MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 27, 2004

FROM: Director, Office of Drug Evaluation I, HFD-101

SUBJECT: Iloprost, NDA 21-779, Cotherix, Inc.

TO: File and HFD-110

I. Introduction and Effectiveness Analysis

This NDA has been reviewed critically by Drs. Gordon and Karkowsky, both of whom recommend approval, albeit with some reservation from Dr. Karkowsky about the target population [primary vs. secondary (mostly post-pulmonary embolism) pulmonary hypertension]. The principal effectiveness issues are:

1. Reliance on a single study
2. Whether to indicate the drug for pulmonary hypertension (PHT) generally or only for primary pulmonary hypertension

1. Reliance on a single study

Under FDAMA, we are permitted to rely on a single study plus "confirmatory evidence" (never really defined). In general, based on the FDA guidance (Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products), the single study should be convincing statistically and it helps if there is internal consistency (e.g., in the present case, similar effects on NYHA classification and walking distance). The role of the effectiveness of related therapy is considered only briefly in the guidance but has been explicitly used in the approval (based on studies with non-extreme statistical tests) of two angiotensin II blockers to delay renal functional deterioration in type II diabetics (each study supported the other) and less explicitly (but nonetheless pretty clearly) in approving ACEI's for the treatment of CHF, relying on single studies with p-values between 0.05 and 0.01 with the backgroup of multiple drugs in the class showing favorable effect.

In the present case, the strongest external support comes from the closely related prostacyclin analogues epoprostanol (Flolan), delivered through a central venous line, and treprostanil (Remodulin), given through an indwelling subcutaneous catheter, and approved without a clear effect on exercise but an effect on a combined breathlessness – exercise endpoint. There is also a second small iloprost study that generally favors iloprost over placebo but had numerous problems (single blind, changing definitions, etc.) and was not considered seriously.

Results of Study ME 97218

ME 97218 was a 12-week RCT with 201 randomized patients (101 iloprost, 100 placebo), stratified by primary vs. secondary PHT and by NYHA class (III vs. IV). The endpoint was a novel one (most Rx for PHT was approved based on the 6 minute walk as the primary endpoint), the "responder rate," with responders defined as patients with:

>10% increase in walking distance

≥1 grade increase in NYHA class

no deterioration (death, worse hypotension, worse R-sided CHF, ≥30% worse walking distance, cardiogenic hepatic or renal deterioration, new need for I.V. meds, CI<1.31 L/min/m^2; CVP>22, SVO_2<45% on nasal O_2

Walking distance was a secondary endpoint.

Results:

	Iloprost	**Control**	
Responder	17/101 (21%)	5/102 (5%)	p=0.007
Walking Distance at 12 week peak trough	 +22 meter +15 meter	 -3 meter 0	 p=0.032

Considering the components of the primary endpoint (from Dr. Karkowsy).

	Iloprost	**Control**
Walk increase >10%	38/101 (38%)	26/102 (25%)
Change in NYHA >1	25/101 (25%)	13/102 (13%)
Deterioration	6/101 (5%)	15/102 (15%)
(No deterioration)	95/101 (95%)	87/102 (85%)

This shows considerable consistency across these (probably highly correlated) components of the endpoint.

2. Primary vs. Secondary PHT

Drugs for PHT approved to date have studied largely primary PHT (including, however, PHT following scleroderma, etc.), not PHT following pulmonary emboli. Although the present study of iloprost clearly had as a primary endpoint the entire population of both primary and secondary PHT (and showed a highly significant result for the whole group), results were not the same in the two etiologic strata.

	Primary		**Secondary**	
	Iloprost	**Placebo**	**Iloprost**	**Placebo**
Overall Resp	11/53 (21%)	3/55 (5%)	6/48 (13%)	2/47 (4%)
Components Walk >10% NYHA >1	 26/53 (49%) 13/53 (25%)	 17/55 (31%) 4/55 (7%)	 12/48 (25%) 12/48 (25%)	 9/47 (19%) 9/47 (19%)
Overall WD	42	-2	2	8

One certainly cannot conclude that iloprost does not work in secondary PHT but there is a question as to whether there are adequate data to conclude that it does.

The sponsor has urged that the indication be for PHT 1) because the combined group was the primary endpoint (and neither subgroup was proven to show an effect alone, 2) trends did favor iloprost, 3) when walking distance included zero values for patients who died, results are stronger [Note, the figure in labeling showing a 36 m difference at 12 weeks is based on this analysis; I do not agree with this post-facto analysis] in both subgroups.

I conclude that:

1. The data based on a single principal study are convincing and provide substantial evidence of effectiveness of iloprost.

2. The claim should be limited to the primary PHT; the results in secondary PHT can be noted in clinical trials and the primary endpoint identified but that section should note that there are too few data to conclude that effectiveness has been demonstrated.

3. The labeling figure of walking distance should be replaced by one that does not attribute zero walking to people who died.

II. Safety

Safety has been well discussed by Drs. Gordon and Karkowsky. No deaths appeared drug-related. Iloprost clearly can cause hypotension and even syncope, predictable from its vasodilatory properties. In the 129 inhalation patients there were 10 reports of syncope and 10 of hypotension, vs. 6 each in the placebo group, with 3 withdrawals (one each) for syncope, hypotension, and vasodilation. The 6 syncope events reported as serious (MOR, pages 31-2) are unimpressive, often occurring well after the inhalation, and attributable to (1) second degree AV block (treated with a pacemaker), (1) "vasovagal" episodes (with an event more than 6 hours after medication, (1) at the end of an ETT, (1) associated with stair-climbing, (1) associated with probable Iloprost-induced R heart decompensation, and (1) probably resulting from hyperventilation (confirmed in provocative test).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Temple
12/28/04 03:54:12 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: December 23, 2004

FROM: Abraham Karkowsky, M.D., Ph.D.; Group Leader Division of Cardio-Renal Drug, Products HFD-110

TO: Robert Temple, M.D.; Office Director ODE-1

SUBJECT: Approvability of Iloprost (Ventavis®) inhalation for the treatment of pulmonary hypertension (NDA 21-779, Cotherix Inc).

This memo is in support of the approvable recommendation of Iloprost, administered by inhalation, for use to provide symptomatic benefit, limited to patients with primary pulmonary hypertension. The nature of this benefit is a composite of a 10% increase in walk distance, an improvement in NYHA class and without any of the pre-specified criteria defining a worsening of status. It is likely that patients will have benefit for at least 30 minutes after an inhalation treatment, as reflected in an increase in walk-distance during the clinical trial. Benefit at the interdosing interval appears less than at the 30–minute post inhalation time point.

Source Materials:

The following reviews and sources of information were consulted for the purposes of constructing this memo.

- Medical officer review by Dr. Maryann Gordon, M.D., dated 12 November 2004.
- Pharmacology review by Dr. James Willard Ph.D., dated 14 December 2004.
- CMC reviews by Dr. M.D. Cooper Ph.D. and Dr. W.C. Timmer Ph.D. dated 3 and 17 December 2004.
- Clinical pharmacology and biopharmaceutic review by Dr. Robert O. Kumi, Ph.D., dated 1 December 2004.
- Statistical review of efficacy by Dr. Valeria Freidlin, Ph.D., dated 28 October 2004.
- DMETS review from D. P. Toyer, PharmD., dated 15 December 2004.
- Clinical inspection summary by Mary I. Mease dated 13 December 2004.
- DSRCS review of patient labeling by Jeanne Best, M.S.N, R.N., P.N.P. dated 16 December 2004.
- Microbiology reviews by James L. McVey dated 9, 15 and 21 December 2004.

- Proprietary name review; DMETS consult by Scott Dallas R.PH. dated 28 October 2004.
- Statistical review of carcinogenicity by Jasmine Choi, M.S., dated 15 November 2004.
- DDMAC draft label review by Catherine Gray Pharm.D., and Lance McLeroy Pharm.D., dated 18 November 2004.
- The sponsor's submission of 30 June 2004.

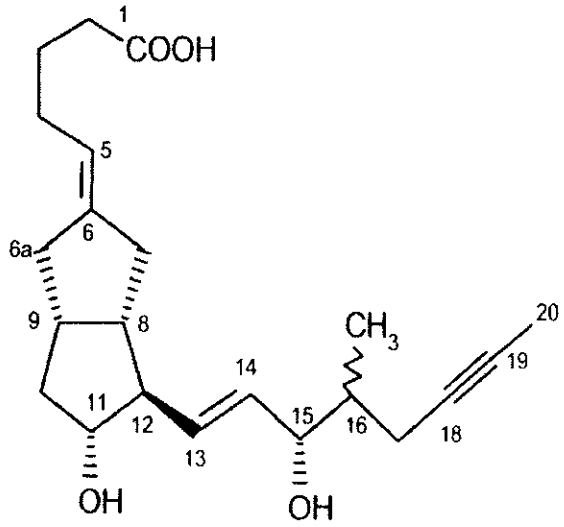
Appears This Way
On Original

Chemistry:

Iloprost is a diastereoisomeric mixture whose IUPAC and USAN name as well as its structure are shown below.

Chemical (IUPAC) 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

Chemical (USAN) Name: (*E*)-(3a*S*,4*R*,5*R*,6a*S*)-Hexahydro-5-hydroxy-4-[(*E*)-(3*S*,4*RS*)-3-hydroxy-4-methyl-1-octen-6-ynyl]-$\Delta^{2(1H),\Delta}$-pentalenevaleric acid



Note: The numbering system in the above structure does not correspond to the IUPAC or USAN chemical names, but to the prostacyclin numbering system.

Chemical Formula:	$C_{22}H_{32}O_4$
Molc. Wt.:	360.49
CAS No.:	78919-13-8

Iloprost contains 6 optically active sites; five of which are fixed. The sixth asymmetric site, the 4-position methyl group (labeled as carbon # 15 in the above diagram, as represented by a wavy line), as a consequence of the synthetic process, is not fixed relative to the other optically-active centers. The to-be marketed product consequently, contains two-distinct chemical entities in a ratio of 53:47 of 4R:4S Iloprost. These entities have different pharmacologic properties and are chemically distinct and theoretically readily separable.

As Drs. Cooper and Timmer note, current FDA policy[1] is to treat such diastereoisomers as separate chemical entities unless they spontaneously interconvert (not apparently the case here).

The sponsor argued that large-scale separation of the enantiomers would be a difficult and complicated process. In addition, neither the kinetic or dynamic properties of the two diastereomers suggest an apparent hazard in their concurrent use. After intravenous administration to dogs or rats, both diastereomers demonstrate rapid and similar clearance. Both isomers have activity in rats and human platelets ex-vivo assays in preventing either ADP or collagen induced platelet aggregation. Both diastereomers also had vasodilatory activity of rabbit mesenteric artery and both decreased blood pressure in anesthetized rat. The potency of the 4S isomer is greater than the 4R isomer. The toxicology of the either the 4R or 4S isomers does not indicate that the less active isomer is substantially more toxic and consequently, its presence does not reflect a substantial hazard to the patient. The effect of the two diastereoisomers on the main pharmacologic properties of Iloprost, that is, vasodilation and platelet inhibition are proportional, with the 4R isomer approximately 1/10 to 1/20 as active in both activities. Lastly, the large safety database of approximately 3,000 treated patients exposed to the diastereomeric mixture already exists and the adverse events profile does not strongly suggest the existence of adverse events other than events reflecting an extension of the known pharmacologic activity of either isomer.

In sum what is currently known about the animal toxicology, animal kinetics and available safety data in humans coupled with the accepted assertion, that separation of the diastereoisomers mixture is a complex process, the requirement to isolate and restudy a single isomer would only delay the approval of this drug. Despite the stated agency's policy, approval of this diasterisomeric mixture appears warranted.

Adequate responses to all chemistry deficiencies have been received. The submission is approvable from the chemistry vantage point.

Delivery Systems:

During the pivotal phase 3 trial, Iloprost was administered with the HaloLite nebulizer, manufactured by Profile Therapeutics. This model of nebulizer is not available in the United States. The ProDose inhaler is a modification of the HaloLite model and currently available. The differences between the two-nebulizers are a more durable compressor unit and an improved patient nebulizer interface with a programmable dose-control disc for the ProDose nebulizer. The ProDose received 510(k) approval predicated on the HaloLite device.

The microchip disc that was initially calibrated to yield the equivalent total dose of 2.5 mcg per treatment (250 mcL) as in the clinical study, in actuality administered 3.8 mcg $\pm$ 14.8%. As a consequence, the ProDose disc was changed to one calibrated to deliver a lower volume (150 mcL). The 5.0 mcg dose was reprogrammed with a chip to

[1] "FDA Policy Statement for the Development of New Stereoisomeric Drugs"

deliver 450 mcL (as opposed to 500 mcL). Upon reprogramming the disc, the amount of delivery approximated that as delivered by the HaloLite device.

The rate of delivery of drug does not appear to be uniform during a single inhalation treatment. During the initial anticipated 2.5 mcg dose the real delivered dose was closer to 2.8 mcg. During the second 2.5 mcg portion of the dose only 2.3 mcg was delivered. The reason for the non-uniformity is unclear. Since there is excess of drug in each ampoule (each ampoule contains 20 mcg of Iloprost), enough for more than a single inhalation, the patient need to be advised that the attempt to obtain more than one treatment per ampoule would not reliably deliver to an effective dose.

Environmental Assessment Exclusion.

The chemistry reviewer accepted the sponsor's assertion that the concentration of the active drug and its not metabolites will not exceed 1 ppb in the environment, with no otherwise extraordinary circumstances suggesting that either the drug or metabolites would adversely alter the environment. A waiver of the environmental assessment is appropriate.

Inspections.

EES report was received on 13 December 2004. The results of the inspections were acceptable.

Microbiology.

"Sterile" Iloprost was recommended as approvable per microbiology.

Pharmacology.

Iloprost is an analog of PGI2, and belongs to the same class as two currently approved treatments for pulmonary hypertension; treprostinil and Flolan. Inhibition of binding to receptors other than PGI2 was not observed except to histamine and purinergic P2 receptors at a concentration of 10 uM. The inhibition curve, at lower concentrations of Iloprost was not studied. The10 uM concentrations far exceed the concentration anticipated at the site of action[2]. The inhibition of binding at 10 uM was limited to the 4S-isomer. The 4R-isomer and the mixture of isomers (Iloprost) did not apparently inhibit binding to the histamine and purinergic receptors.

Activity for both vasodilation and platelet inhibition, at least as measured in animal models, resides with both the 4S and 4R isomers. In general the 4R diastereoisomer was generally 10 to 20-fold less potent than the 4S isomer.

It is unclear if the dilation by Iloprost is homogenous across all vascular beds. In conscious rats that were infused concentrations of 0.1 mcg/kg/min, blood flow was

[2] Consider a dose of 5 mcg administered over 5 minutes, or a rate of approximately 1mcg/min. Assuming a cardiac output of 2 L/min, the concentration in the resulting blood flow from the lung to the myocardium and into the arterial system would be 0.5 mcg/L. The MW of Iloprost is 360, the concentrations would correspond to approximately 1.4 nM, or approximately 4 orders of magnitude lower than the single concentration that inhibited either purinergic or histaminic receptors..

increased significantly as measured by labeled micro spheres to spleen, stomach, and small intestine; it was less significantly increased in skin, colon and lung. There was apparently no increase in blood flow to heart and muscle.

The results of the genotoxicity and mutagenicity studies, with one exception, were benign. In the chromosomal aberration assay with Chinese Hamster Lung Cells, there was a mildly positive response. Dr. Willard notes in his review, that these cells have both surface receptors for prostanoids as well the mechanism for translocation of these receptors into the cell nucleus. The relevance of the finding of chromosomal abnormalities to cells without the capabilities to bind and translocate prostanoids into the nucleus is therefore, unclear. No carcinogenicity effect was observed in mice and rats orally-treated with Iloprost.

With respect to reproductive toxicology, in rabbits or Sprague-Dawley rats, Iloprost at oral doses less than those found to be maternal toxic, showed no significant effects on either dam or fetus. At maternally toxic doses (by the oral route) the number of non-viable fetuses was increased. In Han-Wistar rats intravenous doses of 1 mg/kg to the dam were embryolethal in approximately 1/3 of the litters. In Han-Wistar rats Iloprost infused at approximately 1/10 the embryolethal dose, skeletal and digit abnormalities were observed.

The above observations were included in the labeling as edited by the pharmacologist.

Biopharmaceutics.

ADME

Upon inhalation, Iloprost, a mixture of both diastereoisomers rapidly appears in plasma. None of the assays employed in human studies separated the two (4S from 4R isomers). Peak levels of Iloprost based on 12 PAH patients was 157 $\pm$ 64 pg/mL. The half-life of the combined diastereoisomeric mixture in humans is 7.9 $\pm$ 3.2 minutes. In dogs and rats there does not appear to be interconversion of the two diastereoisomers.

In rats after oral administration, metabolism of the Iloprost diastereoisomers is by ß-oxidation. The metabolism is not substantially dependent of CYP-450 enzymes. The major metabolites of Iloprost are tetranor-Iloprost and tetranor derivatives (glucuronides). A mass balance study was performed by the sponsor in humans (n=8) with tritium labeled Iloprost administered either by the intravenous (2 ng/kg/min x 4 hours) or orally at two different doses (0.1 and 0.48 mcg/kg). Blood was collected for through 24 hours. Urine and feces were collected for up to 1 week. Collection of radioactivity in urine was > 95% complete by approximately 14 hours and 2 days in feces. The total dose recovered was approximately 80% of the radioactivity; with 68% collected from urine and 12% from feces.

Special populations.

Hepatic impairment.

There were no studies performed in hepatically impaired patients with inhaled Iloprost. However, after intravenous infusion of Iloprost at a dose of 1 ng/kg/min in a small number of subjects with Child Pugh class A, B and C (1, 5 and 2 subjects, respectively), CP_{ss} was increased by 50% to 120 % in the various classes of liver dysfunction. $T_{1/2}$ however was not convincingly increased.

It is unclear if there is a safety price that is a consequence of the higher peak concentrations. It is unclear if peak serum concentration is correlated with the drug's benefit, given that the concentration at the site of action (the pulmonary vasculature) is unlikely to be reflective of serum concentrations at steady state. The appropriate recommendation for this population is unclear. The uncertainty of the appropriate recommendation for this population should be incorporated into labeling.

Renal Impairment.

There were no studies performed in patients with renal impairment with inhaled Iloprost. However, after an intravenous infusion of Iloprost at a dose of 1 ng/kg/min to subjects with impaired renal function but not on dialysis (n=7) or who routinely require dialysis (n=8). Peak concentration among those who generally require dialysis was approximately three-fold higher than those not requiring dialysis. Clearance was rapid and by two hours post infusion there was little Iloprost measurable in either group.

It is unclear if there is a safety price that is a consequence of the higher peak concentrations. It is unclear if peak serum concentration is correlated with the drug's benefit, given that the concentration at the site of action (the pulmonary vasculature) is unlikely to be reflective of serum concentrations at steady state. The appropriate recommendation for this population is unclear. The uncertainty of the appropriate recommendation for this population should be incorporated into labeling.

Clinical Efficacy.

The current database for the approval of inhalation Iloprost for the treatment of pulmonary hypertension is dependent on a single, placebo-controlled, double-blind study (study #ME97218). A second smaller study (study #ME98998) was flawed in that the dose used differed from study ME97218. In addition, results were reclassified and modified after the blind was broken. The smaller study adds little to the decision for approval.

Safety of Iloprost is supported by the two extension studies of the placebo-controlled studies of Iloprost by inhalation. In addition, there is some experience, although of limited utility, with Iloprost administered either as an intravenous or oral formulation.

With respect to efficacy, study ME97218 was a placebo-controlled study in patients with pulmonary hypertension. Patients were stratified at baseline based on the origin of pulmonary hypertension (primary versus secondary) and NYHA classification at baseline (NYHA III versus IV). Only a single dosing regimen was used. Patients received as the first inhalation 2.5 mcg over 4.5 minutes. If the initial dose was tolerated,

subsequent doses were 5.0 mcg over 9 minutes. The initial regimen was for six inhalations, no more frequent than every two hours. The number of inhalations could be increased to a total of nine daily.

The primary metric of the study was a combined endpoint comparing the number of responders among those treated with Iloprost to placebo-treated subjects. A responder was one who had a greater than 10% increase in baseline walk distance and had at least one grade improvement in their NYHA classification at the 12-week visit and who did not deteriorate during the course of the study. Deterioration was defined as either death or by the occurrence of two or more of the following criteria:

- Refractory systolic arterial hypotension of > 85 mm Hg.
- Worsening right heart failure (cardiac edema, ascites or pleural effusion), despite adequate background therapy
- Rapidly progressive cardiogenic hepatic failure.
- Rapidly progressive cardiogenic renal failure.
- A decrease in walking distance by ≥ 30% from baseline.
- New and new need for intravenous medication (e.g., catecholamines or diuretics).
- Cardiac index < 1.3 l/min/m^2.
- CVP > 22 mm Hg (via indwelling catheter) despite adequate diuretic therapy.
- SVO2 < 45% despite nasal O_2 therapy (right heart catheterization).

Secondary endpoints were not pre-ordered and included: exercise capacity, NYHA class, dyspnea index, hemodynamic parameters and gas exchange, deterioration of pulmonary hypertension, mortality and quality of life.

Of the 235 patients who were screened, 203 were randomized; 101 to Iloprost inhalation and 102 to placebo. The etiology of the pulmonary hypertension was idiopathic in 108 (108/203= 53%) and secondary forms in the other patients. Among the 95 patients classified as having secondary pulmonary hypertension 57 (57/95=60%) had as their etiology of pulmonary hypertension thromboembolic events. This population is not subsumed in the INDICATION by for either of the prostanoids currently approved to treat pulmonary hypertension. Thirty-nine percent (35/90) had as their etiology some form of collagen vascular disease (systemic sclerosis, CREST, SLE, and overlap syndrome). The etiology of the secondary pulmonary hypertension in the other patients included: post partum, familial, previous appetite suppressant use, and other causes.

With respect to the demographics of those enrolled, the average age was approximately 52 years, approximately 2/3 of those enrolled were female and approximately 3% were other than Caucasian. With respect to concomitant medications, approximately 80% were taking anticoagulants, 66% diuretics, 44% calcium antagonists, 25% ACE antagonists and 44% were on long-term O_2 therapy.

Dropouts were more frequent in the placebo than Iloprost inhalation group. There were four versus 1 death in the placebo and Iloprost groups, respectively.

There were 17/101 (16.9%) responders in the Iloprost group and 5/102 (4.9%) responders in the placebo-treated group. In considering the two stratified subgroups, there were 11/53 responders in the primary pulmonary hypertension group treated with Iloprost and 3/55 among those treated with placebo. There were 6/46 among those with secondary pulmonary hypertension who were responders on Iloprost and 2/47 treated with placebo. The components of the primary end point are included in the table below. In addition, I have included the walk distance both at 30-minutes post inhalation and at pre-inhalation. The pre-inhalation time point was at least 2 hours after the last treatment.

Although there was an overall effect on the composite end point, the small number for each of the stratified groups is not entirely informative. Walking distance at either 30-minutes post inhalation or at least two hours from the previous treatment, limited to those with data available at week 12 (this excludes the deaths and dropouts), however, did not appear to indicate a benefit for those with secondary pulmonary hypertension and who were treated with Iloprost. Since there is inadequate information,

Table 1:Primary endpoint and individual components of the composite as well as walking distance at 30 minutes post-inhalation and at least 2 hours after an inhalation for study ME97218.

	Iloprost	Control
Overall (Responders/ nonresponders) %	17/101 (17%)	5/102 (5%)
PPH (responders/ nonresponders) %	11/53 (21%)	3/55 (5%)
Secondary PH(responders/ nonresponders) %	6/48 (13%)	2/47(4%)
NYHA Class III (responders/ nonresponders) %	10/60 (17%)	4/60(7%)
NYHA IV (responders/nonresponders) %	7/41(17%)	1/42 (2%)
Components of Response criteria		
Walk distance increased by > 10% (responders/nonresponders) %; Overall	38/101(38%)	26/102 (25%)
PPH (responders/nonresponders) %	26/53 (49%)	17/55 (31%)
Secondary PH (responders/ nonresponders) %	12/48 (25%)	9/47 (19%)
NYHA Class III (responders/nonresponders) %	25/60 (42%)	17/60 (28%)
Class IV (responders/nonresponders) %	13/41 (32%)	9/42 21%)
Change in NYHA Class > 1 grade: Overall	25/101 (25%)	13/102 (13%)
PPH	13/53 (25%)	4/55 (7%)
Secondary PH	12/48 (25%)	9/47 (19%)
NYHA Class III	15/60 (25%)	6/60 (10%)
NYHA Class IV	12/48 (25%)	7/42 (17%)
No deterioration by above listed criteria	95/101 (95%)	87/102 (87%)
PPH	49/53 (92%)	46/55 (84%)
Secondary PH	46/48 (96 %)	41/47 (87%)
NYHA Class III	56/60 (93%)	54/60 (90%)
Class IV	39/41 (95%)	33/42 79%)
Overall walking distance at 30 minutes (change in meters ± SD [median]	22.2 ± 71 [20]	-3.2 ± 74 [0]
PPH	42 ± 73 [31]	-2 ±89 [10]
Secondary PH	**2 ± 57 [12]**	**8 ± 47 [0]**
NYHA Class III	17 ± 64 [21]	-5 ± 80 [7]
NYHA Class IV	32 ± 75 [20]	17 ± 57 [2]
Overall walking distance at trough (change in meters ± SD), available at week 12	14.6±68[16]	0.2 ± 67[0.5]
PPH	28 ± 76 [32]	1 ± 75 [10]
Secondary PH	**-0.2 ± 54 [7]**	**10 ± 48 [5]**
NYHA III	8 ± 66 [13]	-0.6 ± 69 [5].3
NYHA IV	24 ± 69 [19]	16 ± 54 [[12]

from other sources or other similar drugs for this predominantly thromboembolic population, the labeling should limit the approval to those with primary disease.

Hemodynamic measurements were performed for those who were available at the 12-week time point at trough, however, it is not clear if trough represents the measurements after the overnight period when Iloprost was not inhaled or reflects the measurement performed at least, two-hour time point after a last inhalation treatment. Although there was a suggestion of a decrease in PVR, the effect was not statistically significant. After the inhalation of either Iloprost or placebo, there was a substantial further decline in PVR but the two treatments did not substantially differ in this effect (data not shown here).

Table 2:Hemodynamic parameters at trough measurement at week 12, change from baseline

	Iloprost		Control		p- value*
PVR (dyn.Sec.cm^{-5})	N=76	-9.2 + 275	N=77	96.2 + 323	0.07
mPAP mm Hg	N=93	-0.2 $\pm$7.3	N=82	-0.1 $\pm$ 6.9	0.96
CO l/min	N=91	0.1 + 0.9	N=80	-0.2 + 0.8	0.32
SVO_2 (%)	N=72	-1.1 $\pm$ 7.6	N=63	-3.2 $\pm$ 6.7	0.43

* ANCOVA for treatment term without baseline adjustment (derived from sponsor's Table TT51).

Clinical Safety.

Safety has been reviewed by Dr. Gordon. There are three databases which contribute to the understanding of the safety profile of Iloprost. The most pertinent of these is the modest database among those randomized in the PAH clinical studies. This database consists of 262 patients exposed to either Iloprost inhalation or placebo in controlled studies and 123 patients who subsequently were enrolled in a long-term extension study. Of these patients, 80 were treated for $\geq$ 1 year and 64 for $\geq$ 24 months. This database reflects the safety in the target population.

Two additional databases are also pertinent to defining the safety of Iloprost. Iloprost has been previously administered as an intravenous infusion or by the oral route. Systemic exposure during an intravenous infusion assures exposure to both diastereoisomers. With respect to oral Iloprost, there were over 2,000 patients who received Iloprost by this route. Since bioavailability of Iloprost is low (approximately 16%) compared to the intravenous exposure and the precise composition of the diastereoisomers after an oral dose is uncertain. The oral safety database, although useful reflects a greater degree of uncertainty.

Inhalation database.

Deaths.

There were 2/129 deaths in the Iloprost treated patient and 5/133 in the control group. There were an additional 15/123 patients that died during the open-label extension portion of the study. The two deaths in the controlled studies and 13 of the deaths during the long-term extension were related to progression of disease. The two remaining deaths consisted of one patient who died of colon cancer and one who apparently drowned.

Serious adverse events.

The serious adverse events listed during the controlled portion of the study (in more than 1 patient and more frequent in the Iloprost group) are listed below.

Table 3: Serious adverse events in the placebo-controlled studies (ME98998 and ME97218)(> 1% and more frequent in the Iloprost –treated patients):

	Iloprost (N=129)	Placebo/control (N=133)
Overall	29 (23%)	30 (23%)
CHF	6 (5%)	11 (8%)
Syncope	6 (5%)	0
Aggravation reaction	4 (3%)	5 (4%)
Pneumonia	2 (2%)	0
Laboratory test abnormal	2 (2%)	0
Dyspnea	2 (2%)	2 (2%)

During the open-label extension the most common serious adverse events were not dissimilar from those noted during the placebo-controlled exposure of patients. Events occurring in > 2 subjects are listed below.

Table 4:Adverse events in (> 2%) during either placebo-controlled or the open-label long term extension studies

	Any Iloprost in studies with > 1 dose (N=215)+
Body as a whole	36 (17%)
Aggravation reaction	11 95%)
Death	7 (3%)++
Surgery	7 (3%)
No drug reaction	5 (2%)
Asthenia	3 (1%)
Infection	3 (1%)
Cardiovascular System	34 (8%)
Congestive heart failure	17 (8%)
Syncope	9 (4%)
Respiratory system	13 (6%)
Dyspnea	4 (2%)
Pneumonia	3 (1%)
Metabolic and nutritional	9 (4%)
Peripheral edema	4 (2%)
Edema	3 (1%)

+ The database consists of 28 patients treated with Iloprost during the controlled portion of ME 98008, Plus 26 control patients who completed the study plus 4 who terminated early but received long term Iloprost. In addition there were 101patientstreated with Iloprost during the double-blind portion of study ME97218 and 58 patients treated with placebo who received open-label Iloprost.
++ Not all deaths were classified as an adverse event

Labs.

As Dr. Gordon notes, no patient discontinued Iloprost during the double-blind portion of the study as a consequence of a lab abnormality. Three patients on Iloprost had

Elevated LFTs (> 3x of AST, ALT or Alk Phos) during the controlled portion of the study. Two of these patients had baseline elevations, the third had a transient increase which was labeled as a heparin allergy. The value returned to normal levels at the 4-week follow-up.

There were four Iloprost and nine placebo patients with abnormal (> 1.5 x ULN creatinine values) during the double-blind portion of the studies. One patient had a pre-mortal increase in creatinine, reflective of overall poor perfusion. Two subjects had baseline elevations with no significant increases over baseline. One patient a 56 year old female Caucasian had a worsening of creatinine from 150 uM/L at baseline to 195 uM/L at 12weeks. No explanation was supplied for this patient's increase in creatinine.

There were seven patients with abnormalities in either platelets or hemoglobin below the lower limit of normal. All patients had similar abnormalities at baseline (5 with low platelets and 2 with low hemoglobin).

ECG.

A definitive QT study supports the lack of effect of Iloprost inhalation on repolarization. Study C-200-004 was a parallel 4 arm study that enrolled 161 normal volunteers. One group received a single dose of moxifloxacin (400 mg), one group received 2.5 mcg by inhalation every 2 hours. The third group received ascending doses of Iloprost, as tolerated starting with 5 mcg and increasing to 7.5, 10, 12.5, 15, and 20 mcg) every two hours. The fourth group received placebo.

ECGs were performed at baseline and between inhalations (at midpoint and just previous to next inhalation) and after the last dose at 5, 15, 60 minutes, 4, 8, and 15.5 hours after the final inhalation. In the ascending dose group, dose escalation was limited in 13 patients by adverse event. The most frequent of these was chest pain (5 patients), nausea (2 patients), headache (3 patients), tachycardia, dizziness, atrial flutter (1 patient each). Repolarization, as assessed by QT, QTcb, QTcf or QTcI for moxifloxacin was prolonged but not for either the fixed low-dose Iloprost inhalation or the ascending dose Iloprost inhalation group. Since there does not appear to be any long-lasting accumulating metabolites, the results of this study indicate no effect of Iloprost inhalation of repolarization, with a substantial safety margin.

Safety from intravenous studies.

A second database that defines the safety of Iloprost consists of those patients who received intravenous Iloprost. This database consisted of 12 placebo-controlled studies of at least two weeks duration and exposed 764 and 709 patients to Iloprost and placebo, respectively. The population was composed of patients with peripheral atherosclerotic occlusive disease 425/764 (56%); atherosclerotic peripheral vascular disease, with ischemic ulcers 154 /764 (20%); TAO 74/764, (9.7%); diabetic patients with ulcerated/necrotic ulcers critical limb ischemia (56/764) 7.3%; and critical limb ischemia 53/764 (6.9%). The dose for all these studies ranged from 1.5- 4 ng/kg/min for a six hour infusion period 6-7 days per week (32.4 - 86.4 mcg/day assuming a 60-kg person). The duration of treatment ranged from 2-4 weeks.

During the double-blind intravenous studies there were five deaths four in the Iloprost and one in placebo-treated patients. In the subsequent 30-day post-treatment period there were 8 Iloprost and 12 placebo patients who died.

The adverse events leading to withdrawal (in more than two Iloprost patients) during intravenous placebo-controlled studies is shown below. The most common events leading to discontinuation were headache and hypotension.

Table 5: Intravenous Iloprost database: adverse events leading to discontinuation (on > 2 Iloprost patients).

	Iloprost (n=764)	Placebo (n=709)
Nervous system	12 (2%)	2 (< 1%)
Headache	8 (1%)	1 (1%)
Cardiovascular System	16 (2%)	9 (1%)
Hypotension	4 (1%)	3 (< 0.5%)
Digestive system	7 (1%)	3 (< 0.5%)
Vomiting	4 (1%)	1 (< 0.1%)

Laboratory abnormalities for those treated with intravenous Iloprost were not submitted.

Safety from oral Iloprost studies.

The third database consists of 3161 patients in 12-randomized in placebo-controlled studies of > 2 weeks duration. Of these patients, 2033 were treated with oral Iloprost and 1128 with placebo. The studies evaluated the use of Iloprost to treat peripheral vascular disease (n= 1341/2033); Raynaud's syndrome (n= 314/2033); thromboangiitis obliterans (216/2033); rheumatoid arthritis (138/2033); and multiple sclerosis (24/2033). The doses in these studies ranged from 50 - 200 mcg BID. The main difficulty with the interpretation of the oral data with respect to safety is that the bioavailability of oral formulations of Iloprost are low (approximately 16%). Adequate information as to whether the more active of the two diastereomers is preferentially cleared is poorly documented.

For the oral population the mean $\pm$ SD duration of treatment was 15.9 $\pm$ 15.6 weeks (median 8 weeks) and the mean $\pm$ SD daily dose was 173.5 $\pm$ 96 mcg (median 148 mcg). The corresponding duration for the placebo group is not stated. A greater fraction of the oral Iloprost patients than placebo patients did not complete the duration of study (38 versus 25%).

Serious Adverse events (in greater than 1% of either population) are shown below.

Table 6: Serious adverse events (> 1%) incidence in patients treated with oral Iloprost.

	Iloprost (n=2033)	Placebo (n=1128)
Overall	367 (18%)	218 (19%)
Body as a whole	208 (10%)	116 (10%)
Pain in extremity	72 (4%)	48 (4%)
Aggravation reaction	62 (3%)	32 (3%)
Surgery	53 (2%)	30 (3%)
Infection	37 (2%)	15 (1%)
Cardiovascular System	126 (6%)	64 (6%)
Peripheral gangrene	28 (1%)	10 (1%)
Angina pectoris	22 (1%)	5 (< 0.5%)
Digestive System	34 (2%)	19 (2%)
Nervous system	33 (2%)	10 (1%)
Respiratory system	32 (2%)	25 (2%)
Skin and Appendages	31 (2%)	30 (3%)
Metabolic and nutritional disorders	28 (1%)	15 (1%)

Common causes for discontinuation more frequent in the Iloprost than placebo group were: headache (9% versus 1%), dizziness (1.1 versus 0.4%), vasodilatation (4% versus 0%), nausea (7% versus 2%), diarrhea (2.2 versus 0.4%) vomiting (2.2 versus 0.4%). The sum of both the serious and adverse events leading to discontinuation reflect the vasodilatory and gastrointestinal effect of prostanoids; suggesting systemic exposure to active Iloprost diastereoisomers when the mixture is administered orally.

After oral administration there were small differences in laboratory abnormalities. In particular there were 3 subjects with > 5 x ULN in SGOT in the Iloprost group and none in the placebo group. The sponsor notes none of these patients had elevated bilirubin (> 2 mg/dL)

DSI

A single study site was inspected, [redacted] and the site was deemed acceptable.

Pediatrics:

Because pulmonary hypertension is an orphan indication, Iloprost was granted a waiver from performing pediatric studies.

Financial Disclosure:

As per Dr. Gordon's review, no financial arrangements were entered into between the sponsor and investigators that could impact on the outcome of the study.

Trade name:

DMETS originally expressed concern about the use of the TRADENAME Ventavis based on orthographic similarities and the possibility of confusion with

Ventolin. Based on reassurance by the sponsor that the distribution of Ventavis will be limited to specialty pharmacies ,which only stock medications for restricted distribution, such as Flolan and Treprostinil and do not normally stock common medications like Ventolin, the likelihood of medication errors is diminished. DMETS accepts the use of Ventavis as a trade name as long as the distribution is limited to such specialty pharmacies.

Additional DMETS comments concerning the proposed packaging of Ventavis are listed at the end of this memo.

Conclusions and Comments:

Approvability of a diastereomeric mixture:

The rationale for the approvability of a diastereomeric mixture was described under Chemistry.

Number of studies:

Only a single study supports approval of the use of Iloprost by inhalation. Approval relies on this study coupled with the benefit observed for Flolan and the suggestion of benefit from treprostinil, who are members of the same class of drugs. Because of the limited data, I have suggested that a conservative approach be taken with respect to limiting the labeling claims.

Population:

The majority of the effect on the primary end-point in the clinical study can be attributed to a beneficial effect in those patients with primary disease. The secondary pulmonary hypertension population that was studied in the single pivotal study had a minimal benefit in considering the primary end point or in considering walk-distance at either pre-dose or post inhalation. Since this population consists predominantly of patients with thromboembolic disease and since no previous prostanoid has been approved for this population, there is insufficient reason to recommend this treatment for the secondary pulmonary hypertension population.

Dose regimen:

Only one dose regimen was studied. An initial dose was 2.5 mcg by nebulization via a HaloLite or its successor ProDose nebulizer, over 4.5 minutes. If the single dose was tolerated the dose was increased to 5 mcg/ treatment over approximately 9 minutes with 6-9 of such inhalations per day. Iloprost was not studied in conjunction with other therapies for pulmonary arterial hypertension. Should the patient's condition deteriorate, there is no information as to whether other medications can be used with Iloprost or whether higher doses or more frequent treatments of Iloprost would be useful. The label should recommend consideration of alternate therapies should the patient's condition deteriorate.

Choice of Inhalers:

The pivotal clinical study (Study # ME97218) employed the HaloLite nebulized. The ProDose nebulizer is predicated on the operating characteristics of the HaloLite

nebulizer and is available in this country. Although some modifications to the microchip disc were required to assure the dose was the same as administered during the clinical trial with the HaloLite nebulizer, the performance characteristics of the ProDose nebulizer appear acceptable.

Other Instructions for dosing:

The ampoule that will be distributed by the sponsor contains 20mcg of Iloprost, which is far greater than needed for a single inhalation treatment (5 mcg). The delivery of Iloprost is not uniform during the time of the single inhalation. Far greater amounts of Iloprost are delivered (approximately 2.8 mcg) during the first portion of an inhalation than is delivered during the latter portion of an inhalation (2.3 mcg). Reliability of delivery of a second inhalation treatment from a single ampoule has not been tested for reproducible delivery of Iloprost. The use of residual Iloprost in the well of the nebulizer at the end of each dose, should therefore, be proscribed by the label.

Interdosing interval:

Based on serum levels, the sum of Iloprost diastereoisomers decrease rapidly after a single inhalation treatment (presumably these levels are reflective of Iloprost concentrations in the pulmonary vasculature). Whether there will remain adequate effects at the interdosing interval is uncertain. In the absence of data that would allow use of Iloprost to be incorporated into a treatment regimen with other drugs, the label should indicate both that timing of dosing should be commensurate with the anticipated need for additional symptom relief, such as when exercise is planned. No recommendation can be made about the concurrent use of Iloprost with other treatments for pulmonary hypertension.

Based on what is known from clinical trials, the minimal time between doses of Iloprost should be two-hours. The maximal number of daily doses should be limited to six - nine per day. The dose of Iloprost per inhalation treatment should be limited to less than 5 mcg, with a total daily dose of < 45 mcg/day.

The benefit of Iloprost at 30 minutes post dose is clearly evident for walking distance and for the composite definition of responder, the primary metric of the study. At the interdosing interval there appears to be a diminishment of benefit and whether there is residual benefit is unclear.

Description of Benefit:

The benefit to a patient based on the single study would suggest that the expectation should be similar to the composite endpoint; a composite of an increase in 10% over baseline walk-distance, an improvement in NYHA classification without the components classified as deterioration.

Withdrawal effects:

Iloprost is administered asymmetrically, with dosing no more frequent than every two hours and a maximum of none daily doses. Patients usually do not have inhalations during the overnight period when they sleep. Although trough measurements of

hemodynamics and walk-distance did not show a rebound effect, it is unclear if the trough is after an overnight fast or after the two hour inter-treatment interval. Whether there is some consequence of withdrawal is unclear.

DMETS Comments:
DMETS comment concerning about additional modifications to the container label and carton labeling follow:

a. Delete use of the terminal zero on the carton labeling (i. e., Contents) and the ProDose Nebulizer Disc (i. e., 5 mg size). b. We recommend reorganizing the information in the net quantity box to read as follows:

b. We recommend reorganizing the information in the net quantity box to read as follows:

NDC10148-101-01 Ventavis (Iloprost Inhalation Solution 20 mcg/2 ml 100 Single-Use ampules Discard Any Unused Portion Rx Only

NDC 10148- 101- 01 Ventavis (Iloprost) Inhalation Solution 20 mcg/ 2 mL 100 Singe-Use Ampules Discard Any Unused Portion Rx Only

c. DMETS notes that the sponsor has submitted a label that will be placed on the ProDose nebulizer disc for our comment and review. We note that the terminal zero should be deleted on the 5 mcg dose. However, DMETS cannot comment whether this is an appropriate label to use with this device.

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/s/

Abraham Karkowsky
12/23/04 01:03:31 PM
MEDICAL OFFICER