN76	PK and PD in PAOD Patients	Oral	Capsule	No
AI07	PK in patients with TAO	Oral and IV	Capsule and Solution	No
AG12	BE of two formulations	Oral	Capsule	No
AS07	BE of two formulations	Oral	Capsule	No
8432	PK in hepatic dysfunction	IV	Solution	Yes
8148	PK in renal insufficiency	IV	Solution	Yes
AM75	PK in hepatic dysfunction	Oral	Capsule	Yes
9357	Food effects	Oral	Capsule	No
	Drug Interactions between iloprost and coadministered drug			
8168	PD: Iloprost-Captopril	IV	Solution	Yes
8412	PD: Iloprost-nifedipine, mepindolol, pentoxifylline	IV	Solution	Yes
A646	PK/PD: iloprost-digoxin	IV	Solution	Yes
B599	PD: iloprost-nifedipine, diltiazem	IV	Solution	Yes
B598	PD: iloprost-nifedipine, diltiazem	IV	Solution	Yes
AD19	PK/PD: iloprost-acetylsalicylic acid	IV	Solution	Yes
	In vitro studies with iloprost			
A09477	Inhibitory effects on CYP	NA	Solution	Yes
A09478	CYP characterization	NA	Solution	Yes
4495	Plasma Protein Binding	NA	Solution	Yes

Table Legend

PK pharmacokinetics
PD pharmacodynamics (platelet function and hemodynamics)
PAH primary arterial hypertension
PAOD peripheral arterial occlusive disease
TAO thromboangitis obliterans

Key Clinical Pharmacology and Biopharmaceutics Findings and Information

1. Pharmacokinetics

Absorption/Absolute bioavailability

- Iloprost absolute oral bioavailability is 13 – 19 % following oral administration
- The absolute bioavailability for inhaled iloprost has not been determined.

Dose Proportionality

Iloprost exposure increased in a dose proportional manner over the 1 to 3 ng/kg IV infusion dose range

Drug Distribution

- Following intravenous administration, iloprost volume of distribution ~ 0.8 L L/kg.
- Iloprost is approximately 60 % bound by plasma proteins at clinically relevant concentrations.
- Albumin is the main plasma protein that binds iloprost; iloprost is approximately 75 % bound by albumin at clinically relevant concentrations.

Metabolism

In vitro information

- Iloprost has a low cytochrome P450 dependent metabolism; only two minor metabolites were formed by CYP enzymes. CYP 1A2, CYP 2C9, CYP 2C19 and CYP 3A4 may be involved in the metabolism of iloprost.
- Iloprost has a low inhibitory potency (IC50 values > 50 μM for all major CYPs) on CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4.

In vivo information

Beta oxidation appears to be the main metabolic pathway of iloprost. Unchanged iloprost comprised ~ 20 % of total plasma radioactivity following IV infusion of ^{3}H-iloprost. The two main metabolites of iloprost are tetranor-iloprost (more abundant) and dinor-iloprost; additional metabolites are mainly conjugated (glucuronides and sulfates) forms of tetranor-iloprost.

Elimination

Following oral and IV administration, disposition of iloprost is biphasic; the alpha phase < 10 minutes and beta phase < 30 minutes. For inhaled iloprost, the decline in drug concentrations is monophasic with $t_{1/2}$ < 12 minutes. Mass balance indicates that iloprost is ultimately excreted in the urine (80 %) and feces (20 %) as iloprost metabolites; no unchanged iloprost is excreted. The breakdown of metabolites is unknown.

2. Pharmacodynamic Effects of iloprost

Ex vivo and *in vitro* effects (platelet aggregation and function)

Several studies evaluated the effect of iloprost on platelet function. Although the magnitude of effect varied in different studies, the following trends were observed:

- For IV and orally administered iloprost or iloprost incubated with blood cells, there was a dose-dependent or concentration-dependent inhibition of ADP and collagen induced platelet aggregation.
- Intravenously and orally administered iloprost increased cAMP content of platelets during infusion (IV) and after administration (oral).
- The *in vitro* sensitivity of platelets to iloprost was not altered by short term pretreatment with iloprost.

In vivo effects (hemodynamics)

- The effect of iloprost on hemodynamic measures lasts for ~ 2 hours; this effect is complete prior to the following inhalation.
- Iloprost decreased systemic blood pressure and increased heart rate or pulse rate.

3. PK/PD drug-drug interaction information

Overall, no clinically relevant PK/PD interactions were observed between iloprost and comedications used in PAH therapy. However, iloprost has the potential to increase the hypotensive effect of vasodilators and antihypertensive agents.

- Iloprost does not alter the exposure of **digoxin** when coadministered once daily.
- Therapeutic doses of **acetylsalicylic acid** (10 to 300 mg QD) do not alter iloprost pharmacokinetics (constant CL) over the 0.5 to 2.0 ng/kg/min iloprost dose range.
- There do not appear to be any relevant pharmacodynamic (hemodynamic) interactions between intravenous iloprost and drugs (**captopril, nifedipine, mepindolol**, and **diltiazem**) commonly coadministered during PAH therapy.
- Pharmacodynamic interactions were observed between iloprost + coadministered drug with respect to platelet function: iloprost combined with **diltiazem** or **nifedipine** decreased platelet aggregation but did not have an effect on platelet count.

4. QT/QTc Information

- Administration of inhaled iloprost does not cause a clinically or statistically significant increase in QTc. At the 2.5 µg dose and at the maximum tolerated/studied dose (20 µg) the QTc changes were +2 and + 3 msec, respectively.
- An iloprost exposure response (QT prolongation) relationship was not evident.

5. Special Populations

- Renal Insufficiency

Iloprost clearance appears to be affected by renal function: Subjects with mean CLcr ~ 0.28 mL/min/kg (Group I) had CL values that were comparable in magnitude to that of normal subjects without renal impairment (CL ~ 20 mL/min/kg); whereas, subjects with CL_{cr} ~ 0.17 mL/min/kg (Group II, requiring dialysis) had CL values (CL ~ 5 mL/min/kg) that were approximately four times lower than those in normal subjects. The terminal half lives were < 1 hr and ~ 7 hr in Groups I and II, respectively.

- Hepatic Insufficiency

Based on a cross study comparison (IV infusion), subjects with hepatic insufficiency in Child Pugh Class B have iloprost CL that is half that of normal subjects. Following oral administration, relative to subjects with normal hepatic function, the CL of subjects in Child Pugh Class A was ~5 times lower and Child Class B were ~15 times lower. Hepatic function did not appear to affect the half-life following oral or IV administration.

6. Drug Delivery Device (Nebulizer)

The HaloLite system was used in all clinical trials, apart from the QT study where the ProDose system was used. The ProDose system, proposed for Ventavis delivery, is comparable (based on *in vitro* data) to the HaloLite system. ProDose requires approximately 10 minutes to deliver a 5 µg dose; the time required to achieve the desired dose depends on the subject's breathing pattern. The ProDose or similar nebulizer should have the following **specifications** (per proposed label) for iloprost delivery:

a) [redacted]

b) a controlled dose at mouthpiece of 2.5 µg or 5 µg per inhalation session as prescribed,

c) no more than 5 µg iloprost should be delivered within minutes

/S/

Robert O. Kumi, Ph.D.
Clinical Pharmacology Reviewer
Division of Pharmaceutical Evaluation I

Date_____

Concurrence:

/S/

Patrick Marroum, Ph.D.
Clinical Pharmacology and Biopharmaceutics Team Leader
Cardio-Renal Drug Products
Division of Pharmaceutical Evaluation I

Date_____

Briefing Attendees
M. Mehta, Ph.D.
A. Rahman, Ph.D.
H. Malinowski, Ph.D.
A. Selen, Ph.D.
C. Sahajwalla, Ph.D.
R. Powell, Pharm.D.
M. Gordon, M.D
M. Desai, M.D.
A. Bhattaram, Ph.D.
P. Jadhav.

II. QUESTION BASED REVIEW

A. What are the general attributes of iloprost?

1. Regulatory Background

FDA-Related Events

The following regulatory events took place in relation to NDA 21-779: Pre-IND meeting on 11/20/03; Guidance Class C on 01/29/04 submitted to IND 65,820; Guidance Class C on 03/09/04 submitted to IND 65,820; Pre-NDA CMC meeting on 05/12/04; Pre-NDA meeting on 05/13/04; and Filing Meeting on 08/13/04

Non-US Regulatory Events (Marketing History)

Iloprost is currently approved as Ilomedin for IV administration in ~ 30 countries for the treatment of occlusive arterial disease. In September 2003, EMEA granted marketing authorization for Ventavis® (iloprost) for the treatment of patients with primary pulmonary hypertension.

2. Highlights of chemistry and physical-chemical properties of the drug substance and product

Ventavis® (iloprost) inhalation solution is a clear, colorless, sterile solution 10 µg/mL iloprost tromethamine formulated for inhalation via a nebulizer. Each 3 mL single-use glass ampule will deliver 2 mL (20 µg iloprost) of the solution to the nebulizer medication chamber.

The compositions of the iloprost formulations are summarized in Table 2; Ilomedin 20 is an approved parenteral formulation of iloprost in Europe, Ilomedin 20 Diluted 1:1 was used in the clinical studies (Phase 1, 2, and 3 studies) and Ventavis is the proposed commercial inhalation formulation.

Table 2: Iloprost inhalation formulations

Ingredient	Ilomedin 20® (mg/mL)	Ilomedin 20® Diluted 1:1 with Saline (mg/mL)	Ventavis® (mg/mL)
Iloprost	0.020	0.010	0.010
Ethanol 96%			0.810
Trometamol			0.121
Hydrochloric acid			0.510
Sodium chloride			9.000
Water for injection			
Total weight	1002.400	1003.550	1003.300

The solution contains no preservatives and the nominal pH of the solution is 8.1. Additional physical-chemical characteristics of iloprost follow:

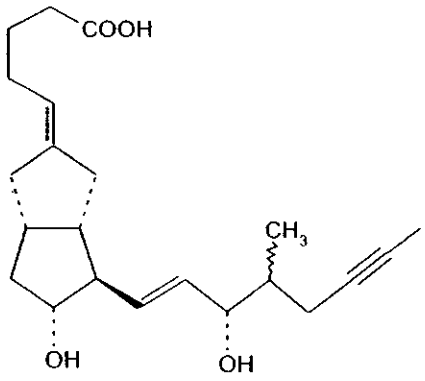
Chemical name 5-{(E)-(1S, 5S, 6R, 7R)-7-Hydroxy-6-[(E)-(3S, 4RS)-3-hydroxy-4-methyl-1-octen-6-ynyl]-bicyclo[3.3.0]oct-3-ylidene}-pentanoic acid.

Stereochemistry Iloprost has 6 asymmetrical carbons (5 of the carbons are fixed) The remaining asymmetric carbon has both an R configuration and an S configuration. Iloprost consists of a mixture of the R and S diastereomers at a ratio of approximately 53:47.

Molecular formula $C_{22}H_{32}O_4$

Molecular weight 360.49

Structural formula



Miscellaneous Iloprost is a chemically stable synthetic prostacyclin (PGI_2) analogue. Iloprost's pharmacological activity is similar to that of natural PGI_2 but has a greater chemical stability and longer half-life compared with PGI_2.

Miscellaneous Formulation Information

Iloprost was administered as an intravenous and oral solution in several studies; in these studies the iloprost solution was similar to that used in Ventavis (diluted Ilomedin 20).

Reviewer's Note on Iloprost Formulations

This review focuses on the solution for inhalation. However, relevant information was obtained with the intravenous and oral formulations; this information was considered in this CPB assessment as necessary.

3. Proposed Mechanism of Action and Indication

The reported primary mechanisms of action of iloprost are pulmonary vasodilatation and inhibition of platelet aggregation and activation. Ventavis (iloprost) is proposed for the treatment of pulmonary arterial hypertension (PAH) in patients with New York Heart Association Class III or IV symptoms

4. Proposed Administration Route and Dosage (Applicant's Rationale)

Ventavis® is intended for inhalation using a nebulizer. The applicant's rationale for using the inhaled route is to provide high local concentrations within the lung, while minimizing the systemic (oral and IV route) side effects of prostacyclin therapy and avoiding complication of indwelling catheters (IV route). Therefore, inhaled iloprost potentially offers a higher therapeutic index than oral or IV iloprost. The dosage at the mouthpiece is as follows: First inhaled dose should be 2.5 µg. If this dose is well tolerated, future dosing should be increased and maintained at 5 µg. The administration frequency should be 6 to 9 times per day during waking hours according to individual need and tolerability.

B. What are the general clinical pharmacology characteristics of iloprost?

1. Design features of clinical studies used to support dosing in PAH

The design features of the clinical studies used to support dosing in patients with PAH are summarized in Table 3. The iloprost dosage studied in the three key trials are:

- Phase 3: 2.5 to 5 µg/dose up to 9 times daily (maximum daily dose 45 µg)
- Phase 2: 50 to 200 µg per day in divided doses
- Phase 1: 5 µg single dose, given 3 times with three different nebulizers

2. Clinical response (efficacy) endpoints

The primary clinical response endpoints in this application are:

a) improved exercise capacity (6 minute walk test) at 12 weeks by ≥ 10% vs. baseline
b) improvement by at least one NYHA class at 12 weeks vs. baseline
c) no deterioration of pulmonary hypertension or death at any time before 12 weeks.

The applicant proposed a composite endpoint comprising the endpoints a, b and c. Secondary endpoints included the Mahler transitional dyspnea index, quality of life indices, and hemodynamic monitoring. Hemodynamic monitoring included various systemic and pulmonary (via catheter) hemodynamic measures such as cardiac output, diastolic, systolic and mean arterial pressures, heart rate, and derived measures. Pulmonary vascular resistance (PVR) was considered the most relevant pharmacodynamic measure because it directly reflects the pulmonary hypertensive state

$$PVR = \frac{80 \times (mPAP - PAWP)}{CO}$$

where, mPAP = mean pulmonary arterial pressure, PAWP is the pulmonary arterial wedge pressure and CO is the cardiac output

Table 3: Design features of the primary clinical studies for iloprost in treating PAH (per applicant)

	ME97218 (Phase 3)	ME98008 (Phase 2)	ME98051 (Phase 1)
Randomization	Yes	Yes	Yes
Blinding	Yes	No	No
Control	Placebo	Common background therapy (excluding prostanoids)	Crossover study
Design	Double-blind parallel	Open-label parallel	Single dose crossover
Study Duration	12 weeks randomized and long-term open label (ongoing Study 303045)	12 weeks randomized and 2 years open label	1 day
Patient Population	PPH or SPH NYHA Class III or IV	PPH or SPH NYHA Class II, III, or IV	PPH or SPH
Sample size	101 iloprost 102 placebo	30 iloprost 33 control	13 iloprost
Primary efficacy endpoint	Composite response[a]	None	None
Secondary efficacy endpoints	6-minute walking distance NYHA Class changes Deterioration of PAH Mortality Mahler Dyspnea Index Hemodynamic parameters and gas exchange Quality of Life Need for transplantation	Composite response[b] 6-minute walking distance NYHA Class changes Deterioration of PAH Mortality Mahler Dyspnea Index Hemodynamic parameters and gas exchange Quality of Life Need for transplantation	Hemodynamic parameters and gas exchange

[a] The composite response endpoint was defined as (1) improvement in the 6-minute walk test at 12 weeks by at least 10% vs. baseline; (2) improvement by at least one NYHA class at 12 weeks vs. baseline; and (3) no death or deterioration of PAH before 12 weeks

[b] Composite response endpoint was retrospectively defined for the phase 2 study as (1) improvement in the 6-minute walk test by at least 10% vs. baseline; (2) improvement by at least one NYHA class vs. baseline; and (3) no death

3. Identification and measurement of iloprost concentrations in plasma

Total iloprost (total = S and R iloprost diastereomers) concentrations were adequately identified and measured in most studies. However, assay information was incomplete in several studies (Study 6210, Study 7312, Study 8432, and Study 8148); the applicant indicated that additional assay information was not available. Only the LC/MS/MS assay distinguished the iloprost stereoisomers (QT study). Please refer to Section for additional assay information.

Activity of iloprost components

In vitro comparisons of iloprost (total) with its individual diastereomers demonstrated that the 4S-iloprost isomer was approximately 3 times more potent than iloprost, and that the 4R- iloprost isomer was approximately 4 times less potent than iloprost, with regard to vasodilatory effects. Similarly, the 4S-iloprost isomer was approximately twice as potent as iloprost, and the 4R- iloprost was considerably less potent than iloprost, with

regard to in vitro blood- pressure-lowering effects. For inhibition of platelet aggregation, the 4S- iloprost isomer was 1.5- 2 times more potent than iloprost, whereas the 4R-isomer was 7 times less potent than iloprost.

According to the applicant, the tetranor metabolite of iloprost (iloprost's main degradation product) had no effect on blood pressure, heart rate, or platelet aggregation in animals (Report 8127). However, this conclusion is based on a nonclinical study in mice and may not be applicable to humans. The *in vitro* activity of iloprost metabolites was not evaluated.

4. Iloprost Exposure-Response

An exposure-response relationship was not formally evaluated in this application. However, in the clinical trials with inhaled iloprost (Phase 1, 2 and 3 trials previously cited), oral iloprost and intravenous (Studies 7312 and 6496), various dose regimens were employed that demonstrated a wide dose-response range.

a) Exposure-response (Efficacy)

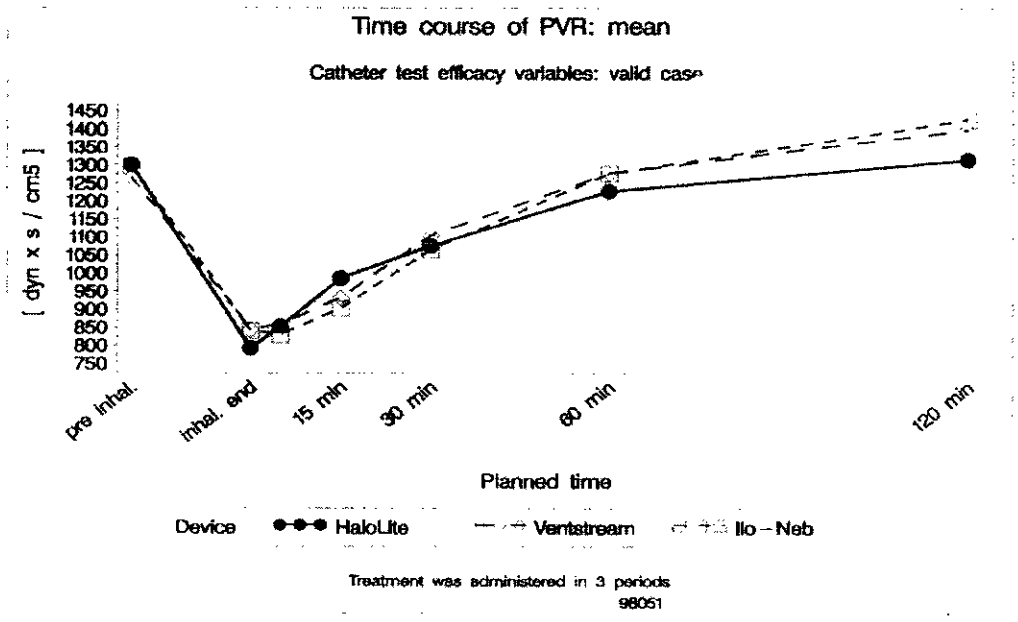
Iloprost effect on platelet function

In the oral and IV studies there was dose dependent inhibition of ADP- and collagen-induced platelet aggregation. Platelet function was not assessed for the inhaled route. These inhibitory effects were observed within 30 minutes of drug administration and persisted for ≥ 3 hours. Due to the sampling schedule the exact time for onset and offset of platelet inhibition is unclear.

Iloprost effect on hemodynamic measures

The effect of iloprost on pulmonary and systemic hemodynamics, including decrease in PVR and decreasing in mPAP relative to preinhalation were evident during inhalation and persisted for 60 to 90 minutes post inhalation (Figure 1).

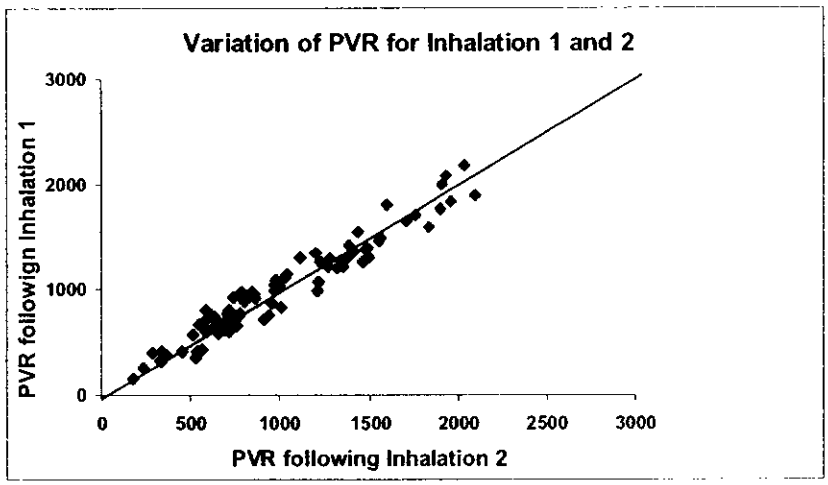
Figure 1: Time course of PVR in Study AX15 (per applicant)



These findings were seen in the acute setting (Phase 1 trial) and in Phase 2 and Phase 3 study. There was no evidence of tolerance development in the long-term trials, as the iloprost dose remained effective throughout the trial without the need for dose increases.

Figure 2 shows that hemodynamic effects for consecutive iloprost doses are not additive, indicating that the time course of effect is independent of the inhalation number.

Figure 2: Time matched plot of PVR for inhalation 1 vs. 2 with line of identity (Phase 2 Study)



Miscellaneous PD Information (time course of PD effects)
Inspection of individual PD time course effects revealed the following trends during and after inhalation:

- PVR: There was a trend towards decreased PVR during and post inhalation in some cases (much clearer than for other PD variables) then a return to baseline.
- mPAP There was no clear trend; curves tended to be flat over the inhalation period, but this may have been a function of measurement times. In a few cases, there appeared to be an early drop in mPAP at the beginning of inhalation and a return to baseline two hours post inhalation
- PAWP: There was no clear trend; generally curves were flat. In some cases there was a slight decline during inhalation.
- CO: There was no clear trend. [Note: Systemic diastolic pressure mirrored the CO pattern]

The applicant reported the following dose thresholds associated with PD effects following administration of IV iloprost:

- Vasodilatation 1.0 ng/kg/min
- Increased heart rate 4.0 ng/kg/min
- Hypotension (rare) 4.0/ng/kg/min
- Aggregation inhibition 0.5 to 1.0 ng/kg/min

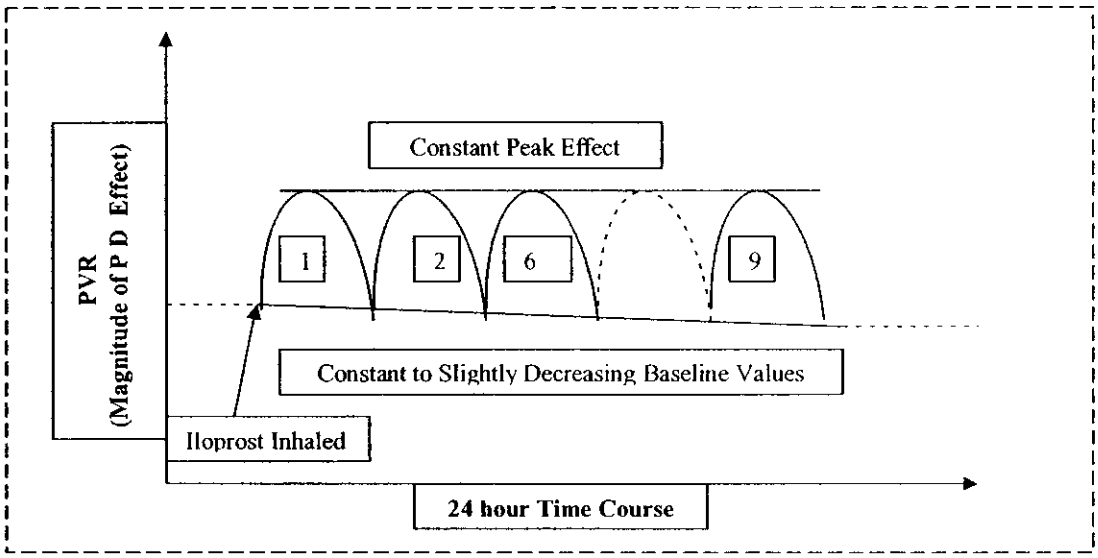
No specific PD thresholds (change in hemodynamic measure) have been defined to show efficacy in the PAH population. However, the standard NIH definition for PAH is:

- mPAP = 25 mmHg vs. 10 – 16 mmHg for normal
- PAWP = 15 mmHg vs. 5 – 13 mmHg for normal
- PVR > 3 Wood's units or ~ 240 dynes/second/cm^2 vs. 0.7 – 1.1 Wood's units or 90 – 250 dynes/second/cm^2 for normal

Schematic of Empirical PD Model

The PD (hemodynamic) clinical observations suggest that the following empirical model suitably describes the time course of drug effect.

Figure 3: Schematic PD Effect Model illustrating iloprost time-course



The antiplatelet effects and hemodynamic effects persist even when the drug is absent as the PK half-life of inhaled iloprost < 12 minutes, but PD effects last for > 1 hr. Theoretically, the efficacy of iloprost is linked to the interaction of iloprost with prostacyclin receptors, therefore, a short plasma half-life resulting in low systemic exposure may not be an accurate predictor of iloprost activity.

b) Exposure-response (Safety)

Systemic side effects such as headache and flushing were dose related, but this relationship could not be quantified. No clear time of onset or offset could be identified although in some cases iloprost therapy was discontinued (mainly with IV) shortly after therapy was initiated due to lack of tolerability. Generally adverse events resolved once iloprost therapy was discontinued. Other common adverse events associated with iloprost therapy include vasodilatation, nausea, trismus, hypotension and syncope.

Dose-Response and Systemic (Plasma) Exposure-Response

The Medical Reviewer indicates that in the QT study an inhaled iloprost dose ≥ 10 µg showed a higher incidence and severity of adverse events (particularly non-cardiac related tightness in the chest) than doses < 10 µg. Supratherapeutic doses (doses > 5 µg) were evaluated in the QT study, but iloprost PK were not accurately determined in the QT study. Iloprost exposure was not determined following inhalation in the Phase 2 or 3 studies, thus a systemic exposure-response relationship could not be evaluated. However, qualitative exposure-response information is available following IV and oral (clathrate) administration of iloprost. The oral and IV doses were generally well tolerated without evidence of dose-limiting toxicity. Ideally, inhaled iloprost should have been compared to IV infusion or to the oral iloprost clathrate formulation in the same patient population to strengthen the cross-route comparisons. Nevertheless, the exposure-safety profile of inhaled iloprost is supported by clinical data obtained with the oral and IV routes (n > 3000) of administration because iloprost's clinical effects (safety) are likely related to systemic exposure. Compared to the inhalation route of delivery, the systemic exposure after IV iloprost (doses up to 2 ng/kg/min for 6 hours) demonstrated a lower Cmax but greater AUC. The daily systemic exposure following oral administration (50 µg BID to 200 µg BID) is similar to or greater than that observed after inhalation of iloprost at the highest recommended dose (5 µg) when administered 6 to 9 times daily.

c) QT and QTc interval

Iloprost does not significantly alter the QTc interval as shown in Table 4.

Table 4: Mean change from baseline in Selected ECG Parameters

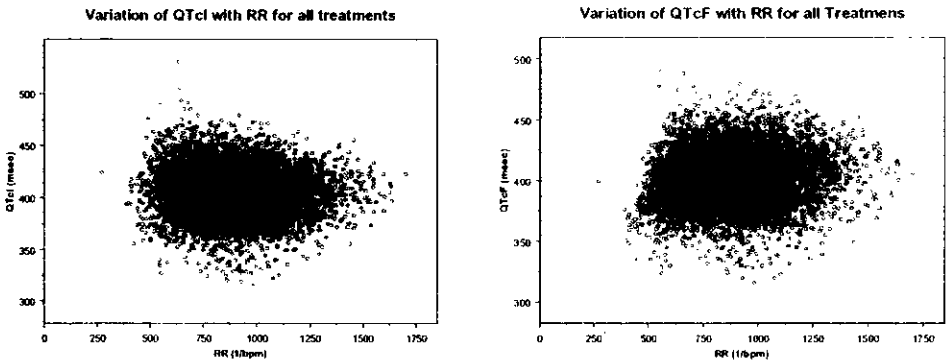
	Moxifloxacin	**Iloprost fixed**	**Iloprost Ascending**	**Placebo**
	400 mg single dose	2.5 µg inhaled iloprost given six times q 2h		
Total N	40	39	41	40
Heart Rate				
Heart Rate in bpm	1	5	7	3
QT or QTc in msec				
QT	1	-12	-14	-10
QTcI	3	-2	-1	-4
QTcF	3	-3	-2	-4
QTcB	4	2	4	-2

A parallel group design with four treatment groups was used to evaluate the QT prolonging potential of iloprost. The treatment groups were oral moxifloxacin (400 mg; positive control), inhaled iloprost (fixed 2.5 µg dose every two hours for 6 doses), inhaled iloprost (ascending dose every two hours for 6 doses; doses were 5, 7.5, 10, 12.5, 15 and 20 µg) and inhaled placebo (time-matched to iloprost ascending dose). ECGs were determined at baseline (Day 0) and on Day 1 (Treatment) over ~ 24 hr period. QT corrections were required for the analyses because QT depended on heart rate (RR used as surrogate for heart rate). The most suitable correction was the individually corrected QT (QTcI) and the Fridericia (QTcF) methods (Figure 4). After placebo and baseline

correction (double delta approach), moxifloxacin QTcI prolongation was +7 msec (Confidence interval: +3 to + 10) indicating that the assay was sensitive. For the iloprost fixed dose treatment there was a + 2 msec (- 2 to + 5 msec CI) QTc change and the maximum tolerated escalation dose arm showed a + 3 msec (- 1 to + 6 msec CI) effect.

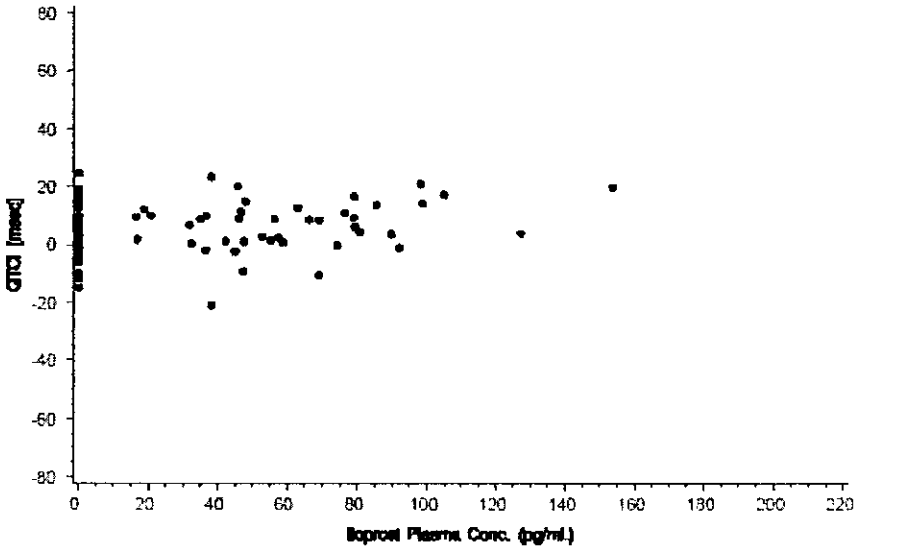
Figure 4: Correction of QT

QTcI vs. RR QTcF vs. RR



There was no evidence of an increase in QT interval associated with increases in measured iloprost concentrations suggesting there is no obvious PK-QTc effect based on the available data (Figure 5). However as noted previously, the iloprost PK determination appeared inadequate.

Figure 5: Maximum change in QTcI vs. plasma concentration (iloprost dose given at 1800 hr (per Applicant)



There were no QTc changes > 30 msec in any subject receiving iloprost.

In sum, the QTc data indicate that no precaution is required for iloprost with respect to its potential QT prolonging effects.

d) Acceptability of applicant's proposed dose and dosage regimen

The proposed dosage regimen is acceptable because sufficient efficacy and safety were shown in the pivotal clinical trial using the proposed regimen (See Medical Review). In the pivotal Phase 3 trial patients (PPH or SPH) initiated iloprost therapy at the 2.5 µg dose level and the dose was increased to 5 µg depending on individual tolerability. Dose titration of iloprost is consistent with the approach adopted for the other US approved PAH treatments: Flolan® (epoprostenol), a prostacyclin solution given by I.V. infusion; Remodulin® (treprostinil), a prostacyclin analogue given by subcutaneous infusion; and Tracleer® (bosentan), an endothelin receptor antagonist given orally.

The two hour interval between doses is reasonable based on the hemodynamic time course (figure 1) shown previously. Inhalation at intervals shorter than 2 hours is likely to result in excessive vasodilatation and severe hypotension that may decrease tolerability. A maximum of nine doses per day, equivalent to 18 hours awake seems reasonable. In the clinical trial the mean number of inhalations was ~ 7 and the median frequency of inhalations was 6. Only eight percent of the subjects inhaled iloprost at night occasionally or regularly. This reviewer agrees with the applicant that increasing the number of inhalations beyond nine times per day may lead to patient fatigue and potential non-compliance.

Unresolved Dosing Issue

One issue that remains subject to debate is the potential lack of drug effect during sleep or totally drug-free periods. The applicant indirectly addressed this issue by evaluating (comparing iloprost to placebo) the hemodynamics and change in walk distance at trough (over night break in dosing of nine or more hours, prior to waking up) at week 12. According to the applicant's analyses, the absolute change in walk distance always favored iloprost with p values ranging between 0.052 and 1.102 . The hemodynamic data displayed a similar trend; hemodynamic measures before inhalation improved or remained stable for the iloprost group whereas most hemodynamic parameters deteriorated significantly for the placebo group. Although the preceding supports a durable treatment effect for iloprost relative to placebo, it does not demonstrate effectiveness while the patient is asleep (presumably over night). Patients may have unanticipated activity at night that will require additional drug support. One should note that the applicant proposed that the label include the following: [redacted] This statement may have been included to minimize the effect of the drug-free periods; however, the statement is not supported by data.

5. Pharmacokinetic characteristics of iloprost and its major metabolites

PK Overview

Iloprost pharmacokinetics were determined following inhalation (via nebulizer), intravenous and oral administration. Clinical PK studies were performed with iloprost in

both healthy volunteers (Reports 6210, AG12, AS07 and 7312) and in patients with PAH (Report AX15), renal insufficiency (Report 8148), hepatic impairment (Reports 8432 and AM75), peripheral arterial occlusive disease (PAOD) (Reports AN76, 9356 and 9357), or thromboangitis obliterans (TAO) (Report AI07). The most relevant and reliable PK information were obtained from studies AX15 (inhalation), 6210, 7312. PK information following oral administration was also considered for some aspects of this review. The discussion that follows focuses on PK of the intended administration route (inhalation), however, information for other routes will be included as necessary.

a) Single Dose PK of iloprost

The single dose PK for iloprost are summarized in Table; no relevant multiple dose PK were available. Due to the short half-life, accumulation is not expected on multiple dosing.

Table 5: Iloprost PK Following Inhalation and IV administration

Study	AX15	6210	7312
Route	Inhaled	IV	IV
n	12	6	8
Subject	PAH Patient	Healthy	Healthy
Age	46 ± 12	30 ± 8	59 ± 5
Sex	3 male, 9 female	6 male	4 male, 4 female
Dose 1	5 µg	1 ng/kg/min for 45 minutes	2 ng/kg/min for 4 hr
Dose 2	NA	3 ng/kg/min for 45 minutes	NA
CL1 ^ (mL/kg/min)	NA	21.0 ± 3.0	24 ± 9
CL 2	NA	20.1 ± 5.2	NA
Vd 1 (L/kg)	NA	0.7 ± 0.4	1.1
Vd 2 (L/kg)	NA	0.8 ± 0.3	NA
C max 1 (pg/mL)	157 ± 64	46 ± 8	81 ± 35
C max 2 (pg/mL)	NA	135 ± 24	NA
AUC 1 (pg/h/mL)	47.8 ± 35.2	2190 ± 360	382 ± 188
AUC 2 (pg/h/mL)	NA	7140 ± 2050	NA
Tmax	11 (8-25)	NA	NA
$T_{1/2\ alpha}$	NA	3.8 ± 1.6; 2.8 ± 1.6	6 ± 4
$T_{1/2\ beta}$	7.9 ± 3.2	20.1 ± 7.2; 26.0 ± 7.2	31 ± 10
Assay	RIA	GC/MS	Radio-HPLC

Iloprost PK following inhalation were more variable than that after oral or IV administration.

b) PK of iloprost in PAH Patients vs. Normal Volunteers

There are no adequate data to compare the PK of inhaled iloprost in PAH patients to normal volunteers. PK data following iloprost inhalation are also absent from two important patient subclasses that may benefit from inhaled iloprost therapy: patients with chronic obstructive disease and asthma.

c) Characteristics of drug absorption

The characteristics of drug absorption were not specifically determined for inhaled iloprost; however, an estimated absolute bioavailability was determined based on a cross-

study and cross-population comparison. By this non-definite approach the absolute bioavailability for inhaled iloprost was ~ 80 %. The reliability of this value is unclear and should not be incorporated in the product labeling. The absolute BA for oral iloprost ranged from 13 to 19 % (solution and clathrate).

It is unknown if any transporters are involved in iloprost absorption.

d) Distribution of iloprost

The volume of distribution was ~ 0.8 L/kg following IV administration. Protein binding of iloprost was characterized in human plasma (Report 4495). Iloprost was 60% bound to human plasma proteins, and this binding was independent of concentration. Approximately 75% of the binding was to albumin, with the remaining 25% binding to other plasma proteins.

e) Mass Balance Information

The mass balance results suggest that the primary route of drug elimination is hepatic; iloprost appears to be primarily metabolized in the liver. In the mass balance study, healthy adult volunteers received tritium labeled iloprost on three separate occasions: intravenous infusion of (2 ng/kg/min for 4 hours) and two oral doses (0.1 and 0.48 µg/kg). Mass balance results following oral and IV administration of radiolabeled iloprost are summarized in Table 6 and 7. Iloprost was approximately 80 % biotransformed.

Table 6: Pharmacokinetic Measures for ^{3}H-labelled compounds (n = 8)

	Iloprost Dose		
PK Measure	2 ng/kg/min IV	0.1 µg/kg PO	0.48 µg/kg PO
Cmax(pg equiv./mL)	408 ± 79	307 ± 81	1051 ± 235
Tmax (min)	NA	29 ± 11	39 ± 24
AUC (pg·h/mL)	2027 ± 538*	641 ± 260	2664 ± 466
CL_{tot} (mL/min/kg)	3.9 ± 0.9	NA	NA
$T_{1/2abs}$ (min)	NA	7 ± 3	9 ± 7
$T_{1/2\alpha}$ (min)	24 ± 11	NA	NA
$T_{1/2\beta}$ (h)	1.7 ± 0.2	1.2 ± 0.2	1.5 ± 0.2
$T_{1/2\gamma}$ (h)	5.0 ± 1.3	NA	NA

* n = 6
NA- not applicable

Table 7: Iloprost pharmacokinetic measures in healthy elderly adults (n = 8)

PK measure	
Iloprost Dose	2 ng/kg/min IV
Cmax(pg equiv./mL)	81 ± 35*
Tmax (min)	240
AUC (pg·h/mL)	382 ± 188*
CL_{tot} (mL/min/kg)	24 ± 9
$T_{1/2\alpha}$ (min)	6 ± 4
$T_{1/2\beta}$ (h)	31 ± 10
BA (%)	NA

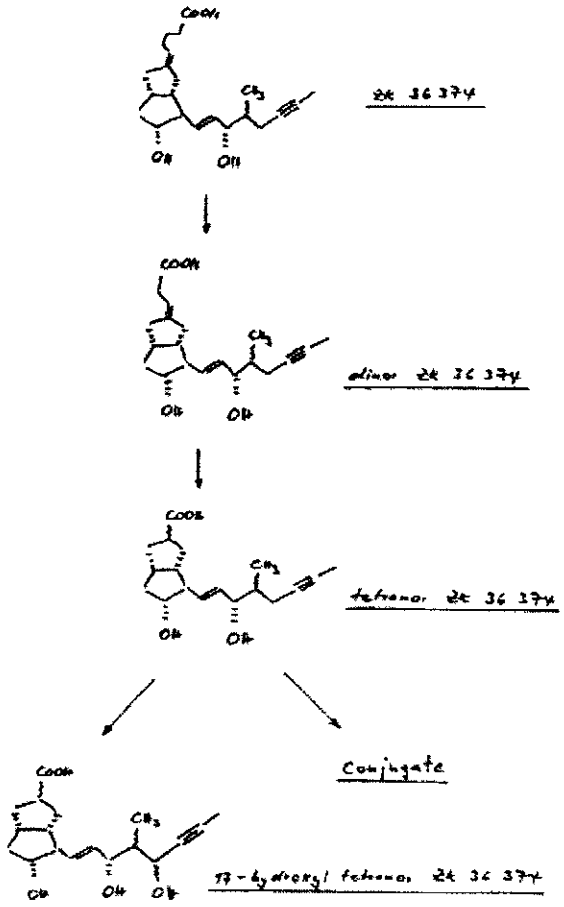
* n = 6; NA- not applicable; ND- could not be determined

Following the end of the infusion, plasma concentrations of total radioactivity declined in a triphasic pattern, whereas, iloprost concentrations declined in a biphasic manner.

f) Metabolism of iloprost (enzymes and hepatic extraction class)

Iloprost is extensively metabolized by ß-oxidation of the upper side-chain. The proposed metabolic pathway of iloprost is based on nonclinical information (Report 5251) obtained in the rat as depicted in figure 6. It is unclear if iloprost follows the same metabolic pathway in rats and humans.

Figure 6: Iloprost metabolic pathway in rats



The oxidation reaction appears to be by specific and non-specific oxidases. CYP enzymes play only a relatively minor role in iloprost metabolism (see Extrinsic Factors affecting Iloprost exposure, Section D). In humans, iloprost is entirely metabolized, with no unchanged drug found in the urine or feces. The major metabolites of iloprost are tetranor-iloprost and tetranor derivatives (e.g. glucuronides); additionally, dinor-iloprost is present after I.V. administration. The applicant reports that there was no selective metabolism of the two iloprost isomers (Report AG12) in humans after oral dosing.

Iloprost appears to be a medium to high hepatic extraction drug: following IV administration CL ~ 20 mL/kg/min (for a 70 kg person CL ~ 84 L/hr).

g) Iloprost excretion

Labeled compounds were excreted mainly by the urine: ~ 80 % of the total radioactivity was found in urine and ~ 20 % in feces. Renal elimination was biphasic with half lives of ~ 2 h and ~ 20 h. Eighty to 90 % of the urinary radioactivity was found within 14 h post administration. The fecal excretion half-life was ~ 20 h. No unchanged iloprost was excreted in either urine or feces.

h) Dose and Time Dependency of iloprost PK

Data were insufficient to determine if there was a dose or time dependency on iloprost PK.

i) Inter and intra-subject variability in iloprost PK

There was high intersubject variability in iloprost PK (Table 5) following inhalation as evidenced by the large standard deviation (CV ~ 60 %) associated with the AUC. The potential sources of variability can be ascribed to the delivery device and a patient's inherent physiology. Drug delivery by nebulizers are generally subject to a higher degree of variability than other delivery modes. Physiologically, a patient's breathing pattern may impact PK because the delivery device is breath actuated. Thus a "slow breather" may take a longer time to achieve the desired dose than a fast breather resulting in PK differences. Additionally, each patient may have different absorption patterns and capacity to process iloprost (e.g. metabolizing capacity).

There were no data available to assess intra-subject variability in iloprost PK following inhalation.

C. What intrinsic factors affect iloprost exposure?

Iloprost exposure was affected by the degree of renal insufficiency (Report 8148) and hepatic insufficiency (Reports AM75 and 8432). The clinical trials did not include subjects with significantly impaired hepatic or renal function, thus no additional long-term safety or effectiveness data are available in these subjects. Data were absent or inadequate to definitively determine if other intrinsic factors, such as age, gender, race or other human factors affected iloprost exposure.

Renal Insufficiency

Two groups of patients suffering from renal insufficiency received an IV infusion of 1 ng/kg/min of iloprost for 60 minutes. The two study groups* were: Group I (n =10) comprising ten subjects that were not subject to dialysis therapy (creatinine > 2 mg/dL) and Group II (n = 11) comprising 11 subjects who routinely required dialysis. However, dialysis treatment was not offered during the course of this study.

Reviewer Comment

* This study was conducted prior to the publishing of the Renal Impairment Guidance and does not conform to the recommendations of the Guidance with respect to study

groups. The Guidance suggests that all subjects should be age matched (as appropriate) and the following groups should be included in the study: normal subjects (no renal insufficiency), and subjects with mildly, moderately and severely impaired renal function and end stage renal disease requiring dialysis. The degree of renal function is expressed as creatinine clearance (mL/min).

Results from the renal impairment study are summarized Figure 7 and Table 8.

Figure 7: Plasma concentration-time profiles in Renal Insufficiency

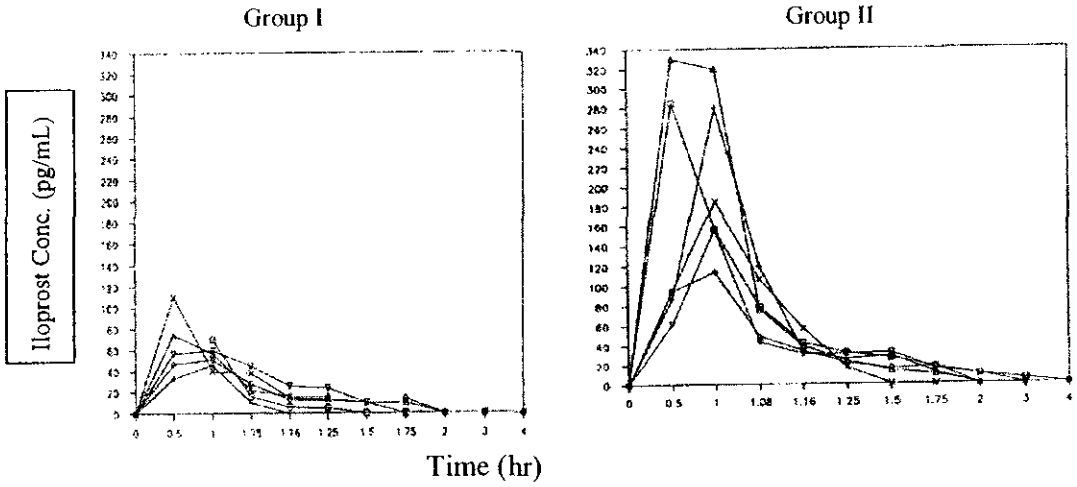


Table 8: Mean ± SD Pharmacokinetic Measures for iloprost in subjects with varying degrees of renal insufficiency following administration of 1 ng/kg/min iloprost IV infusion.

PK Measure	n	Group I	n	Group II
Cl_{cr} (mL/min/kg)	7	0.28 ± 0.13	8	0.17 ± 0.05
C_{60}	7	53 ± 10	7	193 ± 77
AUC (pg·h/mL)	7	54 ± 22	8	230 ± 103
CL_{tot} (mL/min/kg)	7	17.6 ± 5.2	8	5.2 ± 2.2
$T_{1/2\alpha}$ (min)	7	0.06 ± 0.01	8	0.055 ± 0.005
$T_{1/2\beta}$ (h)	7	0.64 ± 0.35	8	0.59 ± 0.16
$T_{1/2\gamma}$ (h)	NA	NA	2	6.95
MRT (h)	7	0.27 ± 0.28	8	0.87 ± 1.36

As is evident from figure 7 and Table 8, patients with renal insufficiency who require dialysis have approximately a three-fold reduction in clearance values compared to those not requiring dialysis. The effect of dialysis on iloprost exposure is unknown. CL for Group I subjects is comparable to that in subjects with normal renal function (based on cross-study comparison), suggesting that Group I subjects do not require a dose reduction; whereas Group II subjects require a dose reduction. It should be noted that 1) the plot of weight normalized CL vs. weight normalized Clcr showed that systemic clearance was not largely determined by Clcr (R^2 = 0.35) and subjects in the two groups had overlapping CLcr. The low dependence of total CL on CLcr (renal function) may be expected because iloprost is extensively metabolized. A possible reason for differing exposure, despite overlapping CLcr in the two groups is the unknown contribution of

other factors, such as the hepatic function status of participating subjects. Patients with severe impairment of renal function and ESRD patients frequently have other underlying conditions that may impact drug CL.

Applicant's Dosing Recommendation for Patients with Severe Renal Insufficiency
The applicant provided a non-specific labeling recommendation in the package insert: ⊏

] This reviewer agrees with the applicant's conclusion, but thinks the dosing recommendations should be more specific for patients with renal insufficiency (see *Reviewer's Dosing Recommendations for Patients with Severe Renal Insufficiency).*

Reviewer's Dosing Recommendations for Patients with Severe Renal Insufficiency
The dosing recommendations that follow rely on the following assumptions:

- The results from the intravenous route are reflective of the inhaled route.
- The cross study comparison (patients with renal dysfunction vs. subjects with normal renal function) of CL is acceptable.

With these caveats in place the dosing recommendations for inhaled iloprost are:

1. Subjects with mild or moderate renal insufficiency (Clcr > 30 mL/min) do not require a dose reduction when undergoing inhaled iloprost therapy (Same as Applicant's).
2. Subjects with severe renal impairment, not requiring dialysis, should have the dose reduced to 1.25 µg iloprost at intervals of at least 3 hours (up to a maximum of six times a day) as initial treatment. The dosage may be adjusted based on individual need and tolerability.
3. Patients with severe renal impairment requiring dialysis or ESRD may receive inhaled iloprost at the dosage prescribed in 2 above. However, the labeling should indicate that the effect of dialysis is unknown; therefore the utility of the recommended dosage for dialysis patients is unclear.

Hepatic Insufficiency
Two studies were carried out in patients with hepatic insufficiency. In Study 8432 patients with liver cirrhosis were treated once with an IV infusion of iloprost (1 ng/kg/min for 60 minutes). Study AM75 was conducted with the oral clathrate capsule; in this study subjects with normal hepatic function (healthy), Child Pugh Class A and Child Pugh Class B received a single 100 µg iloprost dose. Relevant results from the two studies and a reference study are summarized in Tables 9 and 10

Table 9: Pharmacokinetic measures in patients with hepatic impairment receiving IV iloprost

Child Class	n	Age (years)	Cpss* (pg/mL)	$T_{1/2\beta}$ (min)	AUC∞* (pg h/mL)	CL (mL/min/kg
A, B, C	8	55.8 ± 8.6	93.4 ± 31.0	27.5 ± 24.3	125.65 ± 60.4	10.7 ± 3.2
A	1	50.0	66.0	10	62.8	15.2
B	5	54.4 ± 5.9	99.6 ± 37.7	36.2	139.64	11.1± 3.8
C	2	53.0	91.5	14.5	122.1	10.7
Normal	8	59 ± 5	40.5	31 ± 10	48	24 ± 9

*AUC and Cpss were dose normalized to facilitate comparison

Table 10: Mean ± SD Iloprost PK measures in subjects with normal and impaired liver function following oral administration of iloprost capsule

Hepatic Function	N	Age (yr)	Cmax (pg/mL)	T_{max} (h)	$AUC_{0\text{-}8\,h}$ (pg·h/mL)	$T_{1/2}$ (min)
Healthy	4	33.3 ± 9.4	62 ± 19	0.9 ± 0.3	117 ± 36	2.1 ± 0.6
Child A	5	48.8 ± 7.3	215 ± 112	1.5 ± 0.7	639 ± 440	1.1 ± 0.6
Child B	3	49.3 ± 13.2	441 ± 76	1.7 ± 0.8	1725 ± 544	1.5 ± 0.3

Results from studies AM75 and 8432 were leveraged to make inhaled iloprost dosing recommendations for subjects with impaired hepatic function. However, ideally, a hepatic impairment study should be conducted using inhaled iloprost to make definitive dosing recommendations for inhaled iloprost. Qualitatively both studies show (1) decreased iloprost clearance in subjects with hepatic insufficiency relative to normal subjects (no hepatic dysfunction) and (2) comparable $t_{1/2}$ and Tmax for hepatic impairment and normal hepatic function. Quantitatively for Child Class B subjects, the relative clearance differs in the two studies: CL in normal subjects ~ 14 times greater than that in Child Class B (for oral) vs. ~ 2 times greater for IV. An additional relevant finding for oral administration is that CL in normal subjects ~ 5 times greater than that in Child Class A.

Applicant's Dosing Recommendation for Patients with Hepatic Insufficiency

The applicant recommends

Reviewer's Dosing Recommendations for Patients with Hepatic Insufficiency (Discussion)

The dosing recommendations rely on the following assumptions:

- It is likely that the CL ratio (CL in normal vs. CL in hepatic insufficiency) for the inhaled route will be close to that of the IV but fall between that obtained for IV and oral (worst case scenario). However, an exact value for the magnitude of the CL ratio cannot be determined with the available information.
- The number of subjects per group n < 6 is sufficient to describe the PK behavior of iloprost in subjects with hepatic insufficiency.

Clinical Considerations

Key clinical considerations are as follows:

- Subjects with hepatic insufficiency were excluded from the pivotal clinical trial therefore there is no long-term clinical trial information in these subjects

According to the Medical Reviewer, the most severe adverse events (AE) occurred at inhaled iloprost doses ≥ 10 µg (AUC ~ 100 pg·h/mL) as observed in the QT study; these AEs included tightness in the chest (non cardiac-related) and vasodilatation.

Based on the preceding information, this reviewer proposes the following labeling recommendations for the three hepatic impairment classes.

- Child Class A

An initial dose of 2.5 µg should be administered at intervals of at least 3 hours (up to a maximum of 6 times per day) to patients with Child Pugh Class A. Thereafter, the dosage may be adjusted based on individual tolerability.

Based on the 5-fold CL decrease (oral study), the 2.5 µg dose administered to Child Class A would achieve drug exposure equivalent to administering a 12.5 µg dose. There are insufficient comparative data for IV iloprost in Child Class A; however, the CL of normal subjects is expected to be ≤ 2 times greater than that of Child Class A subjects receiving IV iloprost (based on results from Class B following IV administration). Consequently, in effect the exposure in Child Class A receiving inhaled iloprost will be equivalent to a dose ≤ 5 µg to 12.5 µg. This dose range appears reasonable to achieve efficacy without compromising safety, particularly when the dosing interval is ≥ 3 hours vs. ≥ 2 hours for normal subjects.

- Child Class B

There is the potential for obtaining excessive iloprost exposures in Child Class B subjects receiving inhaled iloprost: a 2.5 µg dose would produce and exposure equivalent to a dose between 5 µg (based on IV CL results) and 35 µg (based on oral CL results). This dose range is fairly wide and there is a potential that inhaled iloprost will have exposure equivalent to effective doses ≥ 10 µg, the apparent safety threshold. An initial dose of 1.25 µg will minimize the potential for obtaining excessive exposures in these subjects. Consequently, this reviewer recommends that inhaled iloprost should be initiated at a 1.25 µg dose and dosage may be adjusted using the parameters outlined for Child Class A patients.

- Child Class C

There are no data in Child Class C and there is no clinical experience in these subjects, thus inhaled iloprost should be contraindicated in these subjects.

D. What extrinsic factors influence iloprost exposure and/or response?

The main evaluable extrinsic factor that may influence the iloprost exposure-response is concomitantly administered drugs.

In vitro metabolism information indicating drug interaction potential

In vitro metabolism information indicates that iloprost has a low potential to undergo metabolically-based drug-drug interactions. In the *in vitro* studies, incubation of iloprost with cDNA-expressed CYP1A2, CYP2C9, CYP2C19, and CYP3A4 produced two minor metabolites; these metabolites were also formed with human liver microsomes (Report A09478). No metabolites were detected in the presence of CYP2A6, CYP2C8, CYP2E1 and CYP2D6.

Inhibition/Induction of metabolism by iloprost (*in vitro* information)
In vitro metabolism information indicates that iloprost has a low potential to inhibit CYP metabolism of other drugs. The induction potential of iloprost was not evaluated. *In vitro* metabolism studies with iloprost in human liver microsomes and cDNA-expressed human cytochrome P450 isoenzymes demonstrated minor inhibitory effects of iloprost on the metabolism of model P450 substrates (phenacetin, coumarin, diclofenac, testosterone, paclitaxel, mephenytoin, dextromethorphan). Minor inhibitory effects were seen for CYP2C8, CYP2C19 at iloprost concentrations > 50 μM (exceed therapeutic concentrations), and no inhibitory effects were observed for CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4.

Role of Transporters
The potential role of transporters (e.g. PGP) on iloprost PK was not evaluated in this NDA.

In vivo studies with medications that are likely to be administered in PAH patients
In several clinical PK/PD studies, I.V. iloprost did not show any clinically relevant interactions with drugs commonly used in PAH therapy, including digoxin (Report A646), nifedipine and diltiazem (calcium channel blockers; Reports B599 and 8412), captopril (angiotensin converting enzyme inhibitors; Report 8168), and aspirin (Report AD19). In the pivotal clinical trial the mentioned comedications and other drugs from the drug classes mentioned were allowed; there were no reports of unacceptable side effects due to comedication.

It should be noted that in most drug-drug interaction studies PD, rather than PK, was evaluated; these studies were also conducted primarily in healthy subjects.

Mechanistic basis for PD drug-drug interactions between iloprost and comedications
There is a potential for additive or synergistic effects between hypotensive agents and antiplatelet agents thus caution should be exercised when iloprost is combined with these agents.

E. What are the general biopharmaceutics properties of iloprost?

Administration Route (Absolute Bioavailability Inhaled vs. Oral)
The oral absolute BA was ~ 20 %. No definitive absolute BA information is available for the inhaled route. Following inhalation there is a possibility that some of the drug will be ingested. Based on the oral absolute BA, even if a subject accidentally swallows the entire dose, rather than inhales it, low, potentially subtherapeutic iloprost concentrations will be achieved and there are unlikely to be major safety concerns. It is noted that iloprost solution is intended for inhalation only.

Drug Delivery Device: ProDose (not used in clinical trials, but recommended for Ventavis administration) vs. HaloLite (used in clinical trials)

Background on Devices
Subsequent to completing the Phase 3 trial (clinical study 97218/300180), Profile Therapeutics ceased production of the HaloLite and developed the ProDose system as an improved version of HaloLite. ProDose maintains the same aerosol generation technology and product contact materials of construction as those used for the HaloLite. The ProDose received 510(k) approval April 22, 2004 (K030747) using the HaloLite as the predicate device.

The ProDose system uses Adaptive Aerosol Delivery (AAD®) technology. This technology delivers aerosol only during the inspiration portion of inhalation and will cease delivering drug after the desired dose has been delivered to the mouthpiece. The HaloLite device delivers 2.5 µg of iloprost aerosol with each actuation (i.e., 2 sequential actuations per 5 µg dose).

ProDose vs. HaloLite
The applicant indicates that iloprost inhalation for solution should be administered via a nebulizer such as ProDose; however, this device was not used in the lone pivotal clinical trial. The ProDose system was evaluated only in the QT study, where suboptimal PK sampling was conducted and PK determinations appeared inadequate. Therefore, results from the QT study could not be adequately compared to information from other studies. The HaloLite system was used in the Phase 1, 2 and 3 clinical trials and was found to be efficacious.

The applicant conducted an *in vitro* comparison to demonstrate that the ProDose was comparable to the HaloLite system that had been used in the pivotal clinical trial. The results of these comparisons are summarized in Tables 11 and 12.

Table 11: Design and performance parameters of HaloLite and ProDose

	HaloLite	ProDose
Aerosol Output Rate	≥6.8 µL/sec at 30 lpm	≥6.8 µL/sec at 30 lpm
Dose accuracy	≥90% of doses ±25% of target	≥90% of doses ±25% of target
	100% of doses ±35% of target	100% of doses ±35% of target
Respirable fraction (≤5 µm)	80 ± 10%	80 ± 10%
MMD	3.4 µm	3.4 µm

Table 12 Table: In vitro characterization of aerosol with HaloLite and ProDose nebulizers

Nebulizer	MMD (GSD)	MMAD (GSD)	Dose at mouthpiece (µg)	Nebulization time (min)
HaloLite	3.4 (1.88)	2.7 (2.0)	2.6	4.1
ProDose (2.5 µg)	3.2 (1.95)	2.6 (2.19)	2.5	4.8

The in vitro study demonstrated that the HaloLite and ProDose systems produced comparable aerosols.

Other Delivery Devices
A formal PK/PD study was conducted with HaloLite, Ventstream [Profile Therapeutics plc, Bognor Regis, UK, respectively], and Ilo-Neb® [Nebu-Tec, Elsenfeld, Germany]). All three devices were clinically comparable, suggesting that the results from the Phase 2 using the Ilo-Neb device and Phase 3 study using the HaloLite device are directly comparable.

The applicant also evaluated other ultrasonic devices (Multisonic, Optineb and Optineb IR) but these are not recommended for routine use with undiluted Ventavis solution since they have a high output and deliver more than 5 µg in 4 minutes, which increases the probability for systemic side effects in patients with a high sensitivity to iloprost. The most precise dosing was demonstrated with HaloLite and ProDose (2.5 µg disk). Both can deliver a 5 µg dose with 2 inhalation cycles using one filling of 2 mL of iloprost inhalation solution.

Reviewer Comment on Acceptability of Devices
CDRH is primarily responsible for accepting the change in the delivery device and the final decision is deferred to them. However, from a clinical pharmacology and biopharmaceutics perspective, clinical or PK/PD studies are not required to confirm device comparability, provided (1) the test device delivers the targeted iloprost dose (at mouth piece), (2) produces a similar aerosol, and (3) delivers the aerosol at a comparable rate to the reference device. It is expected that the proposed device will not alter the PK or PD of iloprost, if it satisfies the mentioned parameters. This conclusion is based on the PK/PD findings described previously (Study AX15), where devices delivering the same iloprost dose at differing delivery rates exhibited similar PK and PD properties. The *in vitro* studies showed that ProDose satisfies the described criteria. Consequently, the *in vitro* tests appear acceptable to show device comparability.

F. What analytical methods were used to identify and measure iloprost concentrations?

Several different analytical methods were used to determine iloprost concentrations in human plasma and serum. The relevant analytical methods (used for product labeling or have direct regulatory impact) are tabulated below (Table 13).

The progression of assay development was: [ ] 'increased sensitivity) ⇒ — increased sample throughput while retain method sensitivity) ⇒ [ ] method (developed by Schering but not included in table) to determine 4R- and 4S- iloprost diastereomers. Each assay was validated to some degree (Table 14) individually; cross-assay validation was conducted between the [ ] methods and between the [ ] The cross-assay validation results suggest that the [ ] assays give comparable results.

Table 13: Summary of Bioanalytical Methods Used to Determine Iloprost Concentration in plasma samples

Analytical Method			Clinical Usage		
Report	Date	Title	Study	Route	Brief Study Description
8454/M	02/89	Development and validation of a sensitive and specific — for the determination of iloprost in biological samples	AM75	Oral (capsule)	PK in hepatic insufficiency
AM29	02/99	Revalidation of the — for the quantification of iloprost in biological samples	AX15	Inhalation	PK/PD in PAH patients to compare three Nebulizer Devices
AA19352-01*	08/04	Bioanalytical Method for the determination of 4-(R/S)-iloprost in human plasma (sodium heparin)	7564-100		QT prolongation study
9126	01/91	Bioanalytical determination of iloprost by [ ]	AD19	IV	PK drug interaction between iloprost and acetylsalicylic acid
5783	12/83	Development of [ ] for the determination of ZK 36 374 in plasma	8148	IV	PK in renal insufficiency
			8432	IV	PK in hepatic insufficiency
			6210	IV	PK in man
7312	02/96	Radio-HPLC	7312	Oral and IV	PK/PD of 3H-Labelled Iloprost in Healthy Volunteers

* Method developed by [ ] he remaining methods were developed by Schering

Salient features for each assay are presented in Table 14. Overall assay performance was acceptable for the individual analytical methods; however, none of the methods quantified the metabolite concentrations.

Table 14: Assay Performance in Human Plasma

	AM29	8454/M	9126	5783	AA19352-01
LLOQ (pg/mL)	[				]
ULOQ (pg/mL)	[				]
Precision ((%) , CV	[			] pg/mL	
Accuracy (%), relative bias	[			[	]]
Specificity)	No	Yes	Yes	Yes	Yes for both isomers
Cross Assay Evaluation	Not conducted	Differed from — from -24 % to + 22 % over 30 – 130 pg/mL; r^2 = 0.90	Correlation (r^2) between [ ] = 0.89 over 12.5 to 200 pg/mL	See comment for 8454/M	Not conducted

Table 13: Summary of Bioanalytical Methods Used to Determine Iloprost Concentration in plasma samples

Analytical Method			Clinical Usage		
Report	Date	Title	Study	Route	Brief Study Description
8454/M	02/89	Development and validation of a sensitive and specific — for the determination of iloprost in biological samples	AM75	Oral (capsule)	PK in hepatic insufficiency
AM29	02/99	Revalidation of the — for the quantification of iloprost in biological samples	AX15	Inhalation	PK/PD in PAH patients to compare three Nebulizer Devices
AA19352-01*	08/04	Bioanalytical Method for the determination of 4-(R/S)-iloprost in human plasma (sodium heparin)	7564-100		QT prolongation study
9126	01/91	Bioanalytical determination of iloprost by [ ]	AD19	IV	PK drug interaction between iloprost and acetylsalicylic acid
5783	12/83	Development of [ ] for the determination of ZK 36 374 in plasma	8148	IV	PK in renal insufficiency
			8432	IV	PK in hepatic insufficiency
			6210	IV	PK in man
7312	02/96	Radio-HPLC	7312	Oral and IV	PK/PD of 3H-Labelled Iloprost in Healthy Volunteers

* Method developed by [ ] he remaining methods were developed by Schering

Salient features for each assay are presented in Table 14. Overall assay performance was acceptable for the individual analytical methods; however, none of the methods quantified the metabolite concentrations.

Table 14: Assay Performance in Human Plasma

	AM29	8454/M	9126	5783	AA19352-01
LLOQ (pg/mL)	[				]
ULOQ (pg/mL)	600	130	200	1000	400
Precision ((%) , CV	[			] pg/mL	
Accuracy (%), relative bias	[				] [ ]
Specificity)	No	Yes	Yes	Yes	Yes for both isomers
Cross Assay Evaluation	Not conducted	Differed from — from -24 % to + 22 % over 30 – 130 pg/mL; r^2 = 0.90	Correlation (r^2) between [ ] = 0.89 over 12.5 to 200 pg/mL	See comment for 8454/M	Not conducted

Reviewer's Note on Assay Validation
The assays described were validated to some degree, however, some of these assays do not meet current assay validation guidelines.

III. Detailed Labeling Recommendations
Based on the Clinical Pharmacology and Biopharmaceutics Review changes were made to the applicant's proposed package insert. The OCPB changes are presented in the Appendix as strikeouts and underlined text in red font (Prescribing Information).

APPENDICES

Abbreviated Table of Contents

12 pages redacted from this section of the approval package consisted of draft labeling

Report Number	A09478
Study Title	Identification of the principal human cytochrome P450 enzymes Involved in the metabolism of ZK 36374 in human liver microsomes
Study number	KIST20020031
Study Period	02/02 – 04/02
Objective	The objective of the present study was the identification of the principal human cytochrome P450 enzymes involved in the metabolism of ZK 36374 (Iloprost).

Study Description

The metabolism of 14C- labeled ZK 36374 was investigated in this study. The applicant used standard *in vitro* procedures for evaluating drug metabolism; test conditions were consistent with current OCPB recommendations (*Draft MaPP: In vitro metabolism*). Briefly, a commercially available pool of human liver microsomes and preparations of heterologously expressed human CYP isoenzymes were used in this *in vitro* study. The test systems included test product in buffer without incubation, 60 minute incubation of test product containing control protein with NADPH generating system, and 60 minute incubation of test product in human liver microsomes in the presence of NADPH generating system, and incubation of test product with heterologously expressed CYP systems in the presence of buffer and NADPH generating system. Analyses of metabolite formation of test product and isoenzyme specific model substrates were carried out primarily by HPLC (S-mephenytoin by radiodetection).

Table 1: Iloprost Formulation Information

Type of formulation	Solution
Manufacturer	Schering AG, Germany
Specific radioactivity	1650 MBq/mg
Amount of drug substance per unit	iloprost 40 mM (unlabeled) 2mM (labeled)

Results and Discussion

Following incubation of the test compound, ZK 36374 (iloprost) with c-DNA- expressed CYP 1A2, CYP 2C9, CYP 2C19 and CYP 3A4, two minor metabolites were identified (Table 2); these metabolites were also formed with human liver microsomes. According to the applicant, the turnover rates of the investigated cytochrome P450s for the metabolism of ZK 36374 were too low to confirm the contribution of the individual isoforms (e. g. by use of chemical inhibitors for a specific enzyme). The results support the applicant's conclusion. In the presence of CYP 2A6, CYP 2C8, CYP 2E1 and CYP 2D6 no metabolites could be detected. The retention times for the metabolites, M2 (t = 12.3 minutes) and M1 (t = 11.2 minutes), were shorter than that of the parent compound (t = 15.1 minutes) suggesting that the metabolites are more polar than the parent compound. M2 was only formed by CYP2C19. Both metabolites contributed less than 5 % of total radioactivity.

Conclusions

- Iloprost has a low cytochrome P450 dependent metabolism; only two minor metabolites were formed by CYP enzymes.
- CYP 1A2, CYP 2C9, CYP 2C19 and CYP 3A4 may be involved in the metabolism of iloprost.

Table 2: Listing of CYP model substrate concentration (controls) and biotransformation of iloprost in lymphoblast-expressed human cytochrome P450 isoenzyme and Supersomes

Enzyme	model substrate/ **concentration** (μM)	M1	M2	iloprost	Sum. metabolites	Turnover rate [nmol/h/nmol P450]
Control + NADP	NA	0	0.00	100	0.00	0.00
Human CYP1A2	Phenacetin ZK 376/ **20**	0.68	0.00	99.32	0.68	1.13
Human CYP2A6	Coumarin ZK 43577/ **5**	0	0.00	100	0.00	0.00
Human CYP2C8	Paclitaxel ZK 113917/ **20**	0	0	100	0.00	0.00
Human CYP2C9	Diclofenac ZK 701010/ **10**	0.95	0	99.05	0.95	1.58
Human CYP2C19	S-Mephenytoin ZK 2620/ **30**	0	2.73	97.27	2.73	4.55
Human CYP2D6	Dextromethorphan ZK 23211/ **10**	0	0	100	0.00	0.00
Human CYP2E1	Chlorzoxazone ZK 26937/ **20**	0.00	0.00	100	0.00	0.00
Human CYP3A4	Testosterone ZK 5040/ **50**	1.55	0.00	98.45	1.55	2.58
HLM	NA	1.50	1.43	97.07	2.93	2.29

Report Number	A09477
Study Title	Inhibitory effects of ZK 36374 on cytochrome P450 catalyzed metabolism of model substrates in *in vitro* assays
Study Period	02/02 – 04/02
Objective	To investigate the inhibitory potency of ZK 36374 (Iloprost) on the metabolism of model substrates catalyzed by cytochrome P450 enzymes

Study Description

The influence of ZK 36374 on the activity of cytochrome P450 enzymes was studied in human liver microsomes and in cDNA-expressed CYP preparation, respectively. The applicant used standard *in vitro* procedures (see Appendix to this study) for evaluating drug metabolism; test conditions were consistent with current OCPB recommendations (*Draft MaPP: In vitro metabolism*). A commercially available pool of human liver microsomes was used in this in vitro study [ ]. The microsomes were incubated with isoenzyme specific model substrates at various concentrations (Table 2) and their metabolism was studied in dependence on iloprost concentration. The analysis of parent drug and metabolite concentrations was carried out by HPLC separation.

Reviewer Comment on Methodology

Overall the applicant's methodology is acceptable because it is consistent with the approaches recommended in the Draft MaPP for in vitro studies (FDA In Vitro Metabolism Working Group). The major deviation from the recommendations was the absence of a second CYP3A4 test substrate.

Table 1: Iloprost Formulation Information

Type of formulation	Solution
Manufacturer	Schering AG, Germany
Specific radioactivity	1650 MBq/mg
Amount of drug substance per unit	40 mM

Results and Discussion

The study results are summarized in Table I (applicant's presentation). The applicant reports that minor inhibitory effects were observed on CYP2C8 and CYP2C19, resulting in IC50 values of 195.2 µM and 55.7 µM, respectively, for these two isoenzymes. No inhibitory effect was observed for CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, CYP3A4 within the test concentration range as reflected by IC50 values greater than 100 µM. ZK 36374 is unlikely to achieve *in vivo* concentrations above 50 µM therefore, ZK 36374 has a low potential to inhibiting the metabolism of CYP substrates.

Reviewer Note on Presentation of IC_{50} values

The applicant's presentation of IC_{50} values as greater than 100 µM is potentially misleading because a value of ~ 200 µM, which is > 100 µM was considered relevant for inhibition of CYP2C8 activity. The report did not include the specific IC_{50} values that were greater than 100 µM. The applicant will not be asked to provide these IC_{50} values; however, for consistency, the IC_{50} for CYP2C8 should be included as > 100 µM and not considered as having "minor inhibitory activity".

Table 2: IC_{50} values of ZK 36374 on CYP-catalyzed reactions of model substrates

Reaction	Relevant isoenzyme	Test system	Protein or CYP concentration	Incubation time	IC50 (approximately, graphically estimated)
Phenacetin O-deethylation [1]	CYP1A2	HLM	0.6 mg/mL	60 min	>100 µM
Coumarin 7-hydroxylation [1]	CYP2A6	HLM	0.1 mg/mL	20 min	>100 µM
Paclitaxel 6α-hydroxylation [2]	CYP2C8	Supersomes	120 pmol/mL	30 min	195.2 µM
Diclofenac 4'-hydroxylation [2]	CYP2C9	HLM	0.2 mg/mL	30 min	>100 µM
S-mephenytoin 4'-hydroxylation [2]	CYP2C19	Supersomes	80 pmol/mL	60 min	55.6 µM
Dextromethorphan O-demethylation [2]	CYP2D6	HLM	0.4 mg/mL	60 min	>100 µM
Chlorzoxazone 6-hydroxylation [1]	CYP2E1	HLM	0.4 mg/mL	30 min	>100 µM
Testosterone 6β-hydroxylation [1]	CYP3A4	HLM	0.4 mg/mL	30 min	>100 µM

[1]Results derived from pre study
[2]Results derived from main study

Conclusions

The IC50 values > 50 µM for all major CYPs; iloprost has a low inhibitory potency on CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4.

Appendix

TT 3: Assay conditions for determination of IC50 values

Relevant isoenzyme	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Model substrate	Diclofenac ZK 701010	S-mephenytoin ZK 2620	Dextromethorphan ZK 23211	Testosterone ZK 5048
Substrate concentration	10 µM	30 µM	10 µM	50 µM
Reaction	Diclofenac 4'-hydroxylation	S-mephenytoin 4'-hydroxylation	Dextromethorphan O-demethylation	Testosterone 6β-hydroxylation
Test system	HLM	Supersomes	HLM	HLM
Concentration of protein [mg/mL] or CYP [pmol/mL]	0.2 mg/mL	80 pmol/mL	0.4 mg/mL	0.4 mg/mL
Preincubation	15 min	15 min	15 min	15 min
Reaction time	30 min	60 min	60 min	30 min
Test compound	ZK 36374	ZK 36374	ZK 36374	ZK 36374
Concentration of test compound [µM]	0, 5, 25, 100	0, 5, 10, 20, 40, 80, 100, 200, 300	0, 5, 25, 100	0, 5, 25, 100
Model inhibitor	Sulfaphenazole ZK 3520	Omeprazole ZK 305708	Quinidine ZK 800931	Ketoconazole ZK 111216
Concentration of model inhibitor	50 µM	20 µM	10 µM	2.5 µM

Relevant isoenzyme	CYP1A2	CYP2A6	CYP2C8	CYP2E1
Model substrate	Phenacetin ZK 376	Coumarin ZK 43577	Paclitaxel ZK 133917	Chlorzoxazone ZK 26937
Substrate concentration	40 µM	5 µM	20 µM	20 µM
Reaction	Phenacetin O-deethylation	Coumarin 7-hydroxylation	Paclitaxel 6α-hydroxylation	Chlorzoxazone 6-hydroxylation
Test system	HLM	HLM	Supersomes	HLM
Concentration of protein [mg/mL] or CYP [pmol/mL]	0.6 mg/mL	0.1 mg/mL	120	0.4 mg/mL
Preincubation	15 min	15 min	15 min	15 min
Reaction time	60 min	20 min	30 min	30 min
Test compound	ZK 36374	ZK 36374	ZK 36374	ZK xyz
Concentration of test compound [µM]	0, 5, 25, 100	0, 5, 25, 100	0, 5, 10, 20, 40, 80, 100, 200, 300	0, 5, 25, 100
Model inhibitor	Furafylline ZK 169611	Pilocarpine ZK 889323	Quercetin ZK 44634	DDC [1] ZK 4353
Concentration of model inhibitor	25 µM	25 µM	10 µM	25 µM

[1] Diethyldithiocarbamate
HLM = human liver microsomes

Report Number	4495
Title	Plasma protein binding of ZK 36 374 *in vitro*
Study Period	10/80
Objective	To determine the plasma protein binding of ZK 36 374 (iloprost) in the therapeutic concentration range.

Study Description

Equilibrium dialysis was used to determine plasma protein binding of ^{3}H- ZK 36 374 in human plasma. ZK 36 374 concentrations (in phosphate buffer) evaluated were: 0.03, 0.3 and 30 ng/mL. The dialysis was for 2 hours. In a second procedure the dialysis was carried out versus 4 % human serum albumin solution.

Results

The protein binding of Iloprost is summarized In Table 1.

Table 1: Protein binding of iloprost

Iloprost concentration (ng/mL)	Mean ± SD % bound to plasma proteins	Mean ± SD % bound to albumin	Estimated amount (%) of binding to plasma due to albumin
0.03	58.9 ± 0.9*	45.3 ± 3.0*	77
0.3	62.0 ± 0.9	46.5 ± 1.5	75
30	68.6 ± 0.8	49.5 ± 4.5	72

* n =3, otherwise n = 5

The extent of plasma protein binding was independent of drug concentration over the 0.03 to 30 ng iloprost/mL concentration range, although there was a trend towards increased binding with increasing drug concentration. Based on the results of the overall plasma protein binding and estimated amount of drug bound to albumin, albumin accounts for approximately 75 % of the Iloprost's plasma protein binding. The applicant also determined that there was no adsorption to the dialysis membrane.

Conclusions

- Iloprost is approximately 60 % bound by plasma proteins at *in vivo* (therapeutic) concentrations.
- Albumin is the main plasma protein that binds albumin; iloprost is approximately 75 % bound by albumin at therapeutic concentrations.

Report Number	AX15
Title	A randomized, open- label, multicenter, crossover study of hemodynamic effects and pharmacokinetics in patients with primary or secondary pulmonary hypertension following one short period of inhalation of an iloprost aerosol, for the purpose of assessing the comparability of three distinct nebulizing devices
Investigators/Sites	Dr. W. Seeger et al/ Three centers in Germany
Study period:	September 1998 - August 1999
Objective	To compare the performance of two new nebulizing systems, HaloLite™ and Ventstream™ by Medic- Aid Ltd., with a nebulizing device currently in use for iloprost inhalation therapy, the Ilo- Neb ® system by Nebu-Tec.

Study Design

This was a randomized, open-label, crossover study. Adult patients* with primary (PPH) or secondary pulmonary hypertension (SPH) participated in the study. Each patient received a total of three inhalations, one inhalation per device for approximately nine to 12 minutes. Each inhalation was preceded by a 2-hour washout interval. The target dose for each inhalation was 5 µg iloprost at mouthpiece. Patients were randomized to one of six possible treatment sequences. The three study treatments were:

- A: Iloprost aerosol via HaloLite ™
- B: Iloprost aerosol via Ventstream ™
- C: Iloprost aerosol via Ilo- Neb ®

* Patients are designated "responders"- maximum percentage decrease of pulmonary vascular resistance by at least 20% compared to baseline after inhalation of iloprost aerosol (1.5 ml of a solution containing 10 µ g iloprost/ ml nebulized by the Ilo- Neb . system)

Subject Characteristics **(n = 12)**

Age range: 26 to 71 years
Height range: 153 to 183 cm
Body weight range: 41 to 86 kg.
Sex: 3 males and 9 females

Blood Sampling

Blood samples were collected at the following time points: prior to the start and at the end of inhalation, as well as 2, 5, 15, 30, 60 and 120 minutes after the end of inhalation. The sample taken at 120 minutes after the end of inhalation was also used as "baseline" sample for the respective following treatment.

Drug Concentration, Drug Formulation and Nebulizer Devices

Drug Concentration

The iloprost concentration varied depending on the nebulizer: 7.7 to 15 µg/ ml. The dose of iloprost at the mouthpiece (D_{IM}) was calculated as follows:

D_{IM} = *aerosol output rate at the mouthpiece (ml/min) x iloprost concentration in (µg/ml) x inhalation time in minutes*

Drug Formulation

Iloprost solution, L 401 M, batch number F13401 by Schering, AG, Germany.

Nebulizer Device

- HaloLite™ (Medic-Aid Ltd., Bognor Regis, UK) nebulizer system, an inspiration-triggered inhalation system with compressor (Medic-Aid Ltd., Bognor Regis, UK).
- Ventstream™ (Medic-Aid Ltd., Bognor Regis, UK) with compressor Freeway Lite™ (Medic-Aid Ltd., Bognor Regis, UK).
- EK-100-S Ilo-Neb nebulizer system with the compressor Pulmocar Akku (Sanesco Medizintechnik, Vienna, Austria).

Analytical methods

Iloprost serum concentrations were measured with a validated radioimmunoassay. The assay performed acceptably. Standard curve range: [ ]pg/ml. Limit of quantitation was 25 pg/ml. Quality control (QC) samples: [ ] pg/ ml. The inter and intra-assay coefficients of variation were < 11 % for the [ ] QC samples, and < 22 % for the — pg/mL QC sample. All QC samples were within 10 % of the nominal concentration (-6.9 to + 9.5 %).

Pharmacokinetic (PK) Analyses

The computer program TOPFIT, version 2.1 (Thomae, Schering and Goedecke, Germany) was used for non- compartmental PK analyses. The following iloprost PK measures were calculated for the three devices: Cmax, Tmax, $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}8}$, AUC and $t_{1/2}$.. The $T_{1/2}$ and $AUC_{0\text{-}8}$ could not be estimated in all cases. The AUC and Cmax for the three devices were used to assess the comparability of these three nebulizing devices in PHT patients.

Pharmacodynamic (PD) Measures and Analyses

Hemodynamic (HD) effects were determined: pulmonary and systemic effects detectable by right-heart catheter. Pulmonary vascular resistance (PVR) was the main treatment variable for PD effect. Systemic HD variables measured included heart rate, invasive systemic blood pressure, central venous pressure, cardiac output, and systemic vascular resistance. PVR was determined at baseline, at the end of inhalation and 5, 15, 30, 60 and 120 minutes after the end of inhalation. PVR (units: dyn × s × cm^{-5}) is derived by the equation below.

$$PVR = (mPAP - PAWP) \times 80 / CO = CO$$

where, mPAP = mean pulmonary artery pressure (in mm Hg) PAWP = pulmonary artery wedge pressure (in mm Hg) CO = cardiac output (in l × min- 1)

Reviewer's Note

This review focuses on the changes in PVR because it is the most relevant variable for evaluating pulmonary hypertension. Additional PD (other hemodynamic variables) analyses will be reported in a separate document (OCPB GRP document).

Results

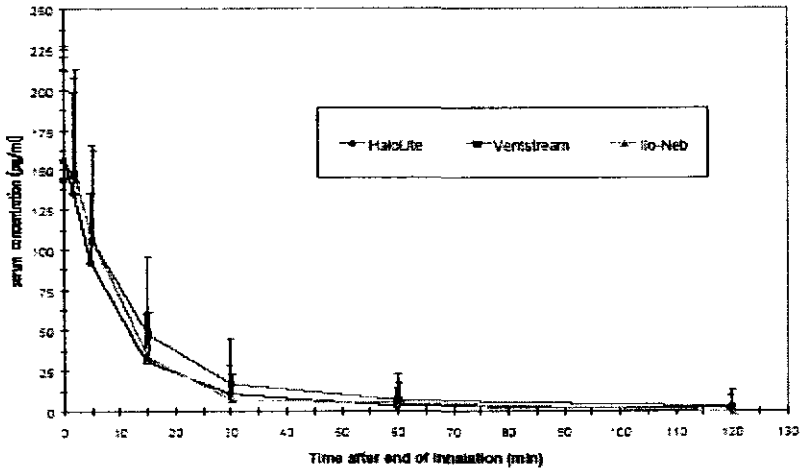
Patient Disposition and Impact on Analyses

The total number of patients recruited per center were: Berlin, 3, Giessen, 6, and Munich, 4. Thirteen patients entered the treatment phase and 12 patients completed the treatments. Patient 8 was withdrawn from the study after very brief iloprost inhalation during the first inhalation period (using the Ilo-Neb device). This patient was replaced by Patient 58. Patient 11 was excluded from PK evaluation of the Ventstream ™ device because no quantifiable exposure had been achieved with this device due to technical problems. In addition some samples could not be obtained in some patients; the applicant indicates that AUC may therefore have been underestimated in Patient 4 after inhalation with the Ventstream ™ device.

Pharmacokinetics

Similar iloprost serum level- time curves were obtained after all three treatments as shown in Figure 1.

Figure 1: Iloprost plasma concentration-time profiles following inhalation with three different nebulizer devices (Applicant's Plot)



After all three treatments, iloprost serum levels rapidly fell below the limit of quantitation of 25 pg/ml. Quantifiable iloprost serum levels were found only in Patient 9 in the respective last sample after inhalation with the HaloLite™ and the Ventstream™ devices. In general, subjects required 9- to- 12- minute inhalation periods to achieve the target 5 µg iloprost dose at the mouthpiece. The Tmax and $T_{1/2}$ for the three nebulizers are tabulated below (Table 1).

Table 1: Median (range) Tmax and Mean ± SD $T_{1/2}$ values for Iloprost Nebulizers in Patients with Pulmonary Hypertension after receiving a 5 µg iloprost dose

	Device					
Measure	n	HaloLite	n	Ventstream	n	Ilo-Neb
Tmax	12	11 [illegible]	11	10	12	12
$T_{1/2}$	11	7.9 ± 3.2	7	11.3 ± 6.8	11	7.4 ± 2.1

Iloprost pharmacokinetic exposure measures are summarized in Table 2. The exposures were highly variable for all treatments.

Table 2: Iloprost pharmacokinetic measures for HaloLite, Ventstream and Ilo-Neb nebulizer devices in patients with pulmonary hypertension

Target variable		Mean	Standard deviation	Minimum	Median	Maximum
Treatment A (HaloLite™)**	N					
Cmax (pg/ml)	12	157	64		148	
AUC (pg·h/ml)	12	47.8	35.2		48.4	
Treatment B (Ventstream™)						
Cmax (pg/ml)	11	155	65		142	
AUC (pg·h/ml)	11	54.2	45.1		40.9	
Treatment C (Ilo-Neb™)						
Cmax (pg/ml)	12	158	70		146	
AUC (pg·h/ml)	12	49.0	34.4		40.7	

** Patient 4 was described as a " slow breather"; the HaloLite nebulizer is activated by inspiratory flow; this treatment occurred third (i. e., last) in Patient 4's treatment sequence.

Iloprost exposure comparisons for three iloprost nebulizer devices

The applicant's relative exposure comparisons are summarized in Table 3.

Table 3: Iloprost Exposure Comparisons

Kinetics variable	Treatment 1	Treatment 2	Multiple significance level	Adjusted *P*-value	Ratio of treatment effects(%)	Simultaneous confidence level (CI, %)	Adjusted lower CI limit (%)	Adjusted upper CI limit (%)
AUC	HaloLite	Ilo-Neb	0.05	0.8615	93.7	95	67.9	129.1
AUC	HaloLite	Ventstream	0.05	0.8320	93.0	95	67.4	128.2
AUC	Ilo-Neb	Ventstream	0.05	0.9979	99.3	95	73.3	134.5
Cmax	HaloLite	Ilo-Neb	0.05	0.9753	97.9	95	76.2	125.9
Cmax	HaloLite	Ventstream	0.05	1.0000	100.0	95	77.8	128.6
Cmax	Ilo-Neb	Ventstream	0.05	0.9718	102.1	95	80.5	129.6

The comparisons indicate the devices are not different with respect to iloprost exposure (based on p-values) following a 5 µg iloprost dose; furthermore, the ratios of treatment effects were all close to 100 %. However, the devices are not bioequivalent (BE). The applicant constructed a 95 % confidence interval (Table 3) rather than the recommended 90 % confidence interval (CI). Using the information for the 95 % CI (standard error estimate), this reviewer estimated the 90 % CI. Based on this estimation (data not shown), none of the devices were BE to each other.

Pharmacodynamic effects on pulmonary circulation (Pulmonary Hemodynamics)

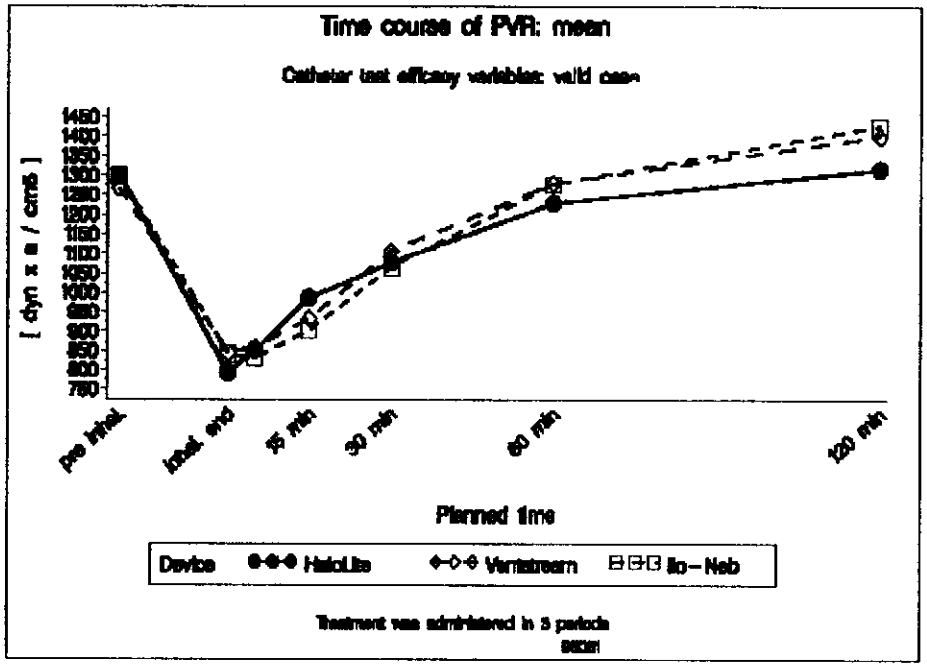
ANOVA revealed that the estimated mean difference between treatments for the maximal change in PVR was less than one percent (Table 4). This finding suggests that the mean effect of each of the three distinct treatment devices on pulmonary vascular resistance is similar.

Table 4: Comparison of iloprost pharmacodynamic effect (PVR) after inhalation by three different nebulizers

Treatment	Vs. treatment	Maximum change (%) for PVR	Adjusted *P*-value	Adjusted Confidence Limits	
				Lower	upper
HaloLite	Ventstream	-0.8	0.9788	-11.19%	9.58%
Ilo-Neb	Ventstream	-0.6	0.9881	-10.96%	9.77%
HaloLite	Ilo-Neb	-0.2	0.9986	-10.59%	10.18%

The time course of PVR is depicted in figure 2. For all three devices, PVR decreased during inhalation relative to baseline and returned to baseline approximately 120 minutes after inhalation.

Figure 2: Time Course of PVR following administration of iloprost via Three Different Nebulizers



ANOVA showed (data not shown in this review) a statistically significant difference (p= 0.0318) in the effects on mean systemic blood pressure (mSAP) brought about by Ilo-Neb. and HaloLite™ treatments, respectively: the HaloLite™ treatment showed a greater influence on mSAP than Ilo-Neb. This finding resulted in a recommendation to monitor patient condition with regard to systemic blood pressure.

Miscellaneous information on nebulizer devices: Possible PK, PD, PK/PD impact
The tested devices exhibited distinct PK, PD, and physical characteristics that may have impacted PK, PD or PK/PD results

- Increasing iloprost concentrations post inhalation: four subjects (#s 7, 9, 12 and 58) had increasing concentrations with Ventstream™ device. For this device, there appeared to be more frequent migration liquid from the mouthpiece of the inhaler into the patient's mouth (potential effect of oral absorption). This migration may have led

to additional absorption of iloprost via the oral mucosa and may have increased Tmax for this treatment. Only Subject 5 on HaloLite™ showed increased concentrations.

- Inhalation time required to achieve targeted 5 µg dose and dosing accuracy: Most subjects required ~ 10 minutes (mode) with Ventstream, ~12 minutes (mode) with Ilo-Neb and varying times with HaloLite (range 8 - 25 minutes; 25 minutes was the time required for the "slow breather"). *In vitro* data indicates that the adaptive aerosol delivery by the HaloLite™ system provides greater dosing accuracy than conventional jet nebulizers such as Ilo- Neb and Ventstream™.
- The HaloLite™ treatment showed a greater influence on mSAP than the other treatments.
    - Droplet size: according to the applicant the mean droplet sizes were comparable for all devices, although the range of these sizes in the aerosols produced by each nebulizer differed. Theoretically, distinct distributions along the passageway according to droplet size may cause specific drug depositions in the respiratory tract, e. g., distinct local availability in the lower respiratory tract, which could be assumed to have an impact on the pulmonary hemodynamic effects of iloprost.

Exploratory PK/PD Analyses

A formal PK/PD analyses were not conducted by the applicant or this reviewer. However, based on the available information, there is no definitive evidence for a relationship of iloprost exposure (e.g. serum levels) to clinical response such as incidence rates of adverse events or efficacy. However, there were some potentially relevant findings:

Systemic Hemodynamics- Effects on SVR (systemic vascular resistance)

- Five out of twelve subjects had a maximum percentage drop in systemic vascular resistance that was related to iloprost systemic exposure (AUC). The largest maximum SVR drop was correlated to the treatment device which led to the greatest systemic exposure (AUC), and the smallest maximum drop correlated to the treatment device of least systemic exposure.
- Seven out of 12 subjects did not show a dependency of SVR change to iloprost exposure.

From the preceding, approximately 50 % showed a potential exposure-response relationship. However due to the small number of subjects and the lack of an overall correlation between iloprost serum levels and systemic effects (e. g., adverse drug reactions) a definitive PK/PD conclusion (e.g. defining an exposure threshold) can not be drawn.

Pulmonary Hemodynamics- Effects on PVR (pulmonary vascular resistance)

The described findings for the systemic HD variables was not supported by the findings with the putative target variable, PVR. Systemic iloprost exposure did not appear to be correlated to the timing and extent of local availability in the pulmonary vasculature. The highest AUC and the lowest AUC were associated with the most pronounced or least pronounced percentage decrease of PVR, respectively, in one subject (# 2).

Reviewer Comment

A direct PK/PD correlation for iloprost may not be expected because iloprost drug concentrations decline rapidly shortly after inhalation is complete (< 30 minutes post infusion); whereas, the PD effects are sustained for longer periods (> 1 hour post infusion). If a PK/PD relationship can be identified in this disease condition it is likely to involve an indirect mechanism (interaction with prostacyclin receptors).

Applicant's Safety Summary

Overall the 5 μg iloprost doses administered by three different nebulizing devices were tolerable and safe for the patients. All adverse events were of mild or moderate intensity. No severe adverse events occurred. No deaths or serious adverse events were observed. No abnormal laboratory values, ECG, or physical findings occurred that were clinically significant. One patient was withdrawn from the study prematurely after two minutes of the first treatment period due to a drop in vital signs (Patient 8). Two main findings from the sponsor's analyses are

- Vasodilatation and headache were the most frequent adverse events
- There is a potential for obtaining clinically significant drops in systemic blood pressure based on the hemodynamic data.

Summary and Conclusions

- The HaloLite, Ventstream and Ilo-Neb nebulizer devices have similar (almost superimposable) plasma concentration-time profiles at the projected 5 μg iloprost mouthpiece dose level.
- When presumed (dose can not be measured directly) equal 5 μg iloprost doses at the mouthpiece were administered over inhalation times of 9 to 12 minutes there was comparable systemic iloprost exposure for HaloLite, Ventstream and Ilo-Neb devices. The ratios of Cmax means and AUC means between treatments (two devices at a time; HaloLite, Ventstream and Ilo-Neb) varied between 93 and 102 %. However, none of the iloprost nebulizer devices were bioequivalent to each other.
- When presumed (dose can not be measured directly) equal 5 μg iloprost doses at the mouthpiece were administered over inhalation times of 9 to 12 minutes there was comparable pulmonary hemodynamic effects for HaloLite, Ventstream and Ilo-Neb devices. All three devices had similar pulmonary vascular resistance time courses at the 5 mg dose level.
- The HaloLite device leads to greater decreases in mSAP than Ilo-Neb despite achieving similar exposure.

Study Report Number	6210
Title:	Pharmacokinetics of iloprost in man after intravenous infusions of 1 and 3 ng/kg/min and oral administration of 1 µg/kg
Study Period :	01/84 to 7/84
Objectives:	To determine the basic pharmacokinetic parameters of iloprost in healthy volunteers after receiving intravenous infusions of iloprost

Study Design

This was an open label study. Healthy male volunteers were given two intravenous infusions of iloprost and oral iloprost on three separate occasions. The washout period between treatments was one week. The iloprost treatments were:

- 1 ng/kg/min iloprost IV infusion for 45 minutes
- 3 ng/kg/min iloprost IV infusion for 45 minutes
- 1 µg/kg iloprost PO

All iloprost administration were performed in the morning after an overnight fast.

Subject Characteristics **(n = 6)**

Mean Age ± SD (years): 30 ± 8
Mean Weight ± SD (kg): 69 ± 6
Mean Height ± SD (cm): 175 ± 3

Blood Sampling

Blood samples were collected at the following time points

- IV administration: predose (0 min) and 15, 30, 45, 47.5, 50, 55, 60, 75, 90, 120, 180 and 240 min after the start of infusion (postdose).
- Oral administration: predose (0 min) and 5, 7.5, 10, 15, 20, 30, 40, 50, 70, 90, 120, 180 and 240 minute after dosing.

Formulations

- Iloprost IV solution, 0.2 µg/mL. SH L 401 A, Batch number 32 051 by Schering AG, Germany.
- Iloprost oral solution, 2 µg/mL (50 mL). SH L 401 A, Batch number 32 051 by Schering AG, Germany.

Analytical Method

The concentration of iloprost in plasma samples was determined by [ ]
this method is not considered validated method using current Regulatory Guidelines. The provided assay information was insufficient to make a definitive assessment of the assay acceptability. Only one calibration curve was evaluated: the concentration range of the curve was pg/mL. The limit of detection was — pg/ml. The inter-assay variation (precision) at the — pg/mL level was — %. The applicant indicates that there is no additional assay information.

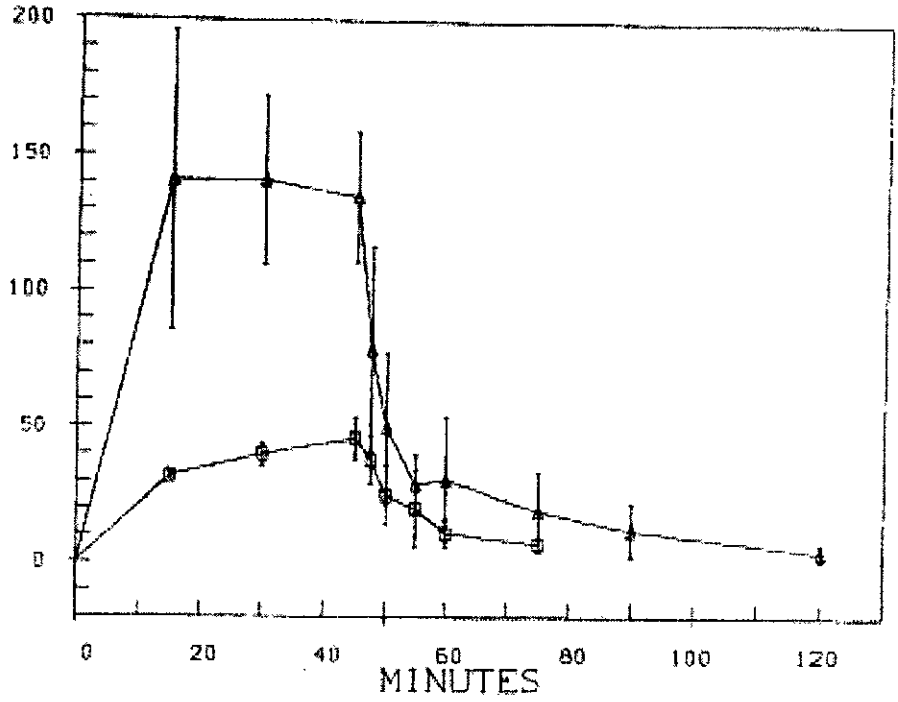
Pharmacokinetic (PK) Analyses

The following iloprost PK measures were obtained: $t_{1/2}$, AUC, CL (dose/AUC), Vd_{iv} (Ro/k x Css) and absolute oral bioavailability, F(using 3 ng/kg/min IV infusion data).

Results
Pharmacokinetics

Intravenous Iloprost Infusion
Iloprost plasma concentration-time profiles following intravenous infusion are shown in figure 1. The mean disposition of iloprost was biphasic (plot know shown); however, one subject appeared to have a third disposition phase .

Figure 1: Iloprost Plasma Concentration-Time Profile following IV infusion



1 ng/kg/min IV iloprost infusion
△ 3 ng/kg/min IV iloprost infusion

Iloprost Pharmacokinetic Measures following intravenous infusion are summarized in Table 1.

Measured concentrations, nominal Css, at the end of the infusion were comparable to those obtained by calculation (conducted by reviewer, but data not shown). Iloprost exposure appeared dose proportional over the limited dose range as evidenced by the similar CL for the 1 and 3 ng/kg/min dose levels.

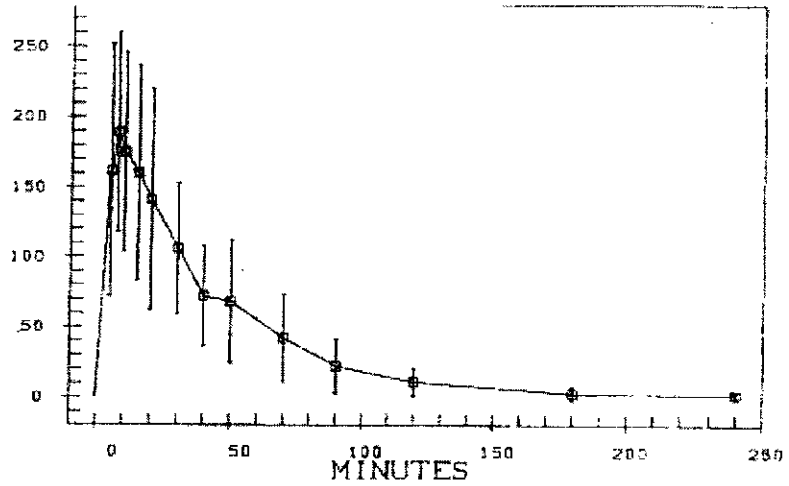
Oral Administration
The plasma concentration time profile for iloprost following oral administration is depicted in figure 2. The mean disposition was triphasic although all three phases could

not be identified in a given subject: alpha phase (n = 3), beta phase (n = 6) and gamma phase (n =2 with $t_{1/2}$ ~ 85 min). Iloprost was rapidly absorbed with Tmax < 15 minutes.

Iloprost mean ± SD PK measures in healthy male volunteers following IV infusion or oral administration (N=6)

Iloprost Regimen	1 ng/kg/min IV	3 ng/kg/min IV	1 µg/kg PO
Css (pg/mL)	46 ± 8[M]	135 ± 24[M]	NA
Cmax (pg/mL)	NA	NA	251 ± 32
Tmax (min)	NA	NA	10 ± 6
$T_{1/2\alpha}$ (min)	3.8 ± 1.6	2.8 ± 1.6	5.7 ± 2.8
$T_{1/2\beta}$ (min)	20.1 ± 7.2	26.0 ± 7.2	28.8 ± 7.8
CL (mL/min/kg)	21.0 ± 3.0	20.1 ± 5.2	NA
CL/F (mL/min/kg)	NA	NA	1.9 mL/min/kg* NR
$AUC_{0-\infty}$ (ng·h/mL)	2.2 ± 0.4	7.1 ± 2.1	8.7 ± 3.5
Vd (L/kg)	0.7 ± 0.4	0.8 ± 0.3	NR
Bioavailability	NA	NA	16 ± 4

[M] based on measured plasma concentrations
NA- not applicable; NR- not reported
* Estimated by reviewer using available data:



1 µg/kg oral iloprost

The sponsor indicates that the bioavailability (F) was 16 %. This F value was obtained using the 3 ng/kg/min IV data and the oral data. With the lower IV dose (1.0 ng/kg/min), F ~ 18 (reviewer calculated).

Conclusions

- Iloprost exposure increased in a dose proportional manner over the 1 and 3 ng/kg IV infusion dose range
- Disposition of iloprost was biphasic; the alpha phase < 10 minutes and beta phase < 30 minutes for oral and intravenous administration
- Iloprost absolute oral bioavailability ~ 16 %

Study Report Number	6496
Title	Effects of iloprost on platelet function in healthy volunteers after intravenous infusion of 1 and 3 ng/kg/min and after oral application of 1 µg/kg
Study Period	01/84 to 7/84
Objectives	To determine the effects of iloprost on platelet function in relation to dose and mode of administration To document tachyphylaxis of the antiaggregatory effect

Reviewer's Note
Study 6496 was part of Study 6210; this report focuses on the platelet function results. Thus only salient portions related to platelet function are reported. For additional study details, please refer to the Review for Study 6210.

Study Design (Measurements)

- Platelet aggregation in platelet rich plasma induced by 2 and 4 µM ADP and 1 and 2 µg collagen before and after iloprost application
- Cyclic AMP content of platelets before and after iloprost application
- In vitro platelet sensitivity to the antiaggregatory activity of iloprost added to citrate whole blood at concentrations 0.2 and 0.5 ng/mL

Analyses
Effects of iloprost on platelet function were evaluated by comparing pre-drug values with those obtained at different time points during and after drug application. The statistical tests included Wilcoxon and Wilcox test for paired comparisons and the paired t-test.

Results
The platelet function results are summarized in Tables 1, 2, and 3. Key findings from the study follow.

1. Effect of iloprost on ADP or collagen induced *ex vivo* platelet aggregation (Table 1)
The degree of inhibition of platelet aggregation depended on both the concentration of aggregating agent and iloprost dose (for IV infusions). Generally, for the IV treatments the duration of the inhibition of platelet aggregation was ≤ 90 minutes; whereas for oral treatment the inhibition duration was ≤ 120. However, these findings are limited by the timing of the samples; the adopted methodology precludes definite determination of the time of maximal inhibition or duration of inhibitory effect.

2. Effect of iloprost on cyclic AMP (cAMP) content of platelets (Table 2)
IV infused iloprost increased the cAMP content of platelets relative to pre-infusion values. The increase in the cAMP content was greater for the 1.0 ng/kg dose than the 3.0 ng/kg dose; however the data were highly variable and the difference is not statistically significant. cAMP content returned to pre-infusion values with 180 minutes post-infusion. Oral administration also increased cAMP content within 15 minutes of dosing.

Table 1: Mean ± SD Maximal change in light transmission in ADP and collagen induced platelet aggregation in platelet rich plasma before and after iloprost administration

Dose of iloprost	Time (min)	Amax 2 µN	4 µM ADP	A 180" 1 µg	2 µg Collagen
	-45	13.3±6.2	30.2±5.3	18.0±10.8	30.4±6.5
1 ng/kg.min	45	6.2±5.8	17.2±7.9	0±2.9	16.2±21.9
i.v.	90	13.5±4.4	28.0±7.9	1.7±10.9	22.2±16.9
	180	12.8±5.1	27.8±2.9	3.8±9.3	34.5±10.6
	-45	13.3±10.5	25.7±10.8	14.5±20.9	32.2±15.8
3 ng/kg.min	45	4.2±5.0	12.8± 9.9	0± 2.8	3.5±14.5
i.v.	90	13.0±10.4	22.7±11.6	9.7±18.4	32.8±22.0
	180	19.0± 8.2	30.2± 7.7	14.7±21.1	36.2±22.4
	-45	31.8±10.1	41.3±10.3	36.2±23.3	48.6± 5.6
1 µg/kg	15	10.2± 6.0	21.3± 6.4	9.8±11.4	34.5±19.6
p.o.	60	15.2± 6.6	26.7± 9.5	14.0±20.8	33.2±22.8
	120	24.7±10.4	38.2±12.8	29.0±20.4	42.8±17.8

Table 2: Mean ± SD and inter-quartile changes in cAMP content in the presence of iloprost

Dose of iloprost	Time (min)	N	MEAN	SD	SE	MIN	Q25	MED	Q75	MAX
	- 45	4	6.48	3.83	1.92	3.50	3.80	5.15	10.40	12.10
1 ng/kg x min. i.v.	+ 45	4	14.90	9.77	4.89	4.90	5.73	15.20	23.70	24.30
	+ 180	6	6.57	2.38	0.97	3.50	3.65	7.50	8.50	8.80
	- 45	6	6.32	4.35	1.78	0.50	3.20	5.65	9.85	13.30
3 ng/kg x min i.v.	+ 45	6	17.68	4.92	2.01	9.60	13.58	18.40	21.90	23.40
	+ 180	6	7.45	5.14	2.10	0.90	3.30	7.30	11.17	15.30
	- 45	6	7.72	6.58	2.69	3.00	3.03	5.35	11.02	20.70
1 µg/kg	+ 15	6	11.60	5.49	2.24	4.80	6.23	11.30	17.17	18.90
p.o.	+ 120	6	6.67	2.77	1.13	2.10	4.95	6.45	9.48	9.70

- In vitro platelet sensitivity to iloprost measured by inhibition of platelet aggregation

Table 3: Mean ± SD Maximal change in light transmission in ADP and Collagen Induced platelet aggregation in platelet rich plasma before and after iloprost administration

Iloprost concentration (ng/ml)		0	0.2	0.5	0	0.2	0.5
	Time (min)						
Day 1	- 45	30.2	14.3	6.3	30.4	18.5	0
	+ 180	27.8	12.0	5.5	34.5	16.8	0
Day 2	- 45	25.7	17.2	4.7	32.2	22.0	0
	+ 180	30.2	11.3	4.3	36.2	13.0	0
Day 3	- 45	41.3	19.3	6.0	48.6	28.4	0
	+ 180	38.2	13.5	7.5	42.8	12.8	0
83 258		A max after 4 µ M ADP			A 180° after 2 µg collagen		

When blood samples containing 0, 0.2 and 0.5 ng/mL iloprost were subjected to ADP or collagen induced aggregation, concentration-dependent inhibition of aggregation was observed. With the 4 µM ADP induction, the maximal reduction in aggregation was approximately 80 % at the 0.5 ng/mL iloprost concentration; whereas, with the 2 µg collagen induction, there was 100 % inhibition in aggregation at the 0.5 ng/mL iloprost concentration. After infusion or oral administration of iloprost, there was no significant difference in the *in vitro* platelet inhibition. This finding suggests that iloprost pretreatment did not alter the platelet inhibiting properties of iloprost; these findings are based on a short term treatment and may not be applicable to long term iloprost treatment.

Applicant's Safety Summary

Iloprost was well tolerated in the study. The main adverse events were pressure in the head, headache and facial flush. There were no significant hemodynamic effects apart from a slight rise of systolic blood pressure at the end of the infusion and an increase in the heart rate at the end of the infusion.

Conclusions

- Iloprost administered IV at 1 and 3 ng/kg/min and orally at 1 µg/kg to healthy volunteers inhibits (> 50 %) ADP and collagen induced platelet aggregation. The magnitude and duration of this effect appear related to drug exposure.
- Intravenously administered iloprost (1.0 ng and 3.0 ng/kg/min) causes ~2.5 fold increase in cAMP content of platelets at the end of the infusion; oral administration increases cAMP in platelets approximately 50 % within 15 minutes of administration.
- The *in vitro* sensitivity of platelets to iloprost is not altered by short term pretreatment with iloprost

Title	Pharmacokinetics and pharmacodynamics of ^{3}H labeled iloprost in healthy volunteers after intravenous infusion (2 ng/kg/min for 4 h) and two oral doses (0.1 and 0.48 µg/kg).
Study Report Number	7312
Study Period	02/83 to 04/86
Objectives	To determine the pharmacokinetics and biotransformation of iloprost To assess the effects on platelet aggregation ex-vivo

Study Design

This was an open label study. Healthy adult volunteers received on three separate occasions an intravenous infusion of tritium labeled iloprost (2 ng/kg/min for 4 hours) and two oral dose (0.1 and 0.48 µg/kg). The radioactive doses were 2.44 (IV), 0.24 (oral lower dose) and 1.27 (oral higher dose) µCi/kg. The time line for drug administration was as follows: intravenous infusion (Day 1), 0.1 µg/kg oral solution (two weeks later) followed by 0.48 µg/kg oral solution (11 months later). Subjects received iloprost in the fasted state.

Subject Characteristics **(n = 8)**

Mean Age ± SD (years): 59.4 ± 5.0
Mean Weight ± SD (kg): 66.6 ± 8.6
Mean Height ± SD (cm): 164.6 ± 8.0
Sex: 4 males and 4 females

Sampling

Blood

- IV administration- blood samples were taken at time 0 min, 15 min, 30 min 45 min and 1 h, 2 h, 3 h , 4 h, 4 h 2.5 min, 4 h 5 min, 4 h 7.5 min, 4 h 10 min, 4 h 15 min, 4 h 20 min, 4 h 30 min, 4 h 45 min, 5 h, 6, 7, 8, 9, 10, 12, 14 and 24 hours post dose
- Oral Administration- blood samples were taken predose (0 min), 2.5, 5, 7.5, 10, 15, 20, 30, 45, 60 and 90 minutes, 2, 3, 4, 5, 6, 8, 10 and 24 hours post dose

Urine

Urine samples were collected over the following intervals: 0 -2 hr, 2 – 4 hr, 4-6 hr, 6-8 hr, 8-10 hr, 10-12 hr, 12–24 hr, 24–36 hr, 36–48 h and daily until Day 7 after dosing

Feces

Feces samples were collected once daily until Day 7 post dose

Formulations

^{3}H-iloprost solution (Batch Number 28 6229 1183), 100 µg/mL. Schering AG, Germany

Analytical Method

The concentration of labeled compounds was determined by liquid scintillation counting and the concentration of unchanged labeled drug was determined by radio-HPLC. Metabolic patterns were obtained in plasma and urine samples by radio-HPLC. Radioactivity was measured in the urine and feces. No additional assay information was provided; however, sample chromatograms were provided.

Pharmacokinetic (PK) Analyses
The following Iloprost PK measures were obtained: $t_{1/2}$, AUC, CL (dose/AUC), and bioavailability (F).

Pharmacodynamic Analyses
Heart rate, blood pressure, and ECGs were monitored during the study. Additionally, ADP-induced platelet aggregation in platelet rich plasma and platelet count in whole blood were evaluated

Results

Subject Disposition
One subject discontinued the study due to side effects. Additionally, one male subject required a dose reduction: IV dose reduce to 1 ng/kg/min after two hours due to nausea.

Plasma Pharmacokinetics
Pharmacokinetic measures obtained in the study are summarized in Tables 1 (total radioactivity) and 2 (iloprost).

Table 1: Pharmacokinetic Measures for ^{3}H-labelled compounds (n = 8)

	Iloprost Dose		
PK Measure	2 ng/kg/min IV	0.1 µg/kg PO	0.48 µg/kg PO
Cmax(pg equiv./mL)	408 ± 79	307 ± 81	1051 ± 235
Tmax (min)	NA	29 ± 11	39 ± 24
AUC (pg h/mL)	2027 ± 538*	641 ± 260	2664 ± 466
CL_{tot} (mL/min/kg)	3.9 ± 0.9	NA	NA
$T_{1/2abs}$ (min)	NA	7 ± 3	9 ± 7
$T_{1/2\alpha}$ (min)	24 ± 11	NA	NA
$T_{1/2\beta}$ (h)	1.7 ± 0.2	1.2 ± 0.2	1.5 ± 0.2
$T_{1/2\gamma}$ (h)	5.0 ± 1.3	NA	NA

* n = 6
NA- not applicable

Following the end of the infusion, plasma concentrations of total radioactivity declined in a triphasic pattern.

The mean disposition of iloprost was biphasic following IV infusion and oral administration . The absolute oral bioavailability (F) was ~ 16 %, based on comparison of IV data and the oral 0.48 µg/kg dose. However, this bioavailability information may not be accurate because it is based on data obtained from pooled plasma samples.

Reviewer's Note
It is not clear why pooled plasma samples (oral administration) were used rather than plasma samples from individuals. The pooling of samples invalidates the data and diminishes the potential contribution of the data with regard to assessing gender differences in PK.

Table 2 : Iloprost pharmacokinetic measures in healthy elderly adults (n = 8)

	Iloprost Dose		
	2 ng/kg/min IV	0.48 g/kg PO Males^	0.48 µg/kg PO Females^
Cmax(pg equiv./mL)	81 ± 35*	101	135
Tmax (min)	240	7.5	7.5
AUC (pg·h/mL)	382 ± 188*	51.9	66.9
CL_{tot} (mL/min/kg)	24 ± 9	NA	NA
$T_{1/2\alpha}$ (min)	6 ± 4	8	8
$T_{1/2\beta}$ (h)	31 ± 10	ND	35
BA (%)	NA	13	19

* n = 6

^ data obtained from pooled plasma of respective sex

NA- not applicable; ND- could not be determined

Mass Balance

The total recovery following the 0.48 µg/kg dose was 69 % and following the 0.1 µg/kg dose the recovery was 91 %. Despite the apparently incomplete recovery, the applicant indicates that excretion could be considered complete because daily elimination was < 0.1 % of the dose both in urine and in feces. The applicant's conclusion appears reasonable based on the available information however, it is possible that some of the labeled compound remains in deep compartments (tissues) that take a time > 1 week to be excreted. The recovery following IV administration was ~ 68 % in urine and ~12 % in feces. Labeled compounds were excreted mainly in the urine: ~ 80 % of the total radioactivity was found in urine and ~ 20 % in feces. Renal elimination was biphasic with half lives of ~ 2 h and 20 h. Eighty to 90 % of the urinary radioactivity was found within 14 h post administration. The fecal excretion half-life was ~ 20 h. Based on exposure comparisons: total radioactivity in plasma vs. iloprost, iloprost is > 80 % biotransformed. Biotransformation of iloprost appeared to proceed predominantly via β-oxidation.

Reviewer Comment

Ideally, the respective breakdown of radioactivity due to each iloprost component (e.g. metabolites, metabolite derivatives and parent compound) should be provided. The applicant indicates that no additional quantitative mass balance information is available.

Metabolic Profiling

Unconjugated Metabolites

The metabolite pattern obtained after oral administration was similar to that found after IV infusion, except for the presence of some additional compounds in the more nonpolar region of the chromatogram.

- Plasma

During IV infusion of ^{3}H-iloprost or within the first twenty minutes after oral administration, a high proportion of the labeled compounds in the plasma was due to unchanged drug. At these early time points, metabolites were present to a minor extent and were mainly in the region of the chromatogram where dinoriloprost and tetranoriloprost (more abundant) were found. At later time points after oral administration more polar compounds were more abundant than the parent compound.

- Urine

The metabolite profile was obtained from pooled 0-24 hr urine samples from female and male subjects, respectively receiving IV iloprost. The metabolite profiles were comparable between the males and females. Over 20 fractions were obtained by radio-HPLC, but none of these contained the unchanged drug. Four main fractions were obtained and they exhibited the same retention behavior as the four isomers of tetranoriloprost which had been isolated and identified in another study (PHFB 5251/II).

Conjugated Metabolites: Glucuronides and Sulfate Metabolites

Based on HPLC comparisons, most conjugated compounds were obtained with tetranoriloprost. This determination was made by comparing chromatograms before and after addition of sulfatase and glucuronidase to plasma samples.

Miscellaneous Analyses Conducted by Applicant

Limited conclusions can be made from this study due to the small number of subjects, however the information in this study suggests that iloprost PK in subjects > 50 (elderly) are similar to those of younger subjects (age < 40 years) in Study 6210.

Pharmacodynamics

Heart Rate (HR) and Blood Pressure (BP)

Heart rate (HR) increased in some patients upon administration of IV iloprost; the greatest change in HR was +17 beats/minute. The blood pressure (BP) also dropped slightly in some patients following IV administration: greatest change in diastolic BP was −18 mmHg and the greatest change in systolic BP was −30 mmHg. No changes in HR or BP occurred with 0.1 µg/kg PO. With the 0.48 µg/kg dose HR increased at the 10 and 20 minute time points but BP was unchanged.

Effects on Platelets (ADP induced aggregation)

The degree of inhibition on platelets appeared to depend on time, dose (for oral) and administration route (IV vs. oral).

- IV infusion: at 1 hour and 4 hours during infusion, platelet aggregation was inhibited by 60 % of maximum amplitude
- Oral administration: 0.48 µg/kg iloprost inhibited platelet aggregation ~ 60 % at 15 minutes post dose and up to 3 hours post dose, whereas 0.1 µg/kg iloprost did not affect the platelet aggregatory response to ADP (up to 180 minutes post dose).

Platelet Count

Platelet count decreased following iloprost administration. The decrease in platelet count appeared dependent on administration route but not on dose; furthermore the changes were not due to simultaneous changes in hematocrit. The mean hematocrit values for the 24-hour period before dosing and after dosing was constant (~ 43).

- IV Infusion: platelet counts in whole blood decreased by 16 % after 1 hour of infusion and baseline values were reached again at the end of the infusion and up to 20 hours after infusion

- Oral administration: Both 0.1 and 0.48 μg/kg resulted in a 52 % decrease in basal values and platelet counts returned to pretreatment levels within 3 hours

It is not clear why oral administration had a greater effect on platelet counts than IV administration.

Applicant's Safety Summary

Facial flush was the most common adverse event occurring following IV and oral iloprost administration. ECG findings were normal in all patients. Overall, iloprost was well tolerated in this study.

Conclusions

- **Metabolism:** Beta oxidation appears to be the main metabolic pathway of iloprost. Iloprost undergoes ~ 80 biotransformation. The two main metabolites of iloprost are dinoriloprost and tetranoriloprost (more abundant); additional metabolites are mainly conjugated (glucuronides and sulfates) forms of tetranoriloprost.
- **Elimination and Mass balance:** iloprost is eliminated in the urine (80 %) and feces (20 %) as iloprost metabolites; no unchanged iloprost is eliminated in the urine or feces. Mass balance was not adequately determined, but the majority of the radioactivity is expected to be in the form of tetranor-iloprost and its derivatives.
- **Pharmacodynamics:** Oral administration of iloprost at doses < 0.5 mg/kg did not alter blood pressure or heart rate. IV administration of iloprost increased heart rate by a maximum of 17 beats per minute. Iloprost IV infusion (0.1 ng/kg/min for 4 hours) and PO iloprost (0.48 μg/kg) decreased platelet aggregation ~ 60 %.

Labeling Recommendation/Discussion

The mass balance information was inadequate because the specific contribution of iloprost and breakdown products was not determined. Consequently, limited useful information was obtained from the mass balance study. The proposed labeling should be revised as follows:

Metabolism

[ ]

Excretion

[ ]

Title:	Pharmacokinetics of iloprost in patients suffering from renal insufficiency after i.v. infusion of 1 ng/kg/min for 1 h
Study Report Number	8148
Investigators/Site	[redacted]
Study Period :	04/87 to 04/88
Objectives:	To investigate the influence of different states of renal insufficiency on the kinetics of iloprost in patients after intravenous infusion of iloprost

Study Design
This was an open label uncontrolled study. Patients suffering from different states of renal insufficiency participated in the study. Each subject was treated with an I.V. infusion of 1 ng/kg/min of iloprost for 60 minutes. There were two study groups*: Group I (n =10) comprising ten subjects that were not subject to dialysis therapy (creatinine > 2 mg/dL) and Group II (n = 11) comprising 11 subjects who routinely required dialysis (no dialysis treatment during the course of this study).

Reviewer Comment
* This study was conducted prior to the publishing of the Renal Impairment Guidance and does not conform to the recommendations of the Guidance with respect to Study Groups. The Guidance suggests that all subjects should be age matched and the following groups should be included in the study: normal subjects (no renal insufficiency), and subjects with mildly, moderately and severely impaired renal function and end stage renal disease requiring dialysis. The degree of renal function is expressed as creatinine clearance (mL/min).

Sampling
Blood samples were collected at 0, 30, 60, 65, 70, 75, 90, 105, 120, 180 and 240 minutes after the start of infusion.

Subject Characteristics **(n = 21)**
Age Range: ± SD (years): 23 - 74
Weight Range: ± SD (kg): 37 – 90 kg
Sex: 11 males and 10 females
Individual ages were provided, but individual body weights were not provided.

Formulation
Iloprost solution, L 401 A (batch number 52 101). Available as 100 µg/mL ampules by Schering, AG, Germany.

Analytical Method
The concentration of iloprost in plasma samples was determined by [redacted] analysis. Assay performance could not be assessed because inadequate assay information was provided. Two calibration curves were evaluated: concentration range was 10 to 150 pg/mL. The applicant indicates that no additional information is available.

Pharmacokinetic and Statistical Analyses

The following Iloprost PK measures were obtained: $t_{1/2}$ (α, β, and γ), AUC and, CL (dose/AUC). Statistical comparisons on sub-groups were performed by Kruskal-Wallis testing, which is contrary to the Renal Impairment Guidance's Recommendation (Point estimates and 90 % confidence intervals). Creatinine clearance was calculated using the Cockroft-Gault equation.

Results

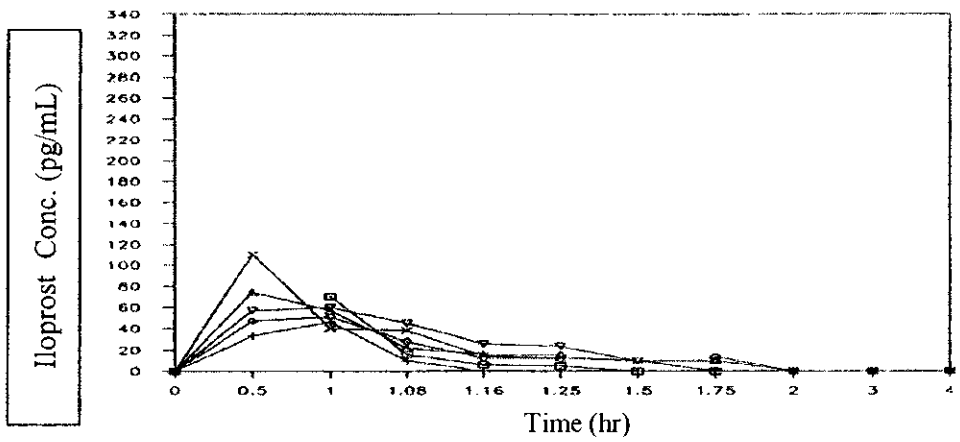
Subject Disposition

Blood samples were taken incorrectly in some patients, therefore their plasma levels were not included in the PK analyses. Consequently, plasma levels were available from only eight subjects in each of the test groups. Patient 3's PK data could not be evaluated due to very low plasma levels throughout the study.

Pharmacokinetics

The plasma concentration-time profile of iloprost in subjects with varying degrees of renal insufficiency are depicted in figures 1 and 2.

Figure 1: Iloprost Plasma concentration-time profile in Group I



Patients in Group I achieved a maximum plasma concentration when the infusion ended; subsequently plasma levels declined in a biphasic manner (semi-log plots not shown). The majority of Group II subjects had similar plasma disposition as Group I subjects, apart from two subjects that exhibited a triphasic decline in plasma levels.

Pharmacokinetic measures for Group I and II subjects are summarized in Table 1.

Figure 2: Iloprost Plasma concentration-time profile in Group II

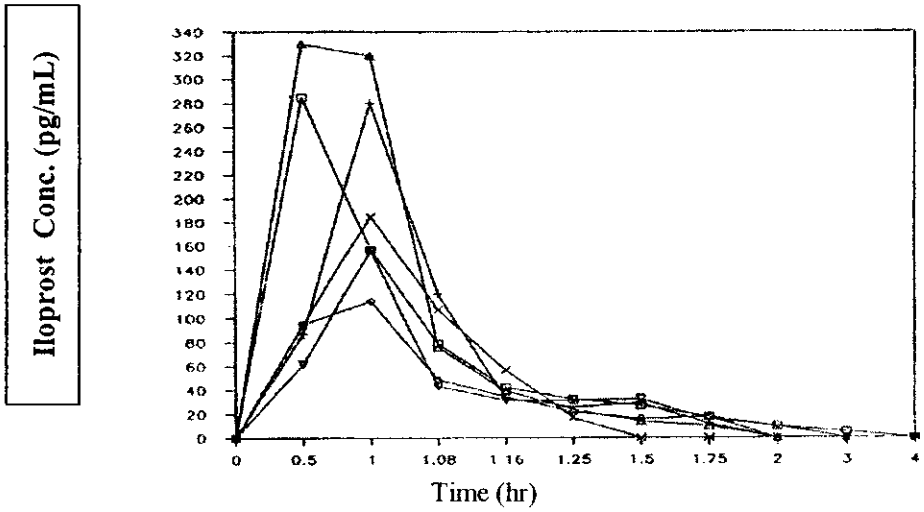


Table 1: Mean ± SD Pharmacokinetic Measures for iloprost in subjects with varying degrees of renal insufficiency following administration of 1 ng/kg/min iloprost IV infusion.

PK Measure	n	Group I	n	Group II
Cl_{cr} (mL/min/kg)	7	0.28 ± 0.13	8	0.17 ± 0.05
Clcr (mL/min)	10	18.1	11	10.2
C_{60}	7	53 ± 10	7	193 ± 77
AUC (pg·h/mL)	7	54 ± 22	8	230 ± 103
CL_{tot} (mL/min/kg)	7	17.6 ± 5.2	8	5.2 ± 2.2
$T_{1/2\alpha}$ (min)	7	0.06 ± 0.01	8	0.055 ± 0.005
$T_{1/2\beta}$ (h)	7	0.64 ± 0.35	8	0.59 ± 0.16
$T_{1/2\gamma}$ (h)	NA	NA	2	6.95
MRT (h)	7	0.27 ± 0.28	8	0.87 ± 1.36

The applicant's analyses (Kruskal Wallis test) indicated that there was a significant difference at the p = 0.01 level between the two groups: C_{60} for Group II > C_{60} for Group I; AUC for Group II > AUC for Group I; CL Group II < CL Group I and CL_{cr} for Group II < CL for Group I. Based on the study findings, a "full" study design is required in order to make appropriate dosing recommendations. The use of only two renal impairment subgroups is acceptable (reduced study design: normal vs. severe impairment) when the drug's clearance is believed to be mainly via non-renal mechanisms, but this is not the case for iloprost.

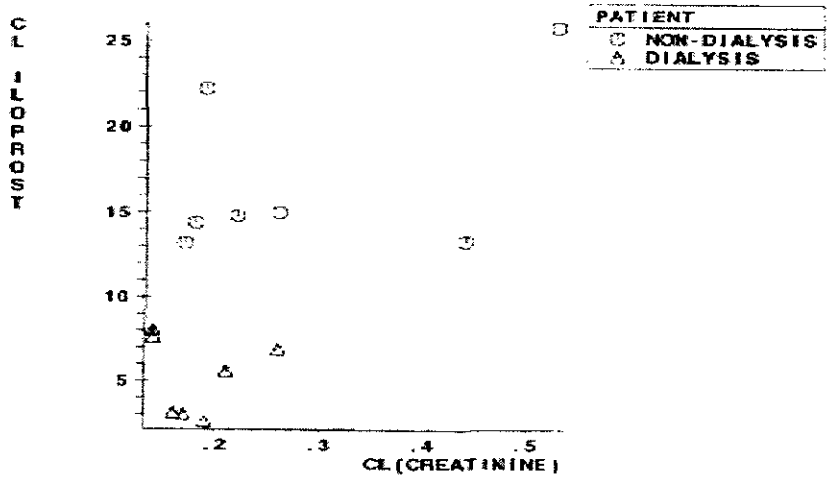
Dosing Adjustment Considerations: Limitation of Analyses

The difference in CL and resulting exposure differences between Groups I and II suggest that patients falling into these groups should be dosed differently. As suggested previously (Pharmacokinetic Analyses Section), the pooling of subjects into only two renal insufficiency groups is contrary to the recommendations of the Renal Impairment Guidance.

1. CL vas CLcr

The plot of weight normalized CL vs. weight normalized Clcr (figure 3) showed that systemic clearance was not largely determined by Clcr (R = 0.35). This finding of little dependence on renal function may be expected because iloprost is extensively metabolized. As stated by the applicant, there was a wide range of pathologically reduced creatinine values where iloprost clearance was in the normal range. However, there appears to be a clear exposure and clearance difference between the two groups. A possible reason for differing exposure, despite overlapping CLcr in the two groups is the unknown contribution of other factors, such as the hepatic function status of participating subjects. ESRD patients frequently have other underlying conditions that may impact CL.

Figure 3: Plot of CL vs. CL_{cr} (Applicant's plot)



The applicant concludes that "creatinine clearance cannot be used as a parameter to select patients at risk of reduced iloprost clearance". This statement is somewhat contradictory to the applicant's ensuing statements: "Only a severe reduction of renal function (measured by creatinine clearance) resulted in a reduction of iloprost elimination from the plasma compartment. In these patients dose adjustment should be carried out very carefully". This contradiction can not be readily resolved without understanding the potential influence of confounding factors: clinically subjects in Group II require dialysis and have lower CL_{cr} than Group I subjects however, CLcr values overlap in the two Groups.

2. Exposure Comparisons for Dose Adjustment Considerations

Based on a cross study comparison, Group I subjects (classified as "mild and moderate renal impairment" by the applicant) had comparable exposure as normal volunteers without renal insufficiency (CL in Group I 17.6 ± 5.2 mL/min/kg vs. healthy volunteers 21 ± 3 mL/min/kg). It is unclear if this cross study/group comparison is acceptable because of interpatient variability (subjects may not be adequately matched in the two studies). However, assuming that the comparison is acceptable, subjects with characteristics of Group I will not require dose adjustment. Group II subjects had a CL of 5.2 ± 2.2 mL/min/kg suggesting that their dose should be reduced 3 to 4 fold relative to Group I or normal volunteers. It should be noted that this dose reduction does not take

into account the potential effect of dialysis; dialysis may reduce iloprost levels and may result in subtherapeutic levels.

Comment on Applicant's Renal Impairment Classification
Per an addendum, the applicant provided CLcr values in mL/min. The range of CLcr values for Group I was 7.0 to 41.4 mL/min (only three subjects had CLcr > 19) and Group II was 7.0 to 13.5 mL/min. Thus according to the Renal Impairment Guidance, both Group I and II have severe renal impairment; Group I are not considered to have mild and moderate impairment as suggested by the applicant; however, the findings in Group I subjects support the conclusion that subjects with CLcr > 30 mL/min will not require iloprost dose reduction, because iloprost CL in these subjects was comparable to that in subjects with renal impairment.

Applicant's Safety Summary
Seven patients had a decrease in blood pressure during treatment. There were no serious adverse events. Generally the IV infusion was well-tolerated by the subjects.

Conclusion/Summary
Iloprost clearance appears to be affected by renal function: Group I subjects had CL values that were comparable in magnitude to that of normal subjects without renal impairment (CL ~ 20 mL/min/kg) whereas Group II subjects (severe renal impairment) had CL values (CL ~ 5 mL/min/kg) that were approximately four times lower than those in normal subjects. As expected based on CL values, the exposure in Group 2 subjects were ~ 4 times as high as those in Group 1.

Dosing Recommendations
The dosing recommendations that follow rely on the following assumptions:

- The results from the intravenous route are reflective of the inhaled route.
- The cross study comparison (patients with renal dysfunction vs. subjects with normal renal function) of CL is acceptable.

With these caveats in place the dosing recommendations for inhaled iloprost are:

1. Subjects with mild or moderate renal insufficiency do not require a dose reduction when undergoing inhaled iloprost therapy.
2. Subjects with severe renal impairment, not requiring dialysis, should have the dose reduced to 1.25 µg iloprost at intervals of at least 3 hours (up to a maximum of six times a day) as initial treatment. The dosage may be adjusted based on individual need and tolerability.
3. Patients with severe renal impairment requiring dialysis or ESRD should not receive inhaled iloprost because the effect of dialysis is unknown.

General Comment
A renal insufficiency study with inhaled iloprost formulation should be considered to confirm that the IV findings are applicable to the inhaled route. In the study, subject groups should conform to that specified in the Guidance for Industry. Additionally particular attention should be paid to appropriate patient matching (e.g. age, weight,

disease status etc). Furthermore, the influence of dialysis should be evaluated to allow for definitive dosing in patients requiring dialysis.

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Title	Pharmacokinetics of iloprost in patients with hepatic dysfunction after intravenous infusion of 1 ng/kg/min for 60 minutes
Report Number	8432
Investigator/Site	[redacted]
Study Period	07/88 to 05/89
Objectives: (sponsor stated)	• To characterize the disposition of Iloprost in patients suffering from different states of hepatic dysfunction • To investigate whether this special population exhibited a different pharmacokinetic profile

Study Design
This was an open label uncontrolled study. Hospitalized patients with liver cirrhosis participated in the study. Each subject was treated once with an IV infusion of iloprost at 1 ng/kg/min for 60 minutes.

Subject Characteristics **(n = 8)**
Sex: 5 males and 3 females
Child Pugh Classification: 5 Class B, 2 Class C and 1 Class A.
Mean Age ± SD; range (years): 55.8 ± 8.6 ; 43 - 68
Mean Weight ± SD; range (kg): 67.0 ± 13.4; 45 - 84
Mean Height ± SD; range (cm): 169 ± 11; 155 - 184

Blood Sampling
Blood samples were obtained at 0, 30 , 60 , 65, 70, 75, 90, 120, 180, 240, 360 and 480 minutes after the start of infusion.

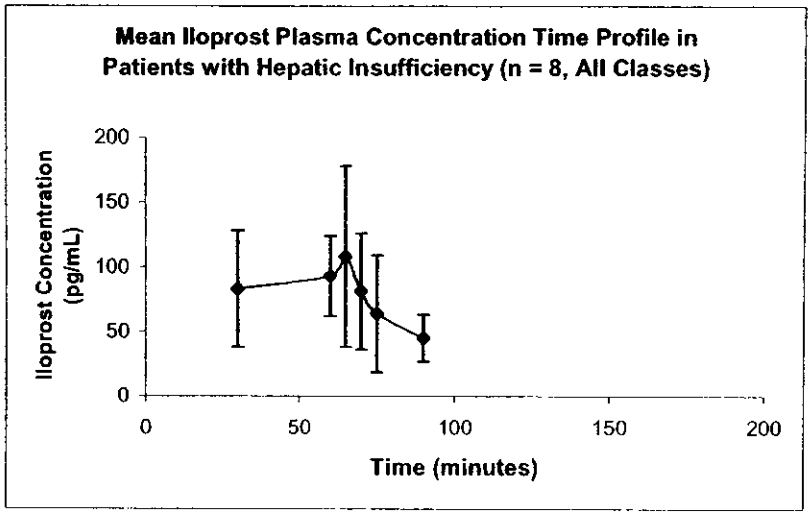
Formulations
Iloprost solution (SH L 401 A), provided as ampules Schering, AG, Germany

Analytical Method
The concentration of iloprost was determined by [redacted] The detection limit was — pg/mL. The applicant indicates that no additional assay information is available.

Pharmacokinetic Analyses
The following Iloprost PK measures were obtained: C_{ss}, $t_{1/2}$, $AUC_{0-\infty}$ and CL* (dose/$AUC_{0-\infty}$).
* The applicant used the equation shown above. However, for a prolonged constant rate infusion, CL = Rate of infusion/C_{ss} whereas IV administration is given by CL= dose/$AUC_{0-\infty}$. For this study, the results from either calculation are of similar magnitude but differ in absolute value. Both results are presented.

Results
Pharmacokinetics
The plasma concentration time-profile for patients with hepatic insufficiency receiving iloprost IV are depicted in figure 1. The concentration data were highly variable.

Figure 1: Iloprost Concentration vs. Time Profile in Patients with Hepatic Insufficiency



Most subjects achieved steady state at the end of infusion (t = 60 minute); subsequently, plasma concentrations declined in a biphasic (n = 2) or monophasic manner (plots not shown).

PK measures obtained in the current study are summarized in Table 1.

Table 1: Pharmacokinetic measures in patients with hepatic impairment receiving 1 ng/kg/min iloprost for 60 minutes

Child Class	n	Age (years)	Cpss (pg/mL)	$T_{1/2\beta}$ (min)	AUC_{∞}, (pg h/mL)	CL (mL/min/kg	CL*, (mL/min/kg)
A, B, C	8	55.8 ± 8.6	93.4 ± 31.0	27.5 ± 24.3	125.65 ± 60.4	10.7 ± 3.2	9.8 ± 4.8
A	1	50.0	66.0	10	62.8	15.2	15.9
B	5	54.4 ± 5.9	99.6 ± 37.7	36.2	139.64	11.1± 3.8	8.9 ± 5.1
C	2	53.0	91.5	14.5	122.1	10.7	8.9

CL*- calculated by Reviewer

The applicant pooled data from all hepatic classes. As shown in Table 1, overall the PK of iloprost appeared comparable across hepatic insufficiency classes however this conclusion is based on a limited number of subjects (n < 6, per group).

Dosing Adjustment Recommendations

The applicant relied on cross study comparisons to make dosing recommendations because this study did not have an adequate control group of subjects.

Table 2 summarizes the cross-study PK measures obtained in healthy subjects and subjects with hepatic insufficiency.

Table 2: Cross Study Comparison- Pharmacokinetic measures in patients with hepatic impairment receiving iloprost infusion for 60 minutes

Child Class	n	Dose (ng/kg/min)	Age (years)	Cpss^ (pg/mL)	$T_{1/2\beta}$ (min)	CL. (mL/min/kg)
A, B, C	8	1	55.8 ± 8.6	93	28 ± 24	10 ± 5
Normal 1a	6	1	30 ± 8	46	20 ± 7	21 ± 3
Normal 1a	6	3	30 ± 8	45	26 ± 7	20 ± 5
Normal 2	8	2	59 ± 5	40.5	31 ± 10	24 ± 9

Cpss^ is dose normalized to facilitate comparison

The most appropriate data for comparison appears to be Normal 2, since these subjects are roughly aged matched. The iloprost CL in hepatic insufficiency is approximately half that of normal subjects, suggesting that dose reduction will be required to achieve similar exposure in the two populations following IV administration.

Effect of Administration Route

It is unclear if the hepatic insufficiency results obtained following IV administration will be identical or applicable to that following inhaled delivery. Ideally this study should have been conducted using the intended route of administration.

Conclusions

- Based on a cross study comparison (IV infusion), subjects with hepatic insufficiency appear to have iloprost CL that is half that of normal subjects
- Due to the small number of subjects in Child Pugh Class A (n =2) and C (n = 1), it is not possible to determine if iloprost PK differs among hepatic insufficiency classes.

Recommendations

1. Assuming that the intravenous route is reflective of the inhaled route, a dose reduction is required in subjects with hepatic insufficiency who use inhaled iloprost. The data are insufficient to determine if different dose reductions will be required for the three Child Pugh classes. The findings support an initial 50 % dose reduction in Child Pugh Class B (n = 5). However, this Reviewer does not think the data provided are sufficient to make a definitive dosage recommendation for inhaled iloprost (see Recommendation 2, Labeling, and Study 8432-AM 75 cross-study comparison. The two main deficiencies of the study are: a) the assumption that Child Pugh Class A and Class B are comparable and b) results from the IV and inhalation route will be similar. These assumptions are in contradiction to the findings from Study AM 75 with oral iloprost, where there was a 15-fold exposure difference between Child Class B and normal vs. 2.5 fold difference between Child Class B and normal in the IV study (Study 8432). Furthermore in AM 75, there was a clear difference in exposure between Child Class A and B; the AUC in Class B was ~ 3 x greater than that in Class A.

2. A hepatic insufficiency study with the inhaled iloprost formulation should be considered to confirm that the IV findings are acceptable. In this study an adequate control group should be included, as well as a sufficient number of subjects from each

of the three hepatic insufficiency groups, per the Guidance for Industry recommendations.

Labeling

- **Applicant's proposal**

- **Reviewer's Comment on Applicant's Labeling Proposal**

The applicant's labeling proposal is unacceptable

Title	Effect of hepatic impairment on pharmacokinetics of iloprost, after a single oral administration of 100 µg iloprost clathrate as an extended release capsule
Study Number	AM75
Investigator/Site	[redacted]
Study Period	09/96 to 01/97
Objectives	To assess the effects of impaired hepatic function on single dose pharmacokinetics of iloprost administered as β-cyclodextrin clathrate extended release formulation

Study Design
This was an open label study. Subjects with normal hepatic function (healthy), Child Pugh Class A and Child Pugh Class B participated in the study. Each subject received a single dose of 100 µg iloprost clathrate with 100 mL of slightly carbonated mineral water on an empty stomach.

Blood Sampling
Blood samples were collected at baseline, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, and 24.0 h post dose.

Formulations
Iloprost clathrate extended release capsule, 100 µg; formulation SH K 529 M (Batch number D0851), Schering, AG, Germany

Analytical Method
Plasma levels of iloprost were analyzed using a validated specific and sensitive RIA. The assay performance was acceptable with the following parameters: mean accuracy measured by relative error was 90 to 105 % and precision measured by CV was 7 to 26 % for QC samples ranging from — pg/mL. The limit of quantitation was — pg/mL.

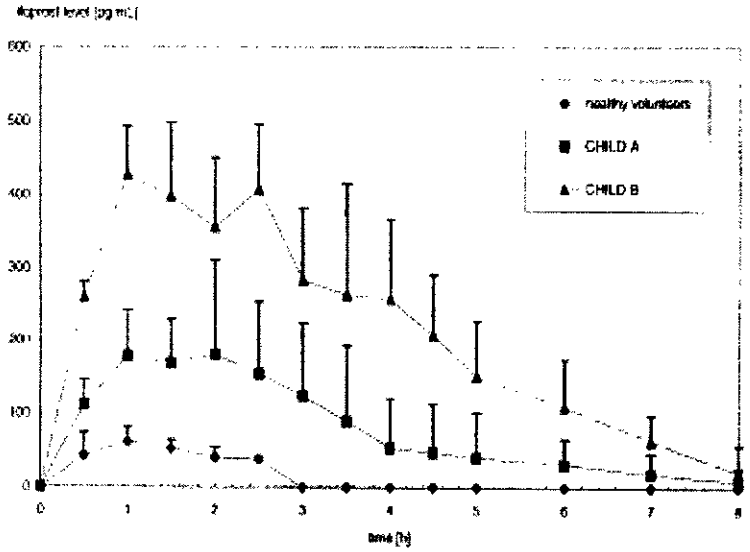
Pharmacokinetic Analyses
The following Iloprost PK measures were obtained using noncompartmental methods: $AUC_{0\text{-}8\ h}$, $AUC_{0\text{-}12\ h}$, AUC, Cmax, Tmax and $t_{1/2app}$.

Results

Subject Disposition
Fifteen subjects participated in the study, however only 12 subjects contributed to the pharmacokinetic data; three subjects in Child Pugh Class B were excluded because they had extensive vomiting, and are unlikely to have absorbed the entire dose.

Pharmacokinetics
The mean plasma concentration time-profile for patients with hepatic insufficiency receiving iloprost clathrate PO are depicted in figure 1. In all subject groups, iloprost plasma concentrations increased to a maximum over the first two hours and thereafter declined; the concentration of most plasma samples obtained after 8 hr were below the limit of quantitation.

Figure 1: Mean Iloprost Concentration vs. Time Profile in Healthy Subjects and Patients with Hepatic Insufficiency (Child Pugh Class A and B)



Demographic and pharmacokinetic measures obtained in the study are summarized in Table 1.

Table 1: Mean ± SD Iloprost PK measures in subjects with normal and impaired liver function following oral administration of iloprost capsule

Hepatic Function	N *	Demographics			Pharmacokinetic Measures			
		Age (yr)	Weight (kg)	Height (cm)	Cmax (pg/mL)	T_{max} (h)	$AUC_{0\text{-}8\,h}$ (pg h/mL)	$T_{1/2app}$ (min)
Healthy	4	33.3 ± 9.4	72.0 ± 5.5	177 ± 6	62 ± 19	0.9 ± 0.3	117 ± 36	2.1 ± 0.6
Child A	5	48.8 ± 7.3	73.2 ± 15.8	171 ± 8	215 ± 112	1.5 ± 0.7	639 ± 440	1.1 ± 0.6
Child B	3	49.3 ± 13.2	79.2 ± 14.2	173 ± 8	441 ± 76	1.7 ± 0.8	1725 ± 544	1.5 ± 0.3

* for demographic variables, healthy (n = 5), Child A = 6 and Child B = 4

As shown in Table 1, the degree of hepatic insufficiency did not appear to have a significant impact on the $t_{1/2}$ or Tmax.

The degree of hepatic function appeared to significantly impact iloprost apparent oral clearance (reflected in AUC and Cmax differences); the differences in exposure indicate that Child Class A require a 5 fold dose-reduction and Child Class B require a 15 fold dose-reduction to achieve exposure similar to that in healthy subjects. A potential limitation of the Child Class B and Child Class A results is the relatively small number of subjects, in each Class, n = 3 and 4, respectively. Ideally, each Class should have six or more subjects.

Effect of Administration Route

It is unclear if the hepatic insufficiency results obtained following oral administration of a sustained release formulation will be identical or applicable to that following inhaled delivery. Ideally this study should have been conducted using the intended route of administration.

Applicant's Safety Analyses
Vasodilatation, headache, nausea and vomiting were the most common adverse events (AEs). Subjects in Child Class B had the highest frequency and severity of AEs. No serious or life-threatening AEs occurred. Overall, iloprost was well tolerated in the study.

Conclusions
- The degree of hepatic insufficiency alters the pharmacokinetics (decreases CL) of iloprost. Relative to subjects with normal hepatic function, the $AUC_{0\text{-}8\ h}$ of subjects in Child Pugh Class A were ~ 15 times higher and Child Class B were ~ 5 times higher
- Mean apparent $t_{1/2}$ were comparable among healthy subjects, Child Class A and Child Class B subjects.

Recommendation/Discussion
1. Assuming that the results of oral iloprost administration are reflective of inhaled iloprost, a dose reduction is required in subjects with hepatic insufficiency who use inhaled iloprost. The data suggest that a five fold dose-reduction is required for subjects in Child Class A and a 15-fold reduction is required in Child Class B. There were no data in Child Class C; therefore, no recommendation can be made for this class of subjects. However, this Reviewer thinks that the information from this study is inadequate to make dosing recommendations for inhaled iloprost (see Recommendation 2, Labeling, and Study 8432-AM 75 cross-study comparison). The main limitation of this study is the assumption that results from the oral and inhaled routes will be similar. This assumption is unlikely to be valid in light of the IV findings: with oral iloprost (Study AM 75) there was a 15-fold exposure difference between Child Class B and normal vs. 2.5 fold difference between Child Class B and normal in the IV study (Study 8432). Most likely the effect of hepatic impairment following inhaled iloprost falls somewhere between that of the oral and IV results, but the exact magnitude of the effect is unknown.

2. A hepatic insufficiency study with the inhaled iloprost formulation should be considered to allow for definitive dosing recommendations in all hepatic function classes. In this study an adequate control group should be included, as well as a sufficient number of subjects from each of the three hepatic insufficiency groups, per the Guidance for Industry recommendations.

Labeling

- **Applicant's proposal**

[ ]

- **Reviewer's Comment on Applicant's Labeling Proposal**

The applicant's labeling proposal is based solely on the IV data, not considering the oral data; this approach is unacceptable. The data from the oral study alone are also inadequate to make definitive labeling recommendations for subjects with hepatic insufficiency that require inhaled iloprost therapy.

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Leveraging Study AM75 and 8432 Information to Make Dosing Recommendations for Subjects with Impaired Hepatic Function:

As indicated in the individual study reports for Study AM75 (oral iloprost) and 8432 (IV iloprost), this reviewer recommends that a hepatic impairment study be conducted using inhaled iloprost. This study will provide definitive dosing information for the proposed product, if approved. However, if a dosing recommendation is critical for subjects with hepatic insufficiency, the information from studies AM75 and 8432 can be leveraged to provide reasonable interim dosing recommendations.

Qualitatively both studies show the following:

- Decreased iloprost clearance in subjects with hepatic insufficiency relative to normal subjects (no hepatic dysfunction)
- Comparable $t_{1/2}$ and Tmax for hepatic impairment and normal hepatic function

Quantitatively for Child Class B subjects, the relative clearance differs in the two studies:

- CL in normal subjects ~ 2 times greater than that in Child Class B
- CL in normal subjects ~ 14 times greater than that in Child Class B.

Neither of the two studies provides sufficient information for Child Class C. In the oral iloprost study, CL in normal subjects ~ 5 times greater than that in Child Class A.

Assumptions

- It is likely that the CL ratio (CL in normal vs. CL in hepatic insufficiency) for the inhaled route will fall between that obtained for IV and oral (worst case scenario); however, an exact value for the magnitude of the CL ratio can not be determined with the available information.
- The number of subjects per group $n < 6$ is sufficient to describe the PK behavior of iloprost in subjects with hepatic insufficiency.

Clinical Considerations

Key clinical considerations are as follows:

- Subjects with hepatic insufficiency were excluded from the pivotal clinical trial therefore there is no long-term clinical trial safety information in these subjects
- According to the Medical Reviewer, the most severe adverse events (AE) occurred at inhaled iloprost doses ≥ 10 µg (AUC ~ 100 p·gh/mL) as observed in the QT study; these AEs included tightness in the chest (non cardiac-related) and vasodilatation.

Recommendation/Discussion

Based on the preceding information, this reviewer proposes the following labeling recommendations for the three hepatic impairment classes.

- Child Class A

The applicant's labeling proposal is acceptable with a minor modification (bolded text):
"An initial dose of 2.5 µg should be administered at intervals of at least 3 hours (up to a maximum of 6 times per day) to patients with Child Pugh Class A. Thereafter, the dose and dosing intervals may be adjusted based on individual tolerability."

Study Report Number	7564- 100 (Protocol Number C200-004)
Title:	A phase I placebo- and positive-controlled study of the effects of inhaled iloprost solution on ECG parameters (with a focus on QTc interval prolongation) in healthy male and female subjects
Investigator	[ ]
Study Period	05/2004- 06/2004
Objectives	• Assess the effects of inhaled iloprost aerosol on 12-lead ECG parameters (change in QTcI, individually corrected QT duration) in healthy male and female subjects. • Evaluate the pharmacokinetics of inhaled iloprost and correlate with QTcI interval assessments. • Evaluate the general safety and tolerability (maximum tolerated dose; MTD) of inhaled iloprost.

Reviewer's Note

This review focuses on the QT analyses; however, the QT results were not reanalyzed thoroughly for this review.

STUDY DESIGN

This was a randomized parallel design study in healthy subjects. Eligible subjects were randomized to receive one of four treatment regimens:

- Group A: oral moxifloxacin, 400 mg (positive control)
- Group B: inhaled iloprost, fixed 2.5 µg dose every two hours for 6 doses (15 µg total)
- Group C: inhaled iloprost, ascending dose* every two hours for 6 doses (doses were 5, 7.5, 10, 12.5, 15 and 20 µg = 70 µg total exposure)
- Group D: inhaled placebo, that was time-matched to group C

Inhalation therapy was double-blind with respect to iloprost vs. placebo (Group C vs. D). The study was not blinded with respect to moxifloxacin or to fixed dose iloprost treatment arms, but all ECGs (including the primary endpoint) were analyzed from digital data in a blinded fashion by the central ECG laboratory.

*Increasing iloprost doses were achieved with longer inhalation times (5 additional minutes per 2.5 µg increase in dose) with the nebulizer. The anticipated inhalation time for the 5 µg dose was 10 minutes and that for the 20 µg dose was 40 minutes.

Subject Characteristics **(n = 161)**

Mean Age ± SD (years):	25 ± 6.7
Mean Weight ± SD (kg):	73.9 ± 11.2
Mean Height ± SD (cm):	174.4 ± 8.8
Gender:	80 males and 81 females
Race:	1 Asian, 19 Black, 137 White, 1 Hispanic and 1 Other

Blood Sampling

Blood samples were obtained after the sixth inhalation in all available subjects in Groups B and C, and 40 % of the subjects in Group D. Blood samples were collected at the following time points: pre-dose (prior to start of 6th inhalation), midpoint of inhalation, end of inhalation, 5, 15, and 60 minutes post-6th inhalation.

Formulations

The study drug formulations used in the study are summarized in Table 1. Iloprost and placebo were delivered via inhalation using a breath-actuated nebulizer (ProDose, Profile Therapeutics).

Table 1: Drug Formulations

Study Drug	Iloprost	Placebo	Moxifloxacin (Avelox$^{(R)}$)
Form.	2 mL solution (3 mL ampule)	2 mL solution (3 mL ampule)	tablet
Strength	10 µg/mL	0 µg/mL	400 mg
Lot or Batch No.	41022	41001	2500KXP
Manufacturer	[ ]		Bayer Pharmaceuticals Corporation

Assay

The concentrations of S- and R-iloprost were determined by a validated LC/MS/MS method. The assay performance was acceptable. The standard curve range was [ ] pg/mL for both isomers: mean R^2 for 4-R iloprost = 0.9968 and mean R^2 for 4-S iloprost = 0.9962. The accuracy (measured by % bias) was [ ], and [ ] % for 4-R and 4-S iloprost, respectively. The precision (measured by % CV) was [ ] for 4-R and 4-S iloprost, respectively. QC sample concentrations were [ ] pg/mL.

PK Analyses

The following PK parameters were calculated for all evaluable subjects using a model independent approach: Cmax, Tmax, AUC_{0-t}, AUC_{0-8}, and $t_{1/2}$. For the analyses, the start of the 6th inhalation was denoted as the zero time and all subsequent times were given numerical values relative to the start of inhalation time.

Pharmacodynamic (QT) Analyses

ECG intervals and morphology were obtained at baseline and at well defined time-points on the single treatment day using the digital 12-lead Holter technology [ ] Three 12-lead ECGs were downloaded from the H-12 flash card approximately one minute from each other at each defined time point.

ECG Measurements

The measurement timeline was as follows:

- Day 0 (Baseline)

ECGs were collected at 0800, 1000, 1200, 1400, 1600, 1800, 1900, 2200, 0200 (next day) and 0730 (next day) hours. Three ECGs were collected at each of these time points.

- Day 1: Fixed dose iloprost and the placebo treatment arms

Starting at 5 minutes after inhalation for the 0800, 1000, 1200, 1400, 1600 time points; midpoint and endpoint of inhalation for the 1800 time point, followed by 5, 15, and 60 minutes post-inhalation; and at 2200, 0200 (Day 2), and 0730 (Day 2) .

- Day 1: Ascending dose iloprost group

For the ascending dose iloprost group, ECG determinations were made at the same time points as for the fixed dose iloprost group. Additionally, an ECG was obtained about 10 minutes into the period of time for inhalation at the 1800 time point.

QT corrections

Three types of QTc were defined: Individual (QTcI), Fridericia (QTcF), and Bazett (QTcB) intervals. QTcI was determined for each subject by iterating the QT- RR relationship using all baseline ECGs (Day – 1) to define which exponent resulted in the slope of this relationship closest to " 0 ". The applicant indicates that QTcI was the primary correction used and that the Bazett ($QTcB = QT/(RR)^{1/2}$) and Fridericia ($QTcF = QT/(RR)^{1/3}$) corrections were considered secondary.

Statistical Analyses

Descriptive statistics and confidence intervals were used to summarize the ECG variables and the corresponding changes from baseline. Ninety- five percent confidence intervals for differences between the treatment and placebo groups are presented.

Exploratory PK/PD

Overall subject plots were performed using the maximum change in the QTc parameter versus Cmax for Day 1 and the maximum change in the QTc parameter versus the plasma concentration at that time.

Results

ECG and QT Information

The total number of digitized ECGs was 69 ECGs for 120 subjects (Groups B, C, and D) and 60 ECGs for 40 subjects (Group A) for a grand total of 10,680 ECGs. Key information from the QT study are summarized in Table 2 and highlighted as follows:

- **Heart Rate (HR)**

Relative to placebo, fixed dose iloprost had a + 2 beats per minute (bpm) change in HR which was not clinically relevant. The escalating dose iloprost arm increased the HR by 4 bpm ($p< 0.01$). Consequently, a QT correction method was required to minimize the effect of heart rate on QT.

- **QT Intervals and QT Corrections (QTc)**

Without correcting for heart rate, the QT interval was negative for iloprost treatments and placebo treatment, only moxifloxacin treatment had a positive value. The QTcI and QTcF produced comparable results for the four treatment arms and these two corrections differed from the QTcB. The differences between QTcB and the other two correction methods were most apparent for the Iloprost fixed dose and iloprost ascending treatments: QTcB was a positive value for these treatments vs. QTcI and QTcF with negative values. Nevertheless all QTc values demonstrated a similar trend: Moxifloxacin > iloprost ascending > iloprost fixed > placebo.

Reviewer's Note

The applicant's analyses demonstrated that QTcI was the most appropriate correction; thus, subsequent discussion and presentations will be based on QTcI. Figures 1 a, b, c, and d, depict the various QTc corrections and the uncorrected QT intervals. These figures indicate that QTcI and QTcF effectively minimize the influence of HR (reflected by RR) on QT.

Figure 1 a Qt vs. RR

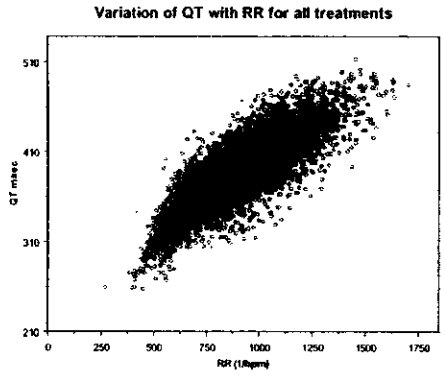


Figure 1b QTcB vs. RR

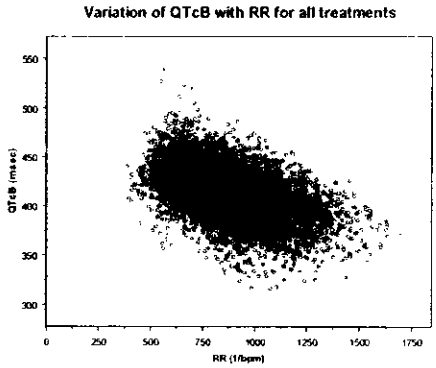


Figure 1c QTcI vs. RR

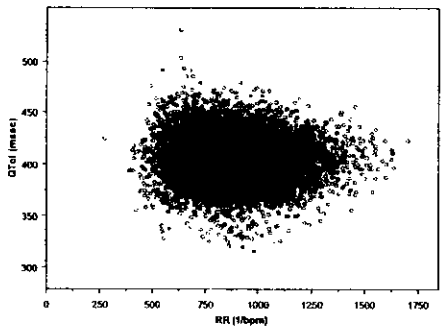
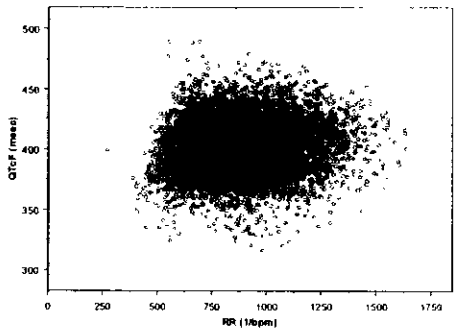


Figure 1d QTcF vs. RR



- **Measurement of QTc Changes**

QTc changes from baseline were assessed using a placebo corrected procedure (double delta manipulation, DD).

$$DD = \{QT\ Treatment_{\ Day\ 1} - QT\ baseline_{\ Day\ 0}\} - \{QT\ Placebo_{\ Day\ 1} - QT\ baseline_{\ Day\ 0}\}$$

The moxifloxacin treatment served as a positive control in this study. After correcting for the placebo effect (DD manipulation), moxifloxacin showed +7 msec change in QTcI from baseline. Using least means squares the change in QTcI was +7 (confidence interval, CI, : +3 to + 10 msec). This range of QTc values is within the range of QTc values, +5 – 10 msec required to establish assay sensitivity. For the iloprost fixed dose treatment there was a + 2 msec (- 2 to + 5 msec CI) QTc change and the maximum tolerated escalation dose arm showed a + 3 msec (- 1 to + 6 msec CI) effect.

Mean change from baseline in Selected ECG Parameters and Outlier Analyses

	Moxifloxacin	Iloprost fixed	Iloprost Ascending	Placebo
Total N	40	39	41	40
Heart Rate				
Heart Rate in bpm	1	5	7	3
Heart rate using 1800-2000 hrs	-1	3	5	3
QT Interval				
QT in msec	1	-12	-14	-10
QT from 1800-2000 hrs	10	-7	-10	-9
QT new >500 msec N (%)	0	0	0	0
QTcI Interval				
QTcI in msec (C.I.)	3	-2	-1	-4
QTcI max mean in msec	23	17	17	14
QTcI 1800-2000 hrs	6	-2	-1	-3
QTcI new >500 msec N	0	0	0	0
QTcI new >450 msec N (%)	0	0	0	0
QTcI 30-60 msec increase N (%)	8 (20%)	4 (10%)	3 (7%)	0
QTcI >60 msec increase (N)	0	0	0	0
QTcF Interval				
QTcF in msec* (C.I.)	3	-3	-2	-4
QTcF using 1800-2000 hrs	7	-3	-1	-4
QTcF max mean in msec	23	17	17	16
QTcF new >500 msec (N)	0	0	0	0
QTcF new >450 msec N (%)	0	0	0	0
QTcF 30-60 msec increase N (%)	9 (23%)	4 (10%)	3 (7%)	3 (8%)
QTcF >60 msec increase N	0	0	0	0
QTcB Interval				
QTcB in msec (C.I.)	4	2	4	-2
QTcB using 1800-2000 hrs	5	0	4	-2
QTcB max mean in msec	25	20	24	18
QTcB new >500 msec (N)	0	0	0	0
QTcB new >450 msec N (%)	1 (3%)	0	0	0
QTcB 30-60 msec increase N (%)	12 (30%)	7 (18%)	11 (27%)	5 (13%)
QTcB >60 msec increase N (%)	0	0	0	0

- **Miscellaneous Analyses**

Outlier Analyses

No subject met the criteria defined for oultiers: QTc change from baseline of > 60 msec or a new > 500 msec change in QTcI duration. Twenty (20 %) of the moxifloxacin group, 10 % of the iloprost fixed 7 % of the ascending dose groups compared with 0 % in the placebo group met the 30-60 msec threshold for the outlier definition.

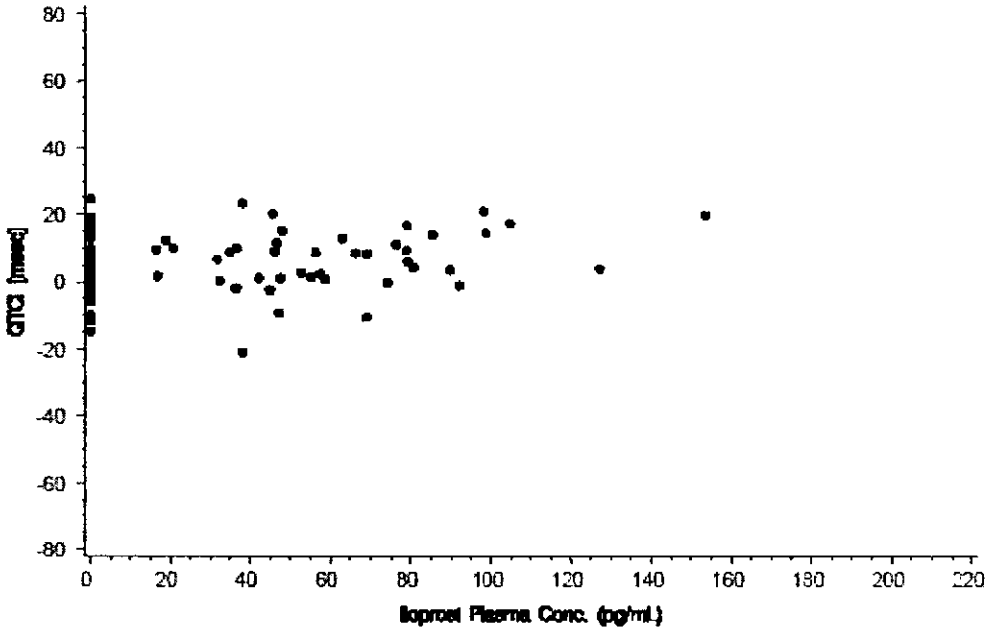
Gender Effect

There was no evidence of any gender effect for the QT data.

PK/PD Analyses

There was no evidence of an increase in QT interval associated with increases in measured iloprost concentrations. There were no changes > 30 msec in any subject receiving iloprost and no obvious PK-QTc effect based on the available data.

Figure 1: Maximum change in QTcI vs. plasma concentration (iloprost dose given at 1800 hr (per Applicant)



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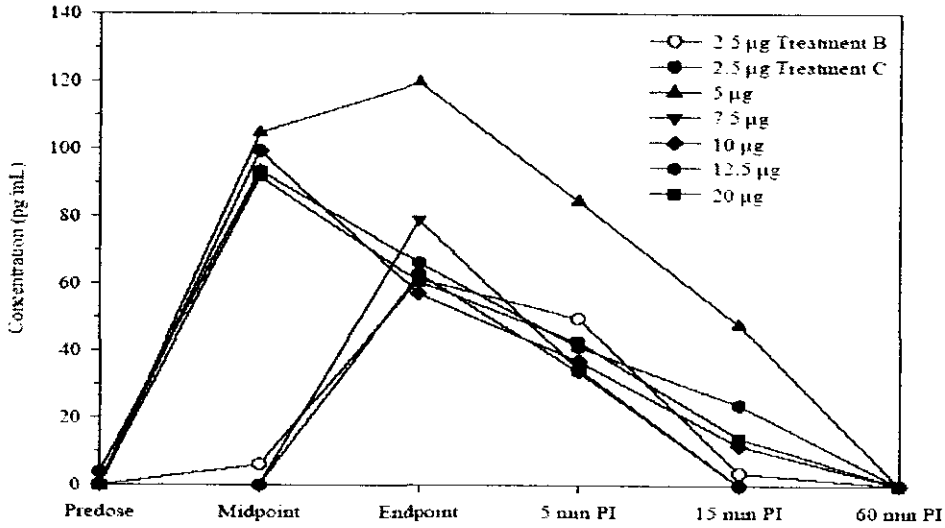
Pharmacokinetics

Mean iloprost plasma concentration-time profiles for Treatments B and C are depicted in figure 1.

Figure 1: Iloprost plasma concentration vs. time profiles (per Applicant)



As shown in Figure 1, after reaching Cmax plasma concentration levels fell rapidly with levels below the assay LOQ within 60 minutes. The limited blood sampling makes it difficult to compare the plasma concentration-time profiles for the different doses.

Iloprost pharmacokinetic measures are presented in Table 3.

Table 1: Mean ± SD iloprost PK measures During Treatments B and C (per Applicant)

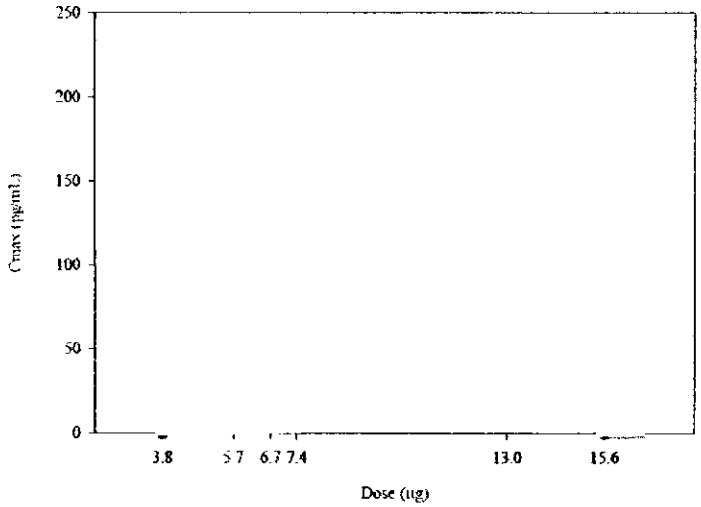
			Parameter				
Treatment	Dose[a]	Statistics	C_{max} (pg/mL)	T_{max}[b] (min)	AUC_{0-t} (pg·min/mL)	$AUC_{0-\infty}$ (pg·min/mL)	$T_{1/2}$ (min)
B	2.5 µg	N	38		38	1	1
		MEAN (SD)	64.7 (38.45)	5.00 (—	421 (342.0)	1073 (NA)	8.70 (NA)
C	2.5 µg	N	1		1	0	0
		MEAN (SD)	63.0 (NA)	12.0 —	309 (NA)	NA (NA)	NA (NA)
	5.0 µg	N	1		1	1	1
		MEAN (SD)	120 (NA)	11.0 —	2004 (NA)	2753 (NA)	10.9 (NA)
	7.5 µg	N	1		1	0	0
		MEAN (SD)	78.9 (NA)	7.00 —	560 (NA)	NA (NA)	NA (NA)
	10.0 µg	N	4		4	3	3
		MEAN (SD)	99.4 (41.16)	10.5 —	908 (1061.7)	2539 (1245.8)	10.4 (4.29)
	12.5 µg	N	3		3	3	3
		MEAN (SD)	125 (24.5)	12.0 (—	3030 (458.4)	3731 (952.2)	13.7 (9.41)
	20.0 µg	N	29	28	29	25	25
		MEAN (SD)	94.5 (35.12)	20.0 —	92 (1350.4)	4087 (1309.1)	17.1 (9.82)

[a]For Treatment C, dose is MTD at the 6th dose.
[b]For T_{max}, Median (Minimum, Maximum) is shown.

There was significant intersubject variability in iloprost exposure at all dose levels as depicted in figure 2 (Cmax values) and reflected in high SD (Table 1). The applicant

indicates that this variability, in part, may reflect differences in dose inhalation due to individual differences in breathing patterns; the applicant's explanation seems reasonable.

Figure 2: Individual Subject Cmax vs. Iloprost Dose (per Applicant)



There was no clear dose-exposure relationship; this may have been due to the limited data at the various dose levels.

Reviewer's Note

The applicant indicates that "the purpose of the PK component of this study was to document systemic exposure to inhaled iloprost. It was not intended to provide definitive data on the pharmacokinetic properties of inhaled iloprost and the timing of blood sampling was limited to those required to correlate electrocardiographic with serum drug levels". This approach is reasonable for the stated purpose however it does not allow one to accurately compare the findings from this study to other iloprost PK studies or to conduct concentration response analyses.

Applicant's Safety Summary

There were no serious adverse events (AEs) during the study. However, as expected in a dose regimen designed to achieve maximum tolerability, the severity of AEs appeared to increase (greatest number of moderate AEs) with escalating doses of iloprost (Treatment C). The most commonly reported AEs were headache, dizziness, nausea, chest discomfort, cough, and flushing. Seventeen subjects reached the maximum tolerated dose (MTD) criteria. These included 13 subjects in Group C in most of whom the MTD was reached at doses of 12.5 μ g to 15 μ g. The remaining subjects in Treatment C tolerated dose escalation up to 20 μ g without reaching the maximum tolerated dose. There were no clinically meaningful changes in clinical laboratories, vital signs, or physical examinations.

CONCLUSIONS:

- Administration of inhaled iloprost does not cause a clinically or statistically significant increase in QTc. At the 2.5 µg dose and at the maximum tolerated/studied dose (20 µg) the QTc changes were +2 and + 3 msec, respectively.
- The exposure of iloprost was highly variable at the various dose levels; furthermore no conclusion could be made regarding a dose-response relationship due to insufficient data at each dose level.

Recommendation

As demonstrated in the study, iloprost administered at doses four times higher than the recommended clinical dose does not cause clinically significant changes in QTc;

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Study Report Number	8412
Title	Single Blind Randomized, placebo-controlled study for the investigation of drug interactions of iloprost with nifedipine, mepindolol sulphate and pentoxifylline in healthy volunteers
Study Period	09/87 to 09/88
Investigator/Site	[redacted]
Study Drugs (Formulations)	Iloprost- SH L 401A, Nifedipine capsules, 20 mg – Adalat, Mepindolol sulfate- Corindolan tablets, 5 mg SH E 222 CD and Pentoxifylline- Trental tablets, 400 mg
Objectives	To determine the drug interactions between iloprost and frequently used pharmaceuticals such as β-blockers, calcium antagonists, and phosphodiesterase inhibitors

Study Rationale

Patients with primary pulmonary hypertension and other peripheral arterial occlusive disease are frequently treated with calcium antagonists (e.g. nifedipine), beta-blockers (e.g. mepindolol), and phosphodiesterase inhibitors (e.g. pentoxifylline) to improve peripheral perfusion and to treat hypertension. Consequently these agents may be administered with iloprost in a clinical setting. It should be noted that mepindolol is not approved in the US.

Study Design

This was a placebo-controlled single blind randomized study. Healthy volunteers were randomly assigned to one of four treatment sequences. The treatments were as follows:

1. oral administration of nifedipine (20 mg single dose), mepindolol (5 mg single dose), pentoxifylline (400 mg single dose) or placebo
2. one hour infusion of NaCl (0.9 %)
3. one (1.0) ng/kg/min iloprost infusion for one hour
4. two (2.0) ng/kg/min iloprost infusion for one hour

Each subject received four different treatments with a one week washout between treatments.

Subject Characteristics **(n = 12)**

Age range (years): 20 - 37
Sex: 12 males

Pharmacodynamic Analyses

Hemodynamic Measures

Several hemodynamic measurements were observed during the study including, blood pressure, heart rate, and orthostatic reaction. Blood pressure and heart rate were measured before the oral intake of the treatment drug and every ten minutes during the infusion phases and at the end of the infusion phase.

Platelet Function

Platelet parameters were measured: maximum amplitude of aggregation, slope of aggregation curve, spontaneous deaggregation.

The reference treatments are as follows (reference vs. test): 1) saline infusion vs. iloprost alone, 2) saline infusion vs. individual oral treatments, 3) iloprost infusion + placebo vs. iloprost + oral treatment (active drug).

Reviewer's Note
Only selected pharmacodynamic parameters will be reported in this review.

Results

Subject Disposition
Thirteen male subjects were treated with i.v. infusions of 1 and 2 ng/kg/min iloprost and oral treatments of nifedipine, mepindolol, and pentoxifylline; however, one subject did not complete the study due to a common cold.

Pharmacodynamics
Pharmacodynamic (PD) data were summarized briefly in the report's text (not tabulated); however, several plots were included that depict mean pharmacodynamic data. The key PD effects of iloprost coadministration with the previously specified drugs from the various drug classes follow.

Effect of Treatment on Hemodynamic Measures

- Blood Pressure- Neither iloprost nor iloprost-drug combinations produced a significant change in blood pressure. Changes in systolic or diastolic blood pressure $\leq \pm$ 12 mmHg for all treatments with most changes < 10 mmHg (Figures 1 and 2).
- Heart Rate-Different effects on heart rate were produced by the various drug combinations: mepindolol decreased heart rate significantly (beta-blocking effect) when given alone and in the presence of iloprost; iloprost-nifedipine combination produced the maximal increase in heart rate (+ 9.0/min) at the 3.0 ng/kg/min dosage. The heart rate also increased when with iloprost-placebo, iloprost-mepindolol and iloprost-pentoxifylline treatment (Figure 3).

Effect on Platelet Function (Iloprost-containing Regimens)

- Iloprost 1.0 and 2.0 ng/kg/min IV infusions led to a dose dependent suppression of the maximal amplitude due to collagen induced aggregation (Figure 4).
- For ADP induced platelet aggregation, the presence of iloprost resulted in an approximately parallel shift of the regression curves towards suppression (figure 5) when the iloprost dose increased.
- Relative to placebo (NaCl), iloprost led to negative changes in deaggregation at low ADP dosages, however for high ADP dosage, high positive changes occurred. Co-incubation of iloprost with mepindolol, nifedipine or pentoxifylline led to less deaggregation.

Figure 1: Variation of diastolic blood pressure during iloprost and iloprost + drug treatments

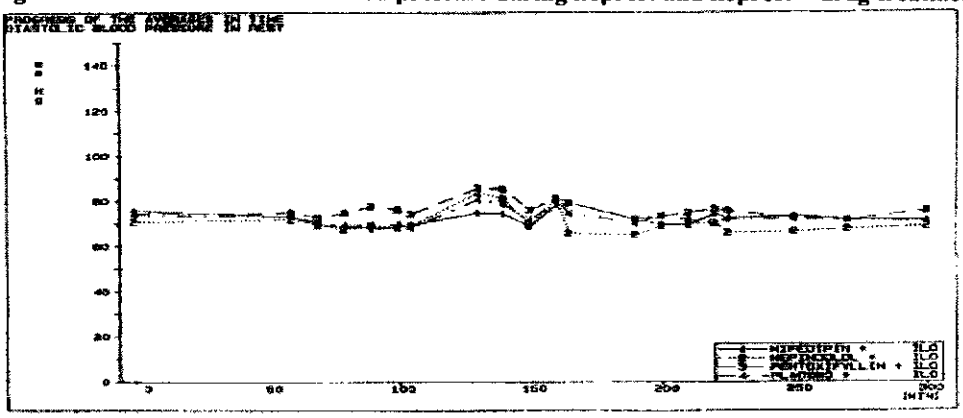


Figure 2: Variation of systolic blood pressure during iloprost and iloprost + drug treatments

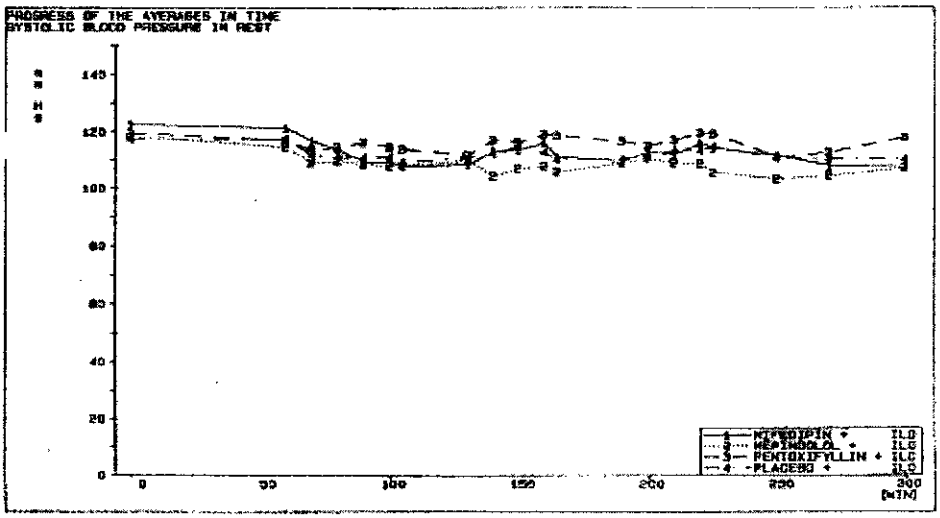


Figure 3: Variation of heart rate during iloprost and iloprost + drug treatments

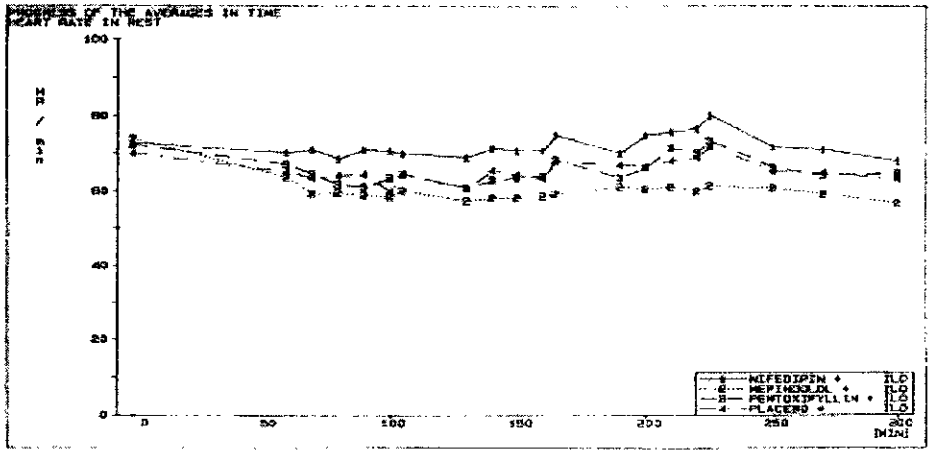


Figure 4: Effect of drugs on collagen-induced platelet aggregation

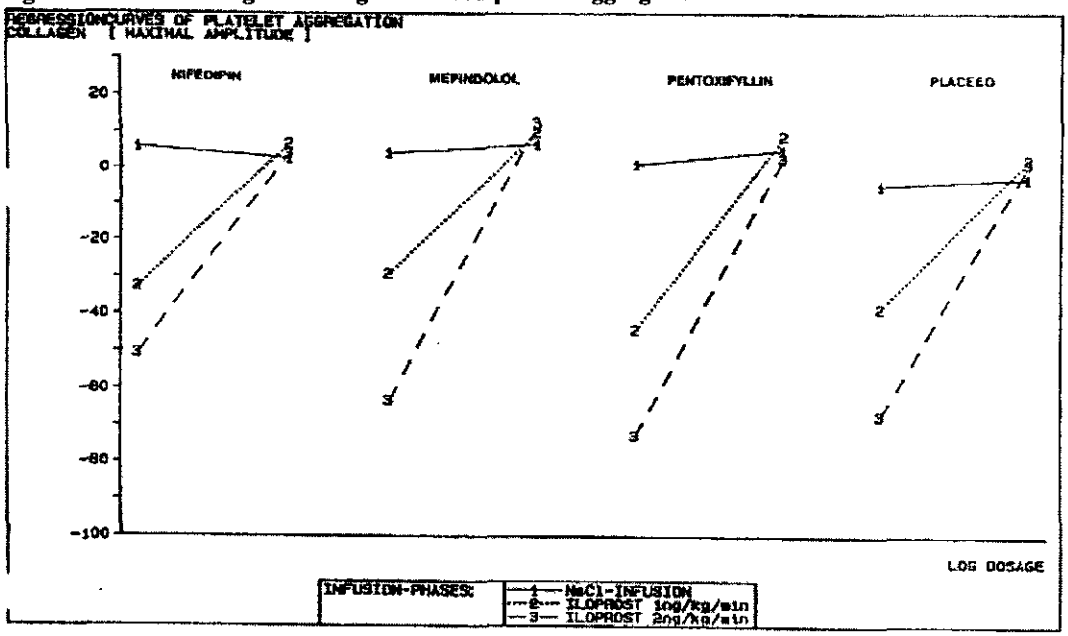
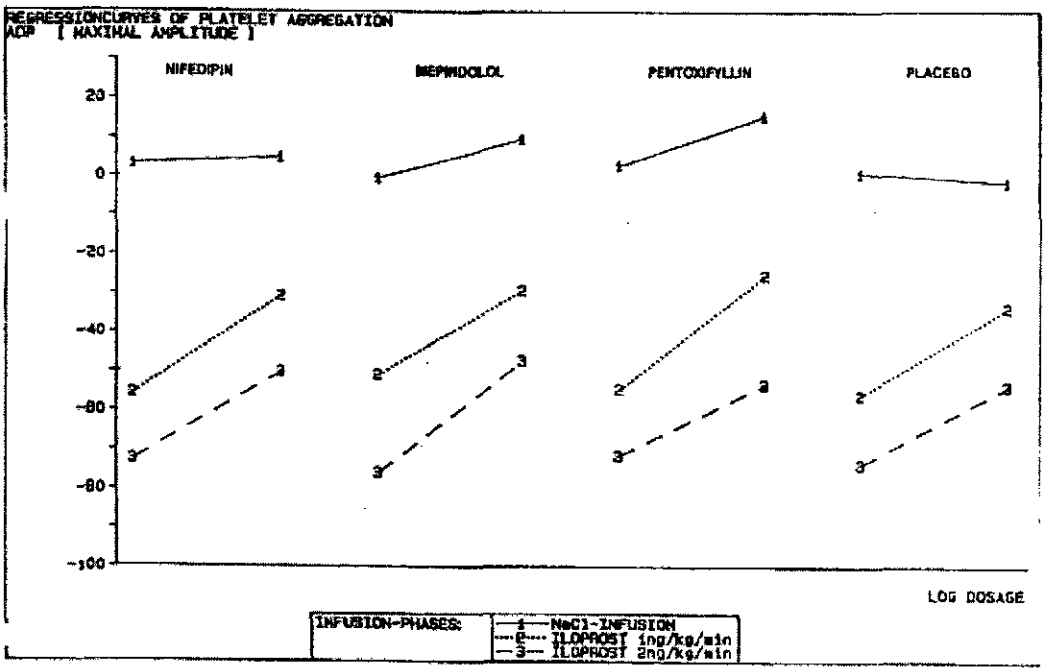


Figure 5: Effect of drugs on ADP-induced platelet aggregation



Applicant's Safety Summary
Administration of iloprost + placebo or iloprost + coadministered drugs was generally well tolerated in this study. No interventions were required due to side effects. Side effects reported in iloprost containing regimens included, severe flush, severe headache, and severe vertigo.

Conclusions
There does not appear to be any relevant pharmacodynamic interactions between intravenous iloprost and single oral doses of nifedipine, mepindolol, and pentoxifylline in healthy volunteers.

Discussion/Recommendation
Assuming that IV iloprost information is applicable to inhaled iloprost, inhaled iloprost can be coadministered with nifedipine, mepindolol, or pentoxifylline without dose adjustment because there was no PD interaction. It is unclear if the results (particularly PD) obtained in a single dose study in healthy volunteers will be the same in the target patient population, patients with pulmonary arterial hypertension. Potentially, the PD (hemodynamics) effects in patients with PAH may differ from that of healthy volunteers. However, in the clinical trial patients with PAH were allowed to receive various drugs, including those evaluated in this study. The safety profile of iloprost combined with the study drugs was clinically acceptable. Therefore, iloprost may be coadministered with the drugs evaluated in this study. Ideally, pharmacokinetic (exposure) information should have been obtained in this study to determine if coadministration led to changes in drug exposure.

Labeling
The product labeling should reflect the study findings with respect to the pharmacodynamic (PD) findings. It is unclear why the applicant only mentions the lack of a PD interaction between nifedipine and iloprost. The proposed labeling indicates that iloprost has the potential to increase the hypotensive effect of vasodilating and antihypertensive agents; this caution is not supported by the data from this study but is warranted based on other information on iloprost.

Study Report Number	8168
Title:	Drug interactions between iloprost and captopril: a double blind, randomized, cross-over placebo-controlled study of drug interactions in 10 healthy, male subjects
Study Period	04/88 to 05/88
Investigator/ Site	[ ]
Objectives	To investigate the interaction of iloprost with captopril in healthy subjects

Study Rationale

Iloprost induces a dose-dependent decrease in blood pressure and increases heart-rate. ACE inhibitors like captopril are used as antihypertensives and they decrease blood pressure and may increase heart rate. Consequently there is a possibility of pharmacodynamic (superadditive decrease in blood pressure and alteration in peripheral blood flow) drug-drug interaction between captopril and iloprost. In rats, infusion of iloprost with captopril enhanced the effect of captopril in blood pressure.

Study Design

This was a double-blind, cross-over study. Healthy subjects received iloprost + captopril and iloprost + placebo on two separate occasions. There was a one week interval between treatments. Patients were randomly assigned to one of two treatment sequences. Iloprost was given as a 2.5 hour infusion, one hour after captopril or placebo. Iloprost dosages were given every 30 minutes; iloprost dosages were given in 0.5 ng/kg/min increments over the 0 to 2.0 ng/kg/min iloprost dose range.

Characteristics of Enrolled Subjects **(n = 10)**

Age range (years): 21 - 36
Weight range (kg): 67 - 87
Height range (cm): 173 - 185
Sex: 10 males

Formulations

- iloprost solution, 100 µg/mL ampule (SH L 401 A) by Schering, AG, Germany.
- captopril capsule, 12.5 mg captopril [ ]
- captopril placebo capsule by Schering AG, Germany

Pharmacodynamic Analyses

Hemodynamic (HD) measurements were made during the study: peripheral blood pressure was measured every 30 minutes and heart rate was measured every 10 minutes. HD measures were compared: prevalue vs. treatment (no drug or captopril + iloprost).

Results

Subject Disposition

All 10 enrolled subjects completed the study.

Pharmacodynamics (PD)
Selected PD data are presented in Table 1.

Table: Hemodynamic Measures: Mean Blood Pressure and Heart Rate During Captopril (CPT), Captopril + Iloprost and Iloprost + Placebo (PLCB) Treatment (n = 10)

PD Measure	Prevalue	CPT*		30 min CPT + iloprost 1.0 ng/kg/min	30 min CPT + iloprost 1.5 ng/kg/min	1 hour Post Treatment	
Systolic BP (mm Hg)	118.5	111.8	112.3	112.2	117.0	119.0	116.3
Diastolic BP (mm Hg)	73.5	73.3	71.3	72.3	71.2	76.7	76.0
Pulse Rate	68.8	63.9	63.7	62.0	69.1	63.2	62.5
PD Measure	Prevalue	Placebo*		30 min PLCB + iloprost 1.0 ng/kg/min	30 min PLCB + iloprost 1.5 ng/kg/min	1 hour Post Treatment	
Systolic BP (mm Hg)	117.0	110.2	109.3	113.2	116.0	120.0	120.2
Diastolic BP (mm Hg)	72.0	72.7	74.3	74.3	71.2	80.3	78.7
Pulse Rate	70.8	65.1	61.7	62.7	70.1	61.7	63.6

* two sets of measurements were taken

Systolic blood pressure decreased by ~ 10 % after captopril administration and did not decrease further during the infusion of iloprost. The decrease in systolic blood pressure with placebo was comparable to that with captopril. Diastolic blood pressure did not change with any of the treatments. Heart rate decreased by 10 % after captopril and placebo administration and did not change further in the presence of iloprost.

Applicant's Safety Summary
Side effects were dose-dependent and occurred with both treatments. The most common side effects of iloprost were mild headache, facial flush and feeling of warmth. All symptoms were reversible after termination of infusion. Generally, iloprost was well-tolerated, no treatment had to be discontinued prematurely and there were no deaths or serious adverse events.

Conclusions
Iloprost at low doses does not appear to alter the pharmacodynamic effects of captopril at low doses.

Recommendation
Assuming that the IV iloprost information is applicable to inhaled iloprost, **inhaled iloprost can be coadministered with low dose captopril without dosage adjustment** (*Product Labeling*). This study was conducted at relatively low captopril dose (12.5 mg single dose); the typical dosage for captopril is 25 to 50 mg BID or TID. However, there is a possibility that when higher captopril doses are combined with higher inhaled iloprost doses, there will be an additive or synergistic effect on blood pressure decrease that may pose safety concerns. Consequently, **iloprost and captopril therapy should be initiated at the lowest possible dosages; subsequently dosages may be increased while monitoring for adverse events** (*Product Labeling*).

Title	Iloprost IV Digoxin Interaction Study
Study Report Number	A646
Study Period :	07/87 to 12/89
Investigator /Site	[redacted]
Objectives:	To determine if a pharmacokinetic drug-drug interaction occurs between digoxin and iloprost (administered by IV infusion in therapeutically prescribed doses) in PAOD stage III and IV according to Fontaine

Study Design

This was an open label study. Patients suffering form PAOD with symptoms of pain participated in this study. Each patient was maintained on a stable digoxin regimen and digoxin plasma levels were measured prior to and during iloprost treatment. Iloprost infusions were given six hours daily for 21 days. The treatment schedule follows:

- Day 1 to Day 7: 0.25 mg/day digoxin
- Day 8 to Day 28: 0.25 mg/day digoxin + iloprost* IV infusion
- Day 28 and onwards: 0.25 mg/day digoxin

From Days 8 to 10, the maximum tolerated dose (MTD) of iloprost was determined; the initial dose was 0.5 ng/kg/min and the dose was increased in 0.5 ng/kg/min increments until MTD was achieved (2.0 ng/kg/min).

* From Day 11 to 28 the MTD of iloprost given: MTD determined between Day 8 to 10.

Reviewer's Note

Most subjects were on several concomitant medications (e.g. captopril, nifedipine, diltiazem, and prednisone) thus these other drugs might impact the study results (pharmacodynamic in particular).

Subject Characteristics **(n = 8)**

Mean Age ± SD; range (years): 66.12 ± 13.27;
Mean Weight ± SD; range (kg): 65.25 ± 11.45; 50 - 84
Mean Height ± SD (cm): 162.88 ± 10.40; 152 - 180
Sex: 4 males and 4 females

Blood Sampling

Blood samples were drawn throughout the course of the trial according to the following schedule:

- Day 3, 5, 10, 17, 25, 29, 30 and 31: 8 AM
- Day 4 and 24: 8, 9, 10, 11, 12 AM and 2, 4, and 6 PM.

Formulations

- iloprost solution (100 µg/mL) that was further diluted with saline
- digoxin (no details provided)

Analytical Method

No assay details were provided.

Pharmacokinetic and Statistical Analyses

The following digoxin PK measures were obtained: C_{trough} (8 AM on several days), AUC and Cmax. The following statistical tests were used to compare the digoxin exposure measures on different days of treatment:

- Mac Newman test or Q test of Cochran for qualitative data
- T-test on matched series or ANOVA
- Wilcoxon or Friedman test for quantitative data that are not normally distributed

Reviewer's Comment

The drug-drug interaction evaluation (exposure comparison) should have been conducted using the procedure outlined in the Drug-Drug Interaction Guidance (calculation of geometric mean ratios and 90 % confidence intervals).

Pharmacodynamic Analyses

ECG, blood pressure and pulse rate measurements were taken throughout the course of the trial. ECG was determined on Days weekly (Days 1, 14, 21, and 28). Blood pressure and pulse was determined during concomitant administration of digoxin and iloprost (Days 8 to 28); these measurements were made at the beginning and end of each iloprost dosage change (IV infusion).

Results

Subject Disposition

Although 11 subjects participated in the study, only eight were included in the statistical analyses; the other three patients were excluded form analysis due to protocol violations.

Digoxin Pharmacokinetics

Only five patients were evaluable for 8 AM digoxin concentrations. Selected 8 AM digoxin data are summarized in Table 1.

Table 1: Mean±SD and Range of Digoxin Plasma Concentrations at 8 AM (n =5)

PK Measure	Mean (ng/mL)	Range (ng/mL)
Day 5	1.00 ± 0.50	0.52 – 1.25
Day 10	1.11 ± 0.38	0.81 – 1.55
Day 17	1.15 ± 0.68	0.60 – 2.30
Day 24	1.01 ± 0.53	0.64 – 1.90
Day 29	1.01 ± 0.64	0.28 – 2.05

The reported therapeutic concentration range for digoxin is 0.5 – 2.1 ng/mL, thus results from this study indicate that digoxin concentrations are in the therapeutic range at 8 AM. ANOVA revealed that the difference in 8 AM digoxin concentrations from day to day was not statistically significant. Thus iloprost administration did not affect digoxin exposure. This finding was further supported by the PK data obtained on Day 24 (iloprost + digoxin) compared to Day 4 (digoxin alone). For each of the time points, 8, 9, 10, and 11 AM and 12 noon, 2, 4 and 6 PM, the mean digoxin concentrations on Day 24 were not statistically significantly different from the Day 4 concentrations.

Digoxin exposure measures on Day 4 and Day 24 were:

- $AUC_{0\text{-}24\ hr}$: 30.10 ± 12.25 for Day 4 and 31.92 ± 16.51 on Day 24
- C_{max}: 2.57 ± 1.34 for Day 4 and 2.5 ± 2.56 for Day 24

The 90 % confidence intervals for the ratio of geometric means were not calculated per the recommendation in the Drug Interactions Guidance. However, based on the comparison (Day 4 and 24) of the paired concentration data and the 8 AM predose comparisons, it is evident that iloprost does not affect digoxin exposure.

Impact of Changing Iloprost Dose on Drug-drug Interaction Results

Fifty percent of the subjects changed their iloprost doses two times or less after attaining their maximum tolerated iloprost dose (MTD, by Day 10). However, iloprost doses were fairly constant before and after Day 24 (intensive PK blood samples were collected on Day 24). The lowest MTD was 1 ng/kg/min and the highest MTD was 2.0 ng/kg/min. The potential impact of different iloprost doses on digoxin PK is unclear, but is unlikely to be significant as the iloprost doses cover a relatively narrow dose range (1ng/kg/min to 2 ng/kg/min). Selected iloprost dosing information is summarized as follows:

- Day 11: Median- 1.25, Mean ± SD- 1.31 ± 0.37
- Day 17: Median- 1.5; Mean ± SD- 1.44 ± 0.56
- Day 24: Median- 1.25; Mean ± SD- 1.31 ± 0.37
- Day 28: Median- 1.25; Mean ± SD- 1.31 ± 0.37

Pharmacodynamics

Selected mean daily systolic pressures, diastolic pressures and pulse rates are presented in Table 2

Table 2: Pharmacodynamic Measurements (n = 7) for iloprost + digoxin (Days 11, 15, 20, and 24) and digoxin alone (Day 28)

Day	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Pulse Rate (beats/min)
Day 11	135.85 ± 14.95	72.37 ± 9.36	73.93 ± 6.24
Day 15	142.83 ± 15.21	71.81 ± 4.80	77.17 ± 7.55
Day 20	147.51 ± 18.42	72.68 ± 4.76	80.95 ± 7.90
Day 24	134.65 ± 16.54	66.81 ± 5.72	73.63 ± 8.27
Day 28	134.99 ± 11.03	67.91 ± 1.87	77.03 ± 9.22

There was no statistically significant difference among daily blood pressure measurements; however, there was a statistical difference ($p < 0.05$) in pulse rate. Mean values on Day 19 and 20 were higher than on other days; the greatest difference in mean pulse rate is ~ 9 bpm (Day 20 vs. Day 10). The reason for this difference is not clear.

The blood pressure measures varied over the course of the day:

- Mean systolic blood pressures were higher at 6 hours and at 0 hours than at other time points; the lowest systolic blood pressure occurred at 90 minutes
- Mean diastolic blood pressures decreased from 0 h to 90 minutes and then increased till the end of the infusion. The highest mean values occurred at 0 and 6 h.

There was no statistically significant difference in pulse rates during the course of the day.

Overall the PD results suggest that iloprost decreases blood pressure during the course of daily treatment, but this decrease may not be evident on a daily basis. On the other hand the pulse rate may vary from day to day, but significant changes in pulse rate may not be apparent on a given day.

Applicant's Safety Summary
The main adverse events in this study were headache and nausea. However, there were no serious adverse events and the combination of iloprost with digoxin was well tolerated. The incidence of adverse events was greatest on Days 8, 9, and 10, when the iloprost MTD was being assessed.

Conclusions
- Iloprost does not alter the exposure of digoxin when coadministered once daily.
- During a single day of treatment (0- 6h), iloprost has the potential to decrease blood pressure, but not heart rate. On a day to day basis (comparison of several days), iloprost does not appear to affect blood pressure, but tends to increase pulse rate. However, these changes in blood pressure and pulse rate can not be attributed to a iloprost-digoxin interaction.

Recommendation
Assuming that the findings from IV iloprost are applicable to inhaled iloprost, **inhaled iloprost may be given with digoxin without dose adjustment** (*Product Labeling*). This finding was appropriately conveyed in the proposed labeling.

Study Report Number	AD19
Title	Plasma levels and clearance of iloprost in healthy and young male volunteers during one-hour i.v. infusions of 0.5, 1.0, 2.0 ng iloprost/kg/min alone and in combination with a perorally administered daily dose of 0, 10, 30, 100 and 300 mg acetylsalicylic acid over 8 days.
Study Period	05/92 to 06/92
Investigator/Site	[redacted]
Objectives:	To evaluate the interactions between iloprost and acetylsalicylic acid

Rationale

Iloprost has vascular and antithrombotic activity. Acetylsalicylic acid (ASA) is an antithrombolytic. It is possible that there will be a pharmacodynamic interaction (additive or synergistic anti thrombotic effect) between the two agents. It is not clear if there will be a pharmacokinetic interaction between the two agents.

Reviewer's Note

This review focuses on the pharmacokinetic part of the report; the PD part was not included in the study report. Furthermore, the applicant did not include the findings from this study in the Proposed Labeling.

Study Design

This was a randomized study. Healthy male subjects participated in this study. Subjects were distributed into five different treatment groups, receiving no or four different peroral pretreatment regimens with acetylsalicylic acid (ASA). Patients received daily doses of 0, 10, 30, 100 and 300 mg acetylsalicylic acid (ASA) over eight consecutive days. On study Day 8 all participants received an additional iloprost infusion over a three hour period, administered by increasing one-hour infusions at the rate of 0.5, 1.0, and 2.0 ng/kg/min.

Reviewer's Note on Study Design

Due to the limited blood sampling, a full plasma concentration-time profile for iloprost could not be obtained; thus, the potential PK interaction between iloprost and ASA could not be evaluated using the approach recommended in the Drug-Drug Interaction Guidance.

Sampling

Blood samples were taken before and at the end of the three iloprost dose steps (0.5, 1.0, 2.0 ng/kg/min) corresponding to 55 minute (first hour), 115 minute (second hour) and 175 minutes (third hour) after infusion.

Characteristics of Enrolled Subjects **(n =40)**

Age range (years): 18 - 45
Sex: 40 Males

Formulations
Iloprost solution (100 µg/mL ampule), by Schering AG, Germany SH L 401 A (Batch number 91191)

Analytical Method
The concentration of iloprost in plasma samples was determined by [illegible] assay. The calibration curve range was from [illegible] pg iloprost/mL. The limit of quantitation was [illegible] pg/mL. Inter-assay CV were: [illegible] pg/mL, [illegible] % at [illegible] pg/mL and [illegible] at [illegible] pg/mL. The assay performance was not ideal, based on the QC information at the [illegible] pg/mL concentration (|CV| > [illegible] Accuracy information was not provided in this report; thus, overall assay performance can not be assessed properly.

Pharmacokinetic and Statistical Analyses
The influence of ASA on IV iloprost was determined by examining the change in iloprost CL (CL with ASA pretreatment vs. CL without ASA). CL was calculated as Css/Ro.

Results
Plasma Pharmacokinetics
There appeared to be a linear correlation between iloprost plasma levels and infused dosage however, there was high interindividual variability (Table 1).

Table 1: Iloprost Plasma Levels and Clearance values with and without ASA pretreatment

	Time after Start of Infusion and Iloprost Dosage		
	55 min post infusion = 60 minutes 0.5 ng/kg/min	115 minutes post infusion = 60 minutes 1.0 ng/kg/min	175 minutes post infusion = 60 minutes 2.0 ng/kg/min
ASA pretreatment Dose (mg)	Conc. (pg/mL)	Conc. (pg/mL)	Conc. (pg/mL)
None (n = 8)	32.1 ± 10.1*	61.1 ± 14.2	148.0 ± 41.4
10 mg (n = 8)	23.3 ^	70.8 ± 27.9	140.4 ± 30.9
30 mg (n = 7)	37.2 ± 10.5	94.4 ± 28.6	147.6 ± 59.1
100 mg (N = 8)	34.6 ± 7.2@	94.9 ± 53.4	175.7 ± 37.0
300 mg (n = 8)	36.1 ± 14.9@	64.2 ± 18.2	142.6 ± 39.5

* n = 4, ^ n = 2, @ n = 6

Iloprost clearance in the presence and absence of ASA is presented in Table 2. Mean total clearance did not change during the infusion period, illustrating an absence of dose-dependency; additionally, clearance was independent of ASA pretreatment. According to the applicant's ANOVA ($\alpha = 0.05$) there was no effect of ASA on iloprost PK.

Reviewer Comment
Per the Drug-Drug Interaction Guidance, drug-drug interactions should be evaluated by comparing exposures in the presence and absence of coadministered drug. However, the adopted study design precludes exposure comparisons. However, the use of CL comparisons to evaluate the drug-drug interaction is reasonable for semi-quantitative assessment ($CL \propto 1/AUC$) given the study design limitations.

Table 2: Mean ± SD total clearance in healthy males during one-hour infusion of iloprost after eight days pretreatment with daily 10 – 300 mg ASA doses (n = 8 per ASA dosage)

iloprost infusion rate [ng/kg/min][1]	mean CL [mL/min/kg] ASA dosage [mg] 0	10	30	100	300	mean ± S.D.[2]
0.5	16.8	21.5	14.6	14.9	16.0	**16.8 ± 4.1**
1.0	17.3	16.4	11.7	13.9	16.9	**15.2 ± 5.9**
2.0	14.4	15.1	18.8	12.0	14.8	**15.0 ± 6.3**
mean ± S.D.[2]	**16.2 ± 4.5**	**17.7 ± 3.9**	**15.0 ± 8.8**	**13.6 ± 4.5**	**15.9 ± 5.2**	

[1] dosing regimen of the infusion:
60 min 0.5 ng iloprost/kg/min
60 min 1.0 ng iloprost/kg/min
60 min 2.0 ng iloprost/kg/min
(total administered dose of 210 ng iloprost/kg)
[2] mean and S.D. of means

Conclusions

- Iloprost Css increased with increasing iloprost doses in an approximately dose-proportional manner; the increase in Css appeared independent of ASA presence.
- Mean clearance of iloprost was relatively constant (15 – 17 mL/min/kg) over the 0.5 to 2.0 ng/kg/min dose range and did not appear to be affected by ASA pretreatment.

Discussion/Recommendation

Assuming IV iloprost drug interaction information is applicable to inhaled iloprost, administration of acetylsalicylic acid (ASA) prior to iloprost inhalation does not require dose adjustment from a pharmacokinetic (PK) standpoint. However, this study was not designed appropriately to maximize the likelihood of observing a PK interaction so it is unclear if concomitant administration will yield different results. Mechanistically, there is some basis to expect a metabolically-based drug-drug interaction between iloprost and ASA: ASA is hydrolyzed primarily in the liver to salicylic acid, further conjugated and eventually eliminated in urine. Iloprost is metabolized by oxidation mainly in the liver, further conjugated and eliminated in the urine.

Labeling

A major deficiency in this study is the absence of pharmacodynamic (antithrombotic activity) information. The applicant indicated that "This study (AD19) will not be used for registration purposes. Therefore no full (PD) report will be written...". It is unclear why the PD portion was omitted because it is clinically relevant. Perhaps the PD portion was omitted due to the suboptimal study design as previously mentioned (Study Design). In the absence of the PD information, this Reviewer recommends that the iloprost-ASA study information be omitted from the label, per the applicants suggestion.

Study Report Number	B598
Title	Acute hemodynamic effects of iloprost and its interaction with calcium channel blockers in patients with primary or secondary pulmonary hypertension.
Study Period	04/88 to 05/90
Investigator/Site	[ ]
Objectives	1. To assess the acute hemodynamic effects of iloprost and to describe the dose-response relationships in patients with primary or secondary pulmonary hypertension 2. To assess the value of the acute pulmonary vascular response to iloprost in predicting the clinical and hemodynamics response to chronic treatment with oral calcium channel blockers 3. To determine if the iloprost dose-response relationship will be altered after acute and chronic treatment with chronic channel blocking agents

Study Rationale

Calcium channel blockers (CCBs) have shown some activity in patients with primary pulmonary hypertension (PPH) and secondary pulmonary hypertension (SPH), but doses required may lead to severe hypoxemia. Potentially, combining iloprost, which is effective in these patients, with CCB may lead to lower doses of the respective agents and minimize their side effects. Prostacyclin and nimodipine demonstrated synergistic activity *in vitro*. Ideally the iloprost-CCB combination would optimize effectiveness and minimize unwanted side effects.

Study Design

This was an open label study. Patients who had undergone right heart catheterization (#1) received iloprost intravenously as an infusion. The iloprost dosage ranged from 0.5 to 4.0 ng/kg/min (0.5 ng/kg increments) and up to 10 ng/kg/min (increments of 2.0 ng/kg) until a maximum dosage was achieved. Infusion continued for 5 to 10 minutes before each dosage increment. The maximum tolerated dosage (MTD) of iloprost was infused for 15 minutes to achieve steady state in hemodynamic values. After hemodynamic evaluation, the calcium channel blocker (CCB), nifedipine or diltiazem, was titrated over an 8-hour period to a MTD. The initial dose of nifedipine was 20 mg and the initial dose of diltiazem was 60 mg. The CCB was prescribed for an eight-week course of therapy. Subsequently, the patients underwent a second catheterization (#2). Iloprost was given again to determine its effects on hemodynamics and on platelet function.

Blood Sampling

Blood samples were obtained at the end of the baseline infusion period (initial iloprost dosing) and at the end of the maximum dose period.

Characteristics of Enrolled Subjects **(n = 37)**

Age range; mean age (years): 15 to 71; 44.9
Weight range (lb.): 99 - 230
Sex: 8 men and 29 women
Race: 33 White, 3 Hispanic, 1 Other (not defined)

Formulations

- iloprost solution (100 µg/mL), ampules [redacted]
- nifedipine for oral administration (no additional information provided)
- diltiazem for oral administration (no additional information provided)

Reviewer's Note

In an addendum (11/06/2004), the applicant indicated that the diltiazem formulation was immediate release (Cardizem or generic form). Similarly, the nifedipine was the immediate formulation (Adalat CC, Procardia or a generic).

Pharmacodynamic Analyses

Several hemodynamic measurements were determined during (pre-Iloprost dosing, iloprost dose-titration, post iloprost-dosing) the study: heart rate, pulmonary arterial pressure, systemic arterial pressure, cardiac output and pulmonary capillary wedge pressure.

Platelet count and platelet aggregation were determined.

Results

Subject Disposition

Only five of the 37 subjects completed the study (underwent catheterization #2). Twenty-four subjects were prescribed at least one cardiovascular medication for the treatment of pulmonary hypertension and thirteen of these subjects were on oxygen at the time of the first catheterization.

Reviewer's Note

The oxygen requirement and the use of concomitant medications may confound the study results with respect to the iloprost-CCB effect on hemodynamic variables. Consequently, findings from this study should be interpreted cautiously.

Iloprost Dosage

The mean maximum infusion dose rate during 1) the first catheterization (n = 37) was 4.92 ng/kg/min (range: 2.0 to 8.0 ng/kg/min) and 2) the second catheterization (n = 5) was 5.40 ng/kg/min (range: 3.0 to 8.0 ng/kg/min). These infusion rates translated to 12.8 µg iloprost in one hour and 12.6 µg iloprost in 0.9 hours for catheterization 1 and 2, respectively.

CCB Dosage (Loading)

CCB was administered successfully in only 16 patients. Nine patients completed the nifedipine loading with a mean maximum dose ~ 140 mg and seven patients completed the diltiazem loading with a mean maximum dose ~ 430 mg. The nifedipine dose exceeds currently recommended nifedipine dosage (30 – 60 mg QD). Ten subjects discontinued the CCB titration prematurely. It should be noted that no patient achieved the targeted maximal CCB dose (nifedipine 240 mg and diltiazem 720 mg). Eleven patients had an

inadequate response to iloprost and were administered alternative forms of medical therapy.

Pharmacodynamics

Hemodynamics

Selected PD data are presented in Table 1.

Table 1: Systemic and pulmonary hemodynamics in PPH and SPH patients during calcium channel blocking (CCB) and CCB plus iloprost therapy following catheterization

	Catheterization 1 (n = 34)		Catheterization 2 (n = 5)	
PD Measure	Baseline	Iloprost MTD	Baseline	Iloprost MTD
Systolic BP (mm Hg)	131± 20	118 ± 20	133 ± 16	122 ± 16
Diastolic BP (mm Hg)	79 ± 12	67 ± 12	71 ± 15	67 ± 13
PVR (Wood Units)	11.8 ± 5.5*	8.5 ± 5.1*	5.7 ± 1.5^	4.5 ± 0.7^
Mean Pulmonary Pressure (mmHg)	55.0 ± 16.5	52.0 ± 18.7	47.0 ± 23.1	44 ± 25.0

* n = 19; ^ n = 4

- Catheterization 1

A comparison between baseline and MTD iloprost shows a drop in blood pressure. Iloprost decreased PVR ~ 28 % and mean pulmonary pressure (MPP) ~ 5 %.

- Catheterization 2

A comparison between baseline and MTD iloprost showed a similar trend as with Catheterization 1 in both systemic and pulmonary effects. A drop in systemic blood pressure was observed; additionally, iloprost decreased PVR ~ 20 % and MPP ~ 7 %.

Reviewer's Comment

The evaluation of the hemodynamic effects of iloprost is complicated due to the high number of drop outs between catheterizations (n = 34 for catheterization 1, iloprost alone vs. n = 5 for catheterization 2, iloprost plus CCB).

Platelet Function

Key findings from the platelet function evaluation follow; platelet aggregation data are summarized in Table 2.

- Catheterization 1 (n = 26)

The mean amount of ADP required for complete aggregation of platelets was 8 μM at baseline and 16 μM at catheterization 1 (iloprost MTD). This increase occurred in 22 out of 26 patients; this finding indicates that iloprost reduced platelet aggregation.

- Catheterization 2 (n = 4)

The mean amount of ADP required for complete aggregation of platelets was 5 μM at baseline and 19 μM at catheterization 1 (iloprost MTD). This increase occurred in 3 out of 4 patients; this finding indicates that iloprost reduced platelet aggregation.

Table 2: Platelet aggregation: Descriptive characterization and confidence intervals

	THRESHOLD ADP DOSE (uM) TO CAUSE COMPLETE SECOND WAVE PLATELET AGGREGATION						P-VALUE [1]	95% CONFIDENCE INTERVAL [2]	
	N	MEAN	ST DEV	MEDIAN	MIN	MAX		LOWER LIMIT	UPPER LIMIT
CATHETERISATION #1									
BASELINE	26	8	10	5					
MAXIMUM DOSE	26	24	19	20					
CHANGE AT MAX	26	16	18	9			0.0001	9	23
% CHANGE AT MAX	26	306	505	300			0.0005	192	600
CATHETERISATION #2									
BASELINE	4	5	4	4					
MAXIMUM DOSE	4	19	22	13					
CHANGE AT MAX	4	15	19	11			0.2281	-16	45
% CHANGE AT MAX	4	348	414	275			0.1913	-311	1007

ADP = ADENOSINE DIPHOSPHATE
CHANGE = CHANGE FROM BASELINE MIN = MINIMUM MAX = MAXIMUM ST DEV = STANDARD DEVIATION

1 P-VALUES ARE BASED ON A TWO-TAILED T-TEST.
2 CONFIDENCE INTERVALS FOR THE MEAN ARE BASED ON THE T-DISTRIBUTION.

Applicant's Safety Summary

Vasodilatation, headache and nausea were the most common adverse events. Vasovagal reactions (n = 3) and hypotension (n = 1) led to discontinuation of iloprost infusion. No deaths occurred during the study.

Conclusions

- Iloprost administered at the maximum tolerated dose (mean ~ 5) produced ~ 25 % decrease in PVR and 5 % decrease in mean pulmonary pressure
- Iloprost decreases platelet aggregation (ADP-induced) as shown by an increased amount of ADP required to produce aggregation (~ 5 µM in the absence of iloprost vs. ~ 17 µM in the presence of iloprost

Recommendation

The current study can not be interpreted with confidence because a high number of drop outs occurred following therapy with iloprost alone, calcium channel blocker (CCB) alone and iloprost-CCB. It appears that iloprost was effective (lowering PVR) and tolerated to some degree over the 2 to 8 ng/kg/min dosage range, however, iloprost therapy had to be discontinued in four subjects due to lack of tolerability. The objectives of this study could not be met: no clear dose-response relationship could be obtained for either iloprost, CCB therapy, or iloprost-CCB therapy. However, Based on the limited data, it did not appear that the iloprost dose-response relationship was altered after acute and chronic treatment with calcium channel blocking agents, suggesting that iloprost may be administered with nifedipine or diltiazem without dose adjustment. Due to the limited data obtained during the brief iloprost-CCB therapy, no definitive recommendation can be made regarding iloprost-diltiazem or iloprost-nifedipine dosing combination.

Labeling

The applicant's proposed labeling text indicates that there was no pharmacodynamic interaction between IV iloprost and nifedipine, but the data used to arrive at this conclusion are insufficient in this reviewer's opinion. Labeling recommendations regarding iloprost-CCB therapy should be obtained from other sources.

Appears This Way
On Original

Title	Hemodynamic effects of intravenous iloprost in patients with primary or secondary pulmonary hypertension during chronic therapy with calcium channel blocking agents
Study Report Number	B599
Study Period	04/88 to 05/90
Investigator/Site	[ ]
Objectives	• To evaluate the hemodynamic effects an safety of intravenously administered iloprost in patients with pulmonary hypertension being treated with chronic calcium channel blocker therapy • To determine whether combination therapy is more effective than monotherapy with calcium channel blockers in lowering pulmonary arterial pressure or pulmonary vascular resistance

Study Rationale

Calcium channel blockers (CCBs) have shown some activity in patients with primary pulmonary hypertension (PPH) and secondary pulmonary hypertension (SPH), but doses required may lead to severe hypoxemia. Potentially, combining iloprost, which is effective in these patients, with CCB may lead to lower doses of the respective agents and minimize their side effects. Prostacyclin and nimodipine demonstrated synergistic activity *in vitro*. Ideally the iloprost-CCB combination would optimize effectiveness and minimize unwanted side effects.

Study Design

This was a open label study. Patients with pulmonary hypertension who were being treated with chronic CCB (nifedipine or diltiazem) therapy participated in this study. The patients underwent right heart catheterization after being on CCB therapy for at least two months. After establishing baseline hemodynamic values using normal saline for 15 minutes, patients received an IV infusion of ascending doses of iloprost. Iloprost was begun at 0.1 ng/kg/min, if tolerated, incrementally increased to 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, and 10.0 ng/kg/min at five to 10 minute intervals. Once a maximum tolerated dose was obtained, this dose was infused for 15 minutes. Subsequently, iloprost was discontinued, and saline infused until hemodynamic values returned to baseline.

Subject Characteristics **(n = 11)**

Mean Age (years): 38
Mean Weight (kg): 153
Mean Height (inches): 64.3
Sex: 3 males and 8 females
Race: All White

Formulations

- iloprost solution (100 µg/mL), Schering AG, Germany lot number 64131
- nifedipine for oral administration (no additional information provided)
- diltiazem for oral administration (no additional information provided)

Reviewer's Note
In an addendum (11/06/2004), the applicant indicated that the diltiazem formulation was immediate release (Cardizem or generic form). Similarly, the nifedipine was the immediate formulation (Adalat CC, Procardia or a generic).

Pharmacodynamic Analyses
Hemodynamic measurements were made during the study: heart rate, systemic arterial pressure, right atrial pressure and pulmonary capillary wedge pressure. The primary comparison was between iloprost + CCB vs. CCB alone. Platelet function was also assessed.

Results

Subject Disposition (CCB Dosage)
Eleven patients entered and completed the study. One (Patient 1011) of the ten patients did not satisfy the inclusion criterion of having been on CCB for two months, but was included in the analyses. Patient 1011 discontinued CCB therapy a month before entering the study; the patient was on nifedipine and switched to hydralazine prior to iloprost treatment. The total daily dosage of diltiazem ranged from 120 to 600 mg. Diltiazem was being used to treat pulmonary hypertension.

Reviewer's Note
Based on the CCB therapy, the study results will be most accurate and applicable to diltiazem-iloprost coadministration rather than other CCB.

Pharmacokinetics

Iloprost Dosage
The mean maximum infusion rate of iloprost was 4.82 ng/kg/min (range: 3.0 to 8.0 ng/kg/min) and the mean duration of infusion was 0.83 hours. This infusion dosage corresponded to 9.8 µg iloprost dose. It is noted that although, blood samples were collected no pharmacokinetic data were included in this report. The report indicates that iloprost serum concentrations will be reported separately as an addendum; however this addendum was not provided in this NDA submission. The applicant indicated that the PK data from this study were not reliable due to problems with the assay.

Pharmacodynamics

Hemodynamics
Hemodynamic data are presented in Table 1. Selected key hemodynamic findings are:

- Mean Pulmonary arterial pressure (mPAP) decreased by 17 % (maximum tolerated iloprost dose vs. baseline)
- Pulmonary vascular resistance (PVR) decreased (maximum tolerated iloprost dose vs. baseline) by 40 %
- Systemic vascular resistance (SVR) decreased by 31 % (maximum tolerated iloprost dose vs. baseline)

Apart from PVR, all the hemodynamic measures returned to baseline values thirty minutes after discontinuing iloprost treatment. The mean PVR was ~9 % decreased (statistically significant) relative to baseline. It is noted that n = 8 in the hemodynamic analyses because three subjects were excluded form the analyses (these subjects required supplemental oxygen during the withdrawal period (iloprost cessation).

Table 1: Descriptive Statistics of Hemodynamics during iloprost infusion (per applicant)

	N	MEAN	ST DEV	MEDIAN	MIN	MAX	P-VALUE [1]	95% CONFIDENCE INTERVAL [2] LOWER LIMIT	UPPER LIMIT
Systolic SP (mm Hg)									
Baseline	11	116.00	11.60	120.00					
Maximum Dose	11	111.00	10.00	115.00					
Change at Max	11	-4.73	6.00	-3.00			0.0258	-9	-1
% Change at Max	11	-3.86	4.90	-2.70			0.0259	-7	-1
Diastolic SP (mm Hg)									
Baseline	11	68.40	6.20	70.00					
Maximum Dose	11	61.50	9.49	62.00					
Change at Max	11	-6.82	6.94	-9.00			0.0006	-11	-2
% Change at Max	11	-10.00	10.00	-12.86			0.0075	-17	-3
Mean SP (mm Hg)									
Baseline	11	87.00	7.53	88.00					
Maximum Dose	11	81.60	8.02	82.00					
Change at Max	11	-6.18	6.15	-7.00			0.0076	-10	-2
% Change at Max	11	-6.96	6.57	-7.95			0.0055	-11	-3
Right Atrial MP (mm Hg)									
Baseline	11	5.73	3.64	5.00					
Maximum Dose	11	5.09	3.83	6.00					
Change at Max	11	-0.64	1.29	-1.00			0.1309	-2	0
% Change at Max	11	-9.24	41.20	-16.67			0.4741	-37	18
Systolic PP (mm Hg)									
Baseline	11	61.50	16.80	65.00					
Maximum Dose	11	56.10	24.28	53.00					
Change at Max	11	-7.27	9.77	-7.00			0.0332	-14	-1
% Change at Max	11	-14.19	17.60	-14.00			0.0233	-26	-2
Diastolic PP (mm Hg)									
Baseline	11	26.70	7.91	27.00					
Maximum Dose	11	21.10	10.80	20.00					
Change at Max	11	-5.64	4.32	-5.00			0.0015	-9	-3
% Change at Max	11	-24.07	19.60	-21.43			0.0022	-37	-11

MIN = Minimum MAX = Maximum ST DEV = Standard Deviation
SP = Systemic Pressure PP = Pulmonary Artery Pressure MP = Mean Pressure CO = Cardiac Output
SVR = Systemic Vascular Resistance PVR = Pulmonary Vascular Resistance

[1] P-VALUES ARE BASED ON A TWO-TAILED T-TEST.
[2] CONFIDENCE INTERVALS FOR THE MEAN ARE BASED ON THE T-DISTRIBUTION.

Platelet Function

Platelet count did not change significantly from baseline to the maximum dose of iloprost. However, iloprost administration resulted in decreased platelet aggregation due

to ADP in the majority of patients (n = 10); Patient 1010 did not have a change in the aggregation results (iloprost maximum dose vs. baseline).

Table 2: Whole blood platelet count (per applicant)

	NB PLATELET COUNT X 1000/uL						1 P-VALUE	2 95% CONFIDENCE INTERVAL	
	N	MEAN	ST DEV	MEDIAN	MIN	MAX		LOWER LIMIT	UPPER LIMIT
BASELINE	9	209	49	191					
MAXIMUM DOSE	9	204	50	192					
CHANGE AT MAX	9	-5	11	-5			0.2004	-15	5
% CHANGE AT MAX	9	-2	7	-2			0.3416	-8	3

Table 3: Platelet aggregation descriptive statistics (per applicant)

	THRESHOLD (ADP) uM TO CAUSE COMPLETE SECOND WAVE PLATELET AGGREGATION						1 P-VALUE	2 95% CONFIDENCE INTERVAL	
	N	MEAN	ST DEV	MEDIAN	MIN	MAX		LOWER LIMIT	UPPER LIMIT
BASELINE	10	8	15	4					
MAXIMUM DOSE	10	25	22	10					
CHANGE AT MAX	10	17	21	7			0.0329	2	32
% CHANGE AT MAX	10	600	946	250			0.0491	3	1357

Applicant's Safety Summary

The most common adverse events were vasodilatation/flushing, headache and nausea. There were also two reports of vasovagal reactions and chest pain. No patients died while enrolled in the trial.

Conclusions

- Iloprost combined with diltiazem or nifedipine significantly decreases mPAP (17 % decrease) PVR (40 % decrease) and SVR (31 % decrease); these changes in hemodynamic measures appear to be due to iloprost.
- Iloprost combined with diltiazem or nifedipine decreased platelet aggregation but did not have an effect on platelet count.

Recommendation

Assuming that IV iloprost findings are applicable to inhaled iloprost, inhaled iloprost can be coadministered with diltiazem to patients on a fixed diltiazem dosage. It is noted that in clinical trials iloprost was coadministered with various calcium channel blockers, and the clinical safety was acceptable.

Labeling

The applicant's proposed labeling text indicates that there was no pharmacodynamic (PD) interaction between IV iloprost and nifedipine, but this conclusion is based on Study B598, not the current Study, B599. This reviewer considers that the information from Study B599 is more useful than that from B598 for making iloprost-CCB labeling recommendations. It is unclear why diltiazem is not mentioned in the label. The label

should indicate that there was no PD interaction between iloprost and diltiazem; the caution regarding the potential increased hypotensive effects when vasodilators and antihypertensives are administered with iloprost is acceptable.

Appears This Way
On Original

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-779	Brand Name	Ventavis (proposed)
OCPB Division (I, II, III)	DPE-I	Generic Name	iloprost
Medical Division	HFD-110	Drug Class	
OCPB Reviewer	Robert O. Kumi	Indication(s)	Pulmonary Arterial Hypertension
OCPB Team Leader	Patrick Marroum, Ph.D.	Dosage Form	Solution, 10 µg/mL
		Dosing Regimen	Initial dose of 2.5 µg Maximum maintenance dose of 5 µg, six to nine times a day
Date of Submission	06/30/ 2004	Route of Administration	Inhalation via nebulizer
Estimated Due Date of OCPB Review	11/16/2004	Sponsor	CoTherix
PDUFA Due Date	12/30/2004	Priority Classification	P
Division Due Date	11/23/2004		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X	1	1	
Isozyme characterization:	X	1	1	
Blood/plasma ratio:	-	-	-	
Plasma protein binding:	X	1	1	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	-	-	-	No studies conducted with inhaled iloprost
multiple dose:	-	-	-	No studies conducted with inhaled iloprost
Patients-				
single dose:	X	1	1	PAH patients* received iloprost via inhalation on three occasions via three different nebulizer devices
multiple dose:	-	-	-	No studies were conducted with inhaled iloprost
Dose proportionality -				
fasting / non-fasting single dose:	X	1	1	Study conducted with IV iloprost
fasting / non-fasting multiple dose:	-	-	-	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	-	-		
In-vivo effects of primary drug:	X	6	6	Most of the studies involved PD evaluations
In-vitro:	1	1	1	
Subpopulation studies -				
ethnicity:	-	-	-	
gender:	-	-	-	
pediatrics:	-	-	-	
geriatrics:	-	-	-	

renal impairment:	X	1	1	Conducted with IV iloprost
hepatic impairment:	X	2	2	Studies conducted with IV and oral iloprost, respectively
PD:				
Phase 2:	X	1	1	
Phase 3:	X	1	1	
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1	1	*Exploratory analysis conducted
Phase 3 clinical trial:	-	-	-	
Population Analyses -				
Data rich:	-	-	-	
Data sparse:	-	-	-	
II. Biopharmaceutics				
Absolute bioavailability:	-	-	-	
Relative bioavailability -				
solution as reference:	-	-	-	
alternate formulation as reference:	-	-	-	
Bioequivalence studies -				
traditional design; single / multi dose:	-	-		
replicate design; single / multi dose:	-	-	-	
Food-drug interaction studies:	-	-	-	
Dissolution:	-	-		
(IVIVC):	-	-	-	
Bio-waiver request based on BCS	-	-	-	
BCS class	-	-	-	
III. Other CPB Studies				
Genotype/phenotype studies:	-	-	-	
QT Study	-	1	1	Thorough QT study was conducted with inhaled iloprost, moxifloxacin and placebo
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	
Literature References	-	-	-	
Total Number of Studies		18	18	*The single dose PK study in patients is the same as the exploratory PK/PD study

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?		
QBR questions (key issues to be considered)	**Are the pharmacokinetics of inhaled iloprost comparable to that of IV iloprost? Is there a PK/PD relationship for iloprost?**	
Other comments or information not included above	Several studies were conducted with IV and oral iloprost, but only three studies were conducted with inhaled iloprost. Consequently most safety information is obtained from IV and oral iloprost.	

Primary reviewer Signature and Date	Robert O. Kumi, Ph.D.
Secondary reviewer Signature and Date	Patrick Marroum, Ph.D.

CC: NDA 21-779, HFD-850(Lee), HFD-110(Robb), HFD-860 (P, Marroum, A. Rahman, M. Mehta)

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/s/

Robert Kumi
12/1/04 04:12:07 PM
BIOPHARMACEUTICS

Patrick Marroum
12/1/04 04:33:55 PM
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