

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

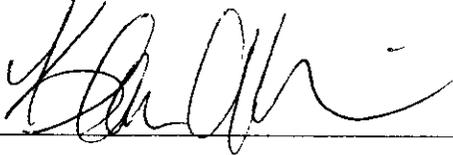
21-779

Administrative/Correspondence

A. ADMINISTRATIVE DOCUMENTS

Patent Certification

CoTherix, Inc., hereby certifies that the provisions of 21 U.S.C. 355 (b) (2) or (j) (2) (A) do not apply to this application



6/23/04

Klara Dickinson
Director, Regulatory Affairs
CoTherix, Inc.
5000 Shoreline Court, Suite 101
South San Francisco, CA 94080

Date

**PATENT INFORMATION SUBMITTED WITH THE
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and
Composition) and/or Method of Use*

NDA NUMBER

21,779

NAME OF APPLICANT / NDA HOLDER

CoTherix, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

Ventavis®

ACTIVE INGREDIENT(S)

iloprost

STRENGTH(S)

10 micrograms/mL

DOSAGE FORM

Inhalation Solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

4,692,464

b. Issue Date of Patent

9/8/1987

c. Expiration Date of Patent

9/8/2004

d. Name of Patent Owner

Schering AG

Address (of Patent Owner)

Muellerstraße 178
D-13353

City/State

Berlin, Germany

ZIP Code

FAX Number (if available)

011+49 30 4681 8007

Telephone Number

011+49 30 4681 7658

E-Mail Address (if available)

gabriele.kapfer@schering.de

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

☐

1

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

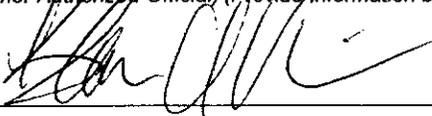
6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide information below)

Date Signed



6/23/04

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Klara A. Dickinson, Director Regulatory Affairs, CoTherix, Inc

Address

5000 Shoreline Court, Suite 101

City/State

South San Francisco

ZIP Code

94080

Telephone Number

(650) 808-6518

FAX Number (if available)

(650) 808-6899

E-Mail Address (if available)

kdickinson@cotherix.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY FOR NDA # 21-779

Trade Name: Ventavis Generic Name: iloprost

Applicant Name: CoTherix HFD # 110

Approval Date If Known: December 29, 2004

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_X_/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 Years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

_____ N/A _____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete

remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # _____ YES /___/ ! NO /___/ Explain: _____
! !

Investigation #2 !

IND # _____ YES /___/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
YES /___/ Explain _____ ! NO /___/ Explain _____
! !

! _____
_____ ! _____

Investigation #2 !
YES /___/ Explain _____ ! NO /___/ Explain _____
! !

! _____
_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

Signature Date
Melissa Robb
Regulatory Health Project Manager, HFD-110

Signature

Date

Norman Stockbridge, M.D., Ph.D.

Acting Director, Division of Cardio Renal Drug Products, HFD-110

Form OGD-011347 Revised 05/10/2004

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

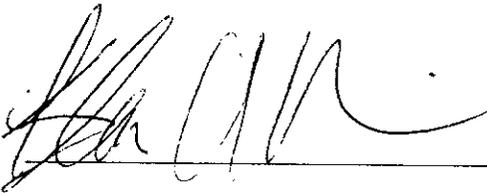
/s/

Norman Stockbridge
12/30/04 11:36:33 AM

A. ADMINISTRATIVE DOCUMENTS

Debarment Certification

CoTherix, Inc., hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or (b) of the Federal Food, Drug, and Cosmetics Act in connection with this application.



Klara Dickinson
Director, Regulatory Affairs
CoTherix, Inc.
5000 Shoreline Court, Suite 101
South San Francisco, CA 94080

6/23/04

Date

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION**



US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to: CDER, DCRDP (HFD-110); 5600 Fishers Lane; Rockville, MD 20857

Transmitted to FAX Number: 650-808-6897

Attention: Klara Dickinson

Company Name: CoTherix, Inc.

Phone: 650-808-6518

Subject: Action Letter

Date: 12/29/04

Pages including this sheet: 19

From: Melissa Robb

Phone: 301-594-5313
Fax: 301-594-5494

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

1/3/05

Project Manager Overview
NDA 21-779
Ventavis (iloprost) Inhalation Solution

Overview:

Iloprost, a prostacyclin analog, is currently approved as Ilomedin for intravenous administration in approximately 30 countries worldwide for the treatment of occlusive arterial disease. Ventavis is an inhalation solution developed by Schering AG, Germany, for the treatment of pulmonary hypertension. The rationale for the inhaled route of administration is to provide high local concentrations, while minimizing the systemic side effects of prostacyclin therapy and avoiding the complications of chronic indwelling catheters. Ventavis was approved in the European Union in September 2003. The sponsor submitted a NDA on June 30, 2004 requesting approval for the treatment of Pulmonary Arterial Hypertension (PAH) in patients with New York Heart Association (NYHA) Class III or IV symptoms, to improve exercise capacity and symptoms.

Office Director Memo
Dr. Robert Temple, December 28, 2004

Dr. Temple concluded that the data submitted based on a single principal study are convincing and provide substantial evidence of effectiveness, the claim should be limited to the primary pulmonary hypertension population, and that the labeling figure of walking distance should be replaced by one that does not attribute zero walking to people who died. He also noted that the results in secondary pulmonary hypertension can be noted in the clinical trials section but that section should state that there are too few data to conclude that effectiveness has been demonstrated.

Secondary Medical Review
Dr. Abraham Karkowsky, December 23, 2004

Dr. Karkowsky wrote a memo supporting an approvable recommendation for the use of Ventavis (iloprost) inhalation solution to provide symptomatic benefit limited to patients with primary pulmonary hypertension. Dr. Karkowsky stated that it is likely that patients will benefit for at least 30 minutes after inhalation treatment, as evidenced by an increase in walk distance during the clinical trial. He also concluded that benefit at the interdosing interval appears less than at the 30 minute post inhalation time point.

Medical Review
Dr. Maryann Gordon, November 12, 2004

Dr. Gordon recommended approval for the treatment of pulmonary arterial hypertension in patients with WHO Class III or IV symptoms. She also recommended satisfactory completion of study C200-002 as a post-marketing action.

Financial Disclosure: Dr. Gordon noted that the sponsor certified that based on the information obtained from the sponsor of the studies, not the applicant, the listed clinical investigators included in the application did not participate in any financial arrangement with the sponsor of the covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study; had no proprietary interest in the product or significant equity interest in the sponsor of the covered study; and was not the recipient of significant payments of other sorts.

Safety Update Review: Dr. Gordon noted that the update provided safety from ongoing long-term study 303045, results from ECG study C200-004 examining the effects on QT interval, and a summary of oral and intravenous and/or intra-arterial iloprost studies not submitted in the original NDA.

Labeling: Dr. Gordon included revised proposed labeling in her review.

Clinical Inspection

The clinical inspection conducted November 1-5, 2004 concluded that the study data collected appears to be acceptable.

Statistical Review

Dr. Valeria Freidlin, October 27, 2004

Dr. Freidlin concluded in her review that primary efficacy analysis of Study ME97218 showed that iloprost is statistically significantly better than placebo relative to the combined responder rate at week 12 based on the ITT-observed cases ($p=0.0067$). Sensitivity analyses of the combined responder rate based on the ITT-LOCF and the Per Protocol populations support the primary efficacy results ($p\leq 0.016$). In addition, she stated that secondary analyses of the change from baseline to week 12 in walking distance and of other secondary endpoints were consistent with the primary efficacy analysis. Dr. Freidlin stated that although Study ME97218 seems to be a solid confirmatory study, for the non-mortality endpoints the usual standard requires efficacy evidence to be confirmed in at least one more study. Finally, Dr. Freidlin stated that as the sponsor did not pre-specify any statistical rule for dealing with multiple secondary endpoints, there is no basis for selective inclusion of favorable p-values for some secondary endpoints in the sponsor's labeling.

Clinical Pharmacology and Biopharmaceutics

Dr. Robert Kumi, December 1, 2004

Dr. Kumi stated in his review that the information provided in the NDA application is acceptable provided that agreement is reached between the applicant and the Agency on labeling.

Dr. Kumi suggested dosage adjustment in patients with moderately impaired hepatic (Child Pugh Class B) or impaired renal ($CL_{cr} \leq 30$ mL/min) function. This initial dose for these two classes of patients should be 1.25 mcg iloprost. Dr. Kumi also noted that the sponsor only is proposing dose controlling disc at 2.5 and 5 mcg.

Labeling: Dr. Kumi included revised proposed labeling in his review.

Dr. Nhi Beasley, December 23, 2004

In her memo, Dr. Beasley proposed labeling revisions to the package insert.

Pharmacology Review

Dr. Jim Willard, December 14, 2004

Dr. Willard stated in his review, that in his opinion, this drug is approvable. He added that there was an uneven quality to the nonclinical studies, since there are many IND submissions dating

back to 1983. Dr. Willard stated that many of the nonclinical studies were conducted in Germany with other indications in mind. In addition, he noted that not all the studies were GLP or quality assured. Dr. Willard also stated that despite these problems, the data was of sufficient quality to determine that it is reasonably safe to proceed with the proposed protocol.

Labeling: Dr. Willard included revised proposed labeling in his review.

**Statistical Review of Carcinogenicity
Dr. Jasmine Choi, November 9, 2004**

Dr. Choi reviewed two carcinogenicity studies, a two year mouse study (Study BC 60) and a two year rat study (Study BC 61). Dr. Choi's findings in both studies were in agreement with the sponsor's. In addition, Dr. Choi stated that the evaluation of the validity of the mouse study showed that sufficient numbers of animals were at risk for a sufficient length of time and in that rat study sufficient numbers of rats lived long enough to present late developing tumors.

Executive CAC Report from meeting on October 26, 2004

The committee found the rat and mouse studies were acceptable and concluded that there were no drug related tumor findings.

**Chemistry Review
Dr. Monica Cooper and Dr. William Timmer, December 3, 2004**

In their review, Dr. Cooper and Dr. Timmer do not make any recommendations about approvability. They are waiting for the Office of Compliance to give their recommendation and the pending issues identified within the DMF for the drug substance and the NDA to be resolved. The review also lists the deficiencies that have been communicated to the sponsor and that the reviewers are waiting for responses to.

Methods of Validation: Package submitted by the sponsor, pending.

Labeling: Dr. Cooper and Timmer included revised proposed labeling in their review.

Categorical Exclusion from the Environmental Assessment: The CE claim submitted by the sponsor was found acceptable.

Dr. Monica Cooper and Dr. William Timmer, December 17, 2004

In their review, Dr. Cooper and Dr. Timmer recommend approval. They also state that the Office of Compliance has given an overall acceptable recommendation for the facilities. Dr. Cooper and Timmer suggest wording to be included in the approval letter for expiration dating.

EES: Acceptable, December 13, 2004

Methods of Validation: To be initiated post approval

**Microbiology Review
Dr. James McVey, December 9, 2004**

Dr. McVey recommended an approvable action as the following deficiencies exist. The [] validation does not include [] in the product. No [] data is provided [] in the product and the [] employed [] for validation. Dr. McVey stated that the impact of the drug product [] should be assessed in order to assure adequate lethality is administered. Dr. McVey stated that the risk to human health cannot be assessed until the data is provided for review.

Labeling: Dr. McVey suggested an additional statement to be added to the labeling for emphasis of the cleaning process of the nebulizer.

Dr. James McVey, December 21, 2004

Dr. McVey concluded in his review that the information provided by the sponsor in response to a discipline review letter supported the sterility claim from a product quality microbiology perspective. He recommended approval of the application.

DDMAC Review

In a review signed November 18, 2004, comments were provided by DDMAC on the draft labeling submitted by the sponsor.

In a review signed December 21, 2004, comments were provided by DDMAC on the draft patient package insert submitted by the sponsor.

DMETS Review

In a review signed October 28, 2004, DMETS recommended not approving the use of the proprietary name Ventavis. They were also concerned about the risk of confusion and medication errors with the established name iloprost and recommended consulting the FDA representative to the USAN council about potential confusion and medication errors with iloprost and alupent (a proprietary name). DMETS also provided label and labeling revisions.

In a follow-up review signed December 15, 2004, DMETS reviewed a request by the sponsor to reconsider the use of the proprietary name Ventavis. DMETS had no objection to the use of the proprietary name Ventavis as long as the product is a component of the proposed restricted distribution program as presented by the sponsor. DMETS added however, that they would have continued concern if Ventavis was marketed via a normal distribution process.

DSRCS Review

In a review dated December 16, 2004, DSRCS provided comments on the sponsor's proposed PPI. DSRCS simplified proposed wording, made it consistent with the PI, removed unnecessary information, and put it in the format that they recommend. In addition, DSRCS noted that the sponsor has not stated how the patient is to receive the patient information. DSRCS believes that if the information is important for a patient's safe and effective use of the product, it should be packaged with the product and printed in at least 10 point font.

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

/s/

Melissa Robb
1/3/05 09:16:24 AM
CSO

SPONSOR'S ORIGINAL PROPOSED LABELING

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

3 Pages Redacted of
Deliberative Process
§ 552(b)(5)

1 **MEMORANDUM**

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

2
3
4
5
6
7
8 **DATE:** December 16, 2004
9
10 **TO:** Norman Stockbridge, M.D., Acting Director
11 Division of Cardio-Renal Drug Products
12 HFD-110
13
14 **VIA:** Melissa Robb, Regulatory Health Project Manager,
15 Division of Cardio-Renal Drug Products
16 HFD-110
17
18 **FROM:** Jeanine Best, M.S.N., R.N., P.N.P.
19 Patient Product Information Specialist
20 Division of Surveillance, Research, and Communication Support
21 HFD-410
22
23 **THROUGH:** Gerald Dal Pan, M.D., M.H.S., Director
24 Division of Surveillance, Research, and Communication Support
25 HFD-410
26
27 **SUBJECT:** DSRCS Review of Patient Labeling for Ventavis (iloprost)
28 Inhalation Solution, NDA 21-779
29

30 **Background and Summary**

31 The sponsor submitted a PPI, including *Instructions for Use* for Ventavis (iloprost) Inhalation Solution,
32 NDA 21-779, on December 13, 2004. We have simplified the wording, made it consistent with the PI,
33 removed unnecessary information (the purpose of patient information leaflets is to enhance appropriate
34 use and provide important risk information about medications, not to provide detailed information about
35 the condition), and put it in the format that we are recommending for all patient information. Our
36 proposed changes are known through research and experience to improve risk communication to a broad
37 audience of varying educational backgrounds. Patient information should always be consistent with the
38 prescribing information. All future relevant changes to the PI should also be reflected in the PPI.
39

40 **We also have the following comment:**

41 The sponsor has not stated how the patient is to receive this patient information. If the information is
42 important for a patient's safe and effective use of the product, it should be packaged with the product and
43 printed in at least 10-point font for legibility.
44

45 Comments to the review Division are bolded, italicized, and underlined. We can provide marked-up and
46 clean copies of the revised document in Word if requested by the review division. Please let us know if
47 you have any questions.
48

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

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

/s/

Jeanine Best
12/16/04 10:43:57 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
12/16/04 10:51:22 AM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION**



US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to: CDER, DCRDP (HFD-110); 5600 Fishers Lane; Rockville, MD 20857

Transmitted to FAX Number: 650-808-6897

Attention: Klara Dickinson

Company Name: CoTherix, Inc.

Phone: 650-808-6518

Subject: 12/9/04 Teleconference Minutes

Date: 12/9/04

Pages including this sheet: 4

From: Melissa Robb

Phone: 301-594-5313

Fax: 301-594-5494

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

Minutes of a Teleconference
December 9, 2004

Sponsor: CoTherix, Inc.
Drug: Ventavis (Iloprost) Inhalation Solution
NDA: 21-779

FDA Participants:

Kasturi Srinivasachar, Ph.D.	Team Leader, Chemistry, HFD-810
Monica Cooper, Ph.D.	Chemist, HFD-810
Jim Willard, Ph.D.	Pharmacologist, HFD-110
Melissa Robb	Regulatory Health Project Manager, HFD-110

CoTherix Participants:

Curtis Ruegg, Ph.D.	Senior Vice President, Technical Operations
Robert VanDyke, M.S.	Senior Director, Technical Operations
Thomas Fuerst, Ph.D.	Chemist, Schering AG
Klara Dickinson	Vice President, Regulatory Affairs
Daven Mody, Pharm.D., MBA	Manager, Regulatory Affairs
Crystal Browning	Associate, Regulatory Affairs

Background:

NDA 21-779 was submitted to the Division on June 30, 2004. The sponsor requested this teleconference to discuss the Agency's concerns regarding the testing [] and heavy metals in the drug substance.

Teleconference:

Dr. Srinivasachar began by discussing the testing of [] He stated that the Division agrees that the sponsor should test [] with each release batch. In addition, the Division agrees with a limit of [] ppm for all [] except [] which should have a limit of [] ppm.

Dr. Srinivasachar inquired about why the sponsor performed [] Dr. Fuerst stated that Schering [] in a cGMP environment. Dr. Fuerst added that the testing by [] is actually more sensitive than what is listed, as the limits stated are on the conservative side.

The sponsor inquired why the Division was requesting the detection of [] at such low levels. Dr. Willard stated this is because the target organ [] is the lung. Since this drug is administered directly into the lungs, the Division is concerned with accumulation, as it will not be eliminated as quickly as the drug product.

The sponsor stated that [] ppm is a very low and noted that the levels were derived from the EMEA guidance on parenteral administration. The sponsor believes that this limit should be higher, as patients will only be receiving a daily dose of iloprost equaling 45 mcg. The sponsor also believes that the pulmonary and oral route of administration are similar, as both require a transfer across a mucosal barrier. Dr. Willard stated that the Division's concern is with the accumulation of [] in the lungs, not the accumulation in the plasma.

Dr. Srinivasachar stated that the Division would find it acceptable if the sponsor was able to show [] ppm of [] in all release batches. Dr. Willard added that in the literature he has seen testing for [] in the area of parts per billion. Dr. Willard stated that the sponsor may have to assay for [] separately.

The sponsor agreed to test [] to a level of NMT [] ppm and [] to a level of NMT [] ppm in all release batches.

Dr. Srinivasachar stated [

]

Ms. Dickinson inquired about the specifications for the drug product submitted to Dr. Cooper and Dr. Timmer for review. Dr. Cooper stated these specifications were acceptable and the sponsor should submit them in an amendment to their NDA application. In addition, Dr. Cooper stated the sponsor should submit an amendment to their NDA application regarding the new agreed upon specifications for the drug substance. Finally, Dr. Cooper stated that the DMF holder should update the DMF with the agreed upon drug substance specifications.

Ms. Dickinson inquired about her e-mail to Dr. Timmer regarding drug product unknown impurities. Dr. Cooper stated she was unable to comment on that e-mail. Ms. Dickinson is going to contact Dr. Timmer to discuss further.

Signature, minutes preparer: *{See appended electronic signature page}*

Concurrence Chair: *{See appended electronic signature page}*

Drafted: 12/9/04 Finaled: 12/9/04

RD:

Srinivasachar	12/9/04
Cooper	12/9/04
Willard	12/9/04

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

/s/

Melissa Robb
12/9/04 02:27:33 PM

Kasturi Srinivasachar
12/9/04 02:37:57 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

12/9/04
Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-779

DISCIPLINE REVIEW LETTER

CoTherix, Inc.
Attention: Klara A. Dickinson
Director, Regulatory Affairs
5000 Shoreline Court, Suite 101
South San Francisco, CA 94080

Dear Ms. Dickinson:

Please refer to your June 30, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ventavis (iloprost) 10 mcg/mL Inhalation Solution.

A product quality microbiology review was completed by the Office of Pharmaceutical Science, and we have the following comments:

1. The validation of [] product should include an assessment of the impact of the drug product on the [] Please provide data summaries to address this issue.
2. A description and validation data summary should be provided for the ampule inspection system employed in manufacturing.

These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

/s/
{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Edward Fromm
12/9/04 04:53:47 PM

Withheld

4

**page(s) of trade
secret
and/or confidential
commercial
information**

(b4)

4

 Pages Redacted of
Deliberative Process
§ 552(b)(5)



DEPARTMENT OF HEALTH & HUMAN SERVICES

12/7/04
Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-779

CoTherix, Inc.
Attention: Ms. Klara A. Dickinson
Director, Regulatory Affairs
5000 Shoreline Court, Suite 101
South San Francisco, CA 94080

Dear Ms. Dickinson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ventavis (iloprost) Inhalation Solution

We also refer to your December 2, 2004 e-mail to Ms. Melissa Robb of the Division of Cardio-Renal Drug Products, requesting a waiver for pediatric studies due to iloprost inhalation solution receiving an orphan designation.

We have reviewed the referenced material and agree that no pediatric studies are required for iloprost Inhalation Solution as the Pediatric Research Equity Act (PREA) is not applicable to drugs with indications that have been granted orphan designation. Please disregard the deferral that was granted to you in our July 14, 2004 acknowledgement letter.

If you have any questions, please call:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Norman Stockbridge
12/7/04 03:52:02 PM

**MEETING MINUTES
PRE-APPROVAL SAFETY CONFERENCE**

Date: November 18, 2004

Time: 9:30

Location: WOC 2, Conference Room E

NDA: 21-779

Drug: Ventavis (iloprost) inhalation solution

Proposed Indication: treatment of pulmonary arterial hypertension in patients with NYHA Class III or IV symptoms,

[J

Sponsor: CoTherix, Inc.

REVIEW DIVISION PARTICIPANTS:

Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardio Renal Drug Products, HFD-110
Thomas Marciniak, M.D.	Acting Deputy Director, Division of Cardio Renal Drug Products, HFD-110
Maryann Gordon, M.D.	Medical Officer, HFD-110
Robert Kumi, Ph.D.	Pharmacokineticist, HFD-110
Monica Cooper, Ph.D.	Chemist, HFD-110
Bill Timmer, Ph.D.	Chemist, HFD-150
Jim Willard, Ph.D.	Pharmacologist, HFD-110
Melissa Robb	Regulatory Health Project Manger, HFD-110

ODS PARTICIPANTS:

Mary Ross Southworth, Pharm.D.	Office of Drug Safety, HFD-430
Cindy Kortepeter, Pharm.D.	Office of Drug Safety, HFD-430
Robert Kang	Office of Drug Safety, HFD-430

Serious Adverse Events To Be Monitored By ODS:

Syncope when initiating treatment

Other Issues to be Addressed by ODS:

None

Comments Provided by ODS:

1. Nebulizer
 - Should package insert be more specific about use of iloprost only with ProDose?
 - Division plans to have package insert state that the ProDose [J should be used with this drug
 - Clinical trials performed with HaloLite, in vitro testing done to show HaloLite and ProDose are equivalent alternatives; accepted by CDRH
2. Dosing disk
 - Not mentioned in "How Supplied" section
 - Unsure of how patients receive dosing disks, i.e. with drug, from physician, with nebulizer

3. Package insert: Dosing and Administration
 - More specific dosing instructions
 - Suggested including a minimum and maximum interval in labeling
 - See page 7, 17, 53 of MO review for dosing examples
 -
4. Add section
 - Issue of systemic effects (SVR)
 - Time to symptom improvement/PVR effects
 - Time to return to baseline of vascular effects
 - See figure page 55 MO review
5. Package insert: Precautions
 - Initiation done where? Only in clinic with nurse? Home nurse?
 - The Division agrees with this proposal and plans to move this sentence about initiating therapy to the WARNINGS section. In addition, this statement will be repeated in the DOSING AND ADMINISTRATION section.
 - The Division would like to put a similar statement at the beginning of the package insert like that of Pulmicort and reiterate this warning there also.
 - Line 163 change Iloprost to Ventavis
 - Have separate paragraph describing concern with syncope
6. Package insert: Clin Pharm/ Pharmacokinetics
 - Line 38 incomplete "6 to 9 minutes"
7. Information for patients. PPI suggested to address the following issues:
 - Specific directions on nebulizer
 - Do not alter dose unless prescribed
 - Do not nebulize with other products
 - Not a bronchodilator
 - No face mask used to reduce contact with eyes, etc.
 - What nebulizers should not be used
 - Syncope/timing of inhalation to exertion
 - Throw out remaining solution
 - Specific dosing recommendations
 - How to use glass ampule

Signature, minutes preparer: *{See appended electronic signature page}*

Concurrence Chair: *{See appended electronic signature page}*

Drafted: 11/19/04

Finalled: 12/14/04

NDA 21-779
Pre-Approval Safety Conference
Meeting Minutes
Page 3

RD:

Stockbridge	12/14/04
Marciniak	12/14/04
Gordon	12/14/04
Kumi	12/13/04
Cooper	11/30/04
Timmer	11/24/04
Willard	11/24/04
Southworth	11/19/04
Kortepeter	11/19/04
Kang	11/23/04

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

/s/

Melissa Robb
12/14/04 11:20:17 AM

Norman Stockbridge
12/14/04 02:43:43 PM

4

 Pages Redacted of
Deliberative Process
§ 552(b)(5)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

11/16/04

NDA 21-779

DISCIPLINE REVIEW LETTER

CoTherix, Inc.
Attention: Klara A. Dickinson
Director, Regulatory Affairs
5000 Shoreline Court, Suite 101
South San Francisco, CA 94080

Dear Ms. Dickinson:

Please refer to your June 30, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ventavis (iloprost) 10 mcg/mL inhalation solution.

A review by the Office of Drug Safety/Division of Medication Errors and Technical Support (DMETS) has been completed, and we have the following comments:

1. Sound-alike and Look-alike Concerns:

Ventolin was identified to have sound and look-alike similarities to the proposed name, Ventavis. Ventolin contains the active ingredient albuterol and is indicated for the relief and prevention of bronchospasm in patients with reversible obstructive airway disease. Both names consist of three syllables and each syllable can be enunciated with a similar phonetic length. The first syllable of each name consists of exactly the same letters and therefore, the first syllable can be enunciated in exactly the same manner. The second syllable of each name only consists of either the vowel "o" or "a" and the short vowel sound in this syllable could easily be misinterpreted. Therefore, when spoken the last syllable of each name must be clearly enunciated to differentiate the names. Also, each name consists of 8 letters, and five of the eight letters are the same and appear in the same corresponding positions. Therefore, when scripted the letters that appear in the fifth, sixth, and eighth positions must be clearly written to differentiate the names. The proprietary name Ventolin has been used to market an inhalation aerosol, inhalation solution, inhalation capsule, syrup, and tablet dosage formulations of albuterol sulfate. However, the proprietary name Ventolin is currently only used to market the aerosol dosage formulations of albuterol sulfate. Even though Ventolin inhalation solution is no longer marketed, physicians can still write orders for Ventolin inhalation solution. It is a well known proprietary name, and healthcare professionals would normally interpret an order for Ventolin inhalation solution as an order for albuterol sulfate inhalation solution. Many healthcare professionals may not even be aware that Ventolin inhalation solution has been discontinued, since these orders would normally be dispensed with a generic albuterol sulfate inhalation solution. Therefore, we have decided it would be prudent to not only evaluate the potential for confusion between Ventavis inhalation solution and Ventolin inhalation aerosol, but also the potential for confusion between Ventavis inhalation solution and Ventolin inhalation solution. An evaluation of Ventavis inhalation solution and Ventolin inhalation aerosol indicates the products differ in their product strength (10 mcg/mL vs. 90 mcg/activation), usual dose (5 mcg vs. 2 inhalations or puffs), frequency of administration (up to 6 to 9 times a day vs. every 4 to 6 hours), dosage formulation (solution vs. aerosol) and packaging configuration (ampule vs. inhaler). An order for a Ventolin inhalation aerosol may also include the abbreviation MDI to indicate a "multi-dose inhaler" or the modifier HFA to identify an inhaler with a non-chlorofluorocarbon propellant. However, if a nonspecific outpatient prescription is communicated as,

"Vent---,
Use as directed,
1 box",

then a pharmacist could interpret the order for 1 box of Ventavis inhalation solution, or 1 box containing a Ventolin inhaler. Orders that only consist of nonspecific information and initially seem acceptable, could be interpreted differently by pharmacists, and therefore increase the risk of confusion and medication errors involving Ventavis and Ventolin.

An evaluation of Ventavis inhalation solution and Ventolin inhalation solution indicates the products can share similar characteristics in the dosage (initial dose 2.5 mcg vs. 2.5 mg) or (1 ampule vs. 1 vial), the route of administration (oral, via nebulizer), dosage formulation (inhalation solution), and packaging configuration (unit dose ampules or vials). Although the maintenance dose of Ventavis should be 5 mcg, the initial dose should be only 2.5 mcg. Therefore, if the initial dosage is communicated on an order, then the dosage may not aid in differentiating the products, because of the overlapping numerals, 2.5, and similarity between the abbreviations for the units, microgram versus milligram, (mcg vs. mg). On outpatient prescriptions, physicians could communicate the dosage as 1 ampule/vial, without actually indicating the dose in milligrams or micrograms. Healthcare professionals commonly use the terms, ampule and vial interchangeably when prescribing inhalation solution products. Thus, the incorrect use of either term to identify a unit of medication per the manufacturer's labeling would normally not aid healthcare professionals to differentiate products. Albuterol sulfate inhalation solution is available in two concentrations, 0.083% and 0.5%. If the concentration is included on orders for albuterol sulfate inhalation solution, then the concentration should aid in differentiating the products Ventavis and Ventolin. However, if the concentration is not included on an order for Ventolin, then a pharmacist can safely dispense the medication without contacting the physician. A pharmacist can decide which concentration to dispense based upon the patient's age. The pharmacist is also assured that each product contains the same amount of medication, 2.5 mg of albuterol. This is because the different concentrations, 0.083% and 0.5%, of albuterol sulfate inhalation solution are in unit dose vials containing different volumes of solution, 3 mL vs. 0.5 mL, respectively. The most distinguishing characteristic that may aid in differentiating the products is the frequency of administration. Ventavis may be administered more frequently than Ventolin (6 to 9 times a day vs. 3 to 4 times a day). However, if Ventavis is only ordered with a frequency of as needed, or as directed, then the frequency of administration may not aid in differentiating the products. Therefore, we are concerned if outpatient prescriptions are communicated as,

"Vent---
Use 1 ampule/vial as directed or
as needed via nebulizer
Dispense 120 vials",

then there is an increased risk of confusion and medication errors involving Ventavis and Ventolin inhalation solutions.

In conclusion, we believe that the sound and look-alike similarities in the names, in addition to the aforementioned product and outpatient prescription similarities increase the potential risk of a medication error involving Ventavis and Ventolin.

Ventavis
Ventolin

Ventavis Inh. Sol.
Ventolin Inh. Sol.

2. Labeling, Packaging, and Safety Related Issues:

In the review of the container label, carton and insert labeling of Ventavis, we have attempted to focus on safety issues relating to possible medication errors. We have identified the following improvements, which might minimize potential user error.

1. CONTAINER (Ampule) AND CARTON LABEL

- a. Please ensure that the established name appears with at least half the prominence as the proprietary name after accounting for differences such as font style, size, and print color.
- b. We suggest that the total drug content and the product strength should be presented directly under the established name utilizing two different lines and within a box or border with the same color background. We suggest the total drug content be the primary expression of strength followed immediately by the concentration per mL. For example,

20 mcg/2 mL 10 mcg/mL)

Expressing the total drug content and product strength in this manner may help prevent practitioners from misinterpreting the total drug content of a drug product. Medication errors can occur when a user or practitioner reads the product strength (e.g., 10 mcg/mL), but fails to read or calculate the total drug content.

2. CARTON LABEL

- a. []
- b. []
- c. In the "Storage" section, we recommend that the present wording should be revised to include an actual storage temperature range for the product in both degrees Celsius and Fahrenheit. We recommend using on of the storage phrases in the FDA Stability Guidance.

3. INSERT LABELING

- a. We recommend increasing the prominence of the proprietary and established names. Please ensure that the established name appears with at least half the prominence as the proprietary name.
- b. We recommend replacing the abbreviation "µg" with the abbreviation "mcg" for micrograms. Post-marketing error reports have shown the abbreviation "µg" has been misinterpreted as an abbreviation for "mg" or milligrams.
- c. The first sentence in the "Description" section presents the product strength as an expression of the salt, 10 mcg/mL iloprost tromethamine, but the rest of the labeling indicates the product strength is expressed based on the active moiety, 10 mcg/mL iloprost. Please revise accordingly.

- d. The following comments pertain to the "Dosage and Administration" section:
- i. We recommend that guidance should be provided on the minimum dosing interval in which a patient may be able to safely repeat their dose (e.g., every 30 minutes, or every hour).
 - ii. We recommend that directions should be included for the user concerning the proper technique and procedure that should be followed to safely open, empty and discard the glass ampules of iloprost inhalation solution.
- c. In the "Description" and "How Supplied" sections, we suggest removing the reference to the actual size of the glass ampule, 3 mL. Removal of this reference should aid in decreasing the risk of confusion between the size of the ampule, (3 mL), and the total volume in the vial, (2 mL).
- f. In the "Stability and Storage" section, we recommend that the present wording should be revised to include an actual storage temperature range for the product in both degrees Celsius and Fahrenheit. In addition, please use one of the storage phrases in the FDA Stability Guidance.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 594-5313.

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Edward Fromm
11/16/04 10:45:31 AM

10/28/04

Office of Drug Safety

MEMO

To: Norman Stockbridge, M.D.
Acting Director, Division of Cardio-Renal Drug Products, HFD-150

From: Denise P. Toyer, PharmD.
Deputy Director, Division of Medication Errors and Technical Support, Office of Drug Safety, HFD-420

Through: Carol A. Holquist, R.Ph.
Director, Division of Medication Errors and Technical Support, Office of Drug Safety, HFD-420

CC: Melissa Robb
Project Manager, Division of Cardio-Renal Drug Products, HFD-150

Date: December 8, 2004

Re: ODS Consult 04-0225-1 Ventavis (Iloprost Inhalation Solution), NDA 21-779

This memorandum is in response to a December 2, 2004 request from your Division to reconsider the acceptability of the proprietary name, Ventavis, based on the sponsor's submission dated November 18, 2004. Additionally, the sponsor submitted revised container labels and carton labeling. A revised package insert labeling was not submitted for review and comment.

Previously, the sponsor submitted Ventavis for consideration, which was the subject of ODS Consult 02-0225, dated October 28, 2004. DMETS did not recommend use of this name due to its orthographic and phonetic similarities to Ventolin. DMETS also expressed concern that the established name Iloprost had orthographic similarities to the proprietary name Alupent, a currently marketed product. DMETS recommended contacting David B. Lewis, FDA representative to the USAN council involving the potential for confusion between Alupent and Iloprost.

Co-Therix's November 18, 2004 submission included a request for reconsideration of the use of the proprietary name, Ventavis based on the following.

1. The submission notes that Co-Therix recognizes the similarities with Ventavis identified in the DMETS review. However, the sponsor feels that the potential for confusion will be lessened due to the 'manner in which distribution of Ventavis will be managed.' The sponsor has voluntarily initiated a plan to implement a restricted distribution program for Ventavis. The product will only be available at a 'small network of specialty pharmacies.' Prior to patient's receiving the medication, physicians must enroll them in a Patient Access Program. [

]

The sponsor notes that Ventavis will not be stocked or dispensed through retail pharmacies, decreasing the potential for confusion between Ventavis and Ventolin or Iloprost and Alupent especially since it is unlikely that Ventolin and Alupent will be stored at or/in a specialty pharmacy.

Ms. Claire Dickerson (Cotherix, Regulatory Affairs) provided additional clarification of the restricted distribution program on December 14, 2004 in a telephone conversation with Dr. Denise P. Toyer, of DMETS. Ms. Dickerson indicated that Ventavis is manufactured in [redacted] and will be distributed by [redacted] in the United States. [redacted] will only distribute this product to [redacted] specialty pharmacies in the United States. According to Ms. Dickerson these pharmacies do not stock medications normally stocked in retail pharmacies (e.g., Ventolin or Alupent). They handle pharmaceuticals that require special monitoring of a specific disease state, distribution, etc. Flolan and Remodulin are examples of two medications currently distributed via the specialty pharmacies. The physician will make the initial contact with the Specialty Pharmacy in lieu of the patient receiving a written prescription. The Specialty Pharmacy will handle all requests for refills, monitoring, education and training, etc.

DMETS Response: *DMETS agrees that a restricted distribution program will decrease the potential concern of confusion between Ventavis and Ventolin. It appears that this program will eliminate the potential for a Ventavis prescription to be dispensed as Ventolin, and vice versa, in several ways. First, prescriptions for Ventavis will not be written and given to patients to be taken to their neighborhood pharmacy. Secondly, the specialty pharmacy will only stock products that are part of a restricted distribution program. The potential for confusion at the dispensing level should not occur because these pharmacies will not stock Ventolin or Alupent. Finally, according to the sponsor, this product will only be stocked in [redacted] of these specialty pharmacies which should also help to decrease confusion.*

DMETS notes that the sponsor is voluntarily implementing this restricted distribution program. If at any time the restricted distribution program were terminated, the potential for confusion between Ventavis/Iloprost and Ventolin and Alupent will exist if Ventavis is available through retail pharmacies and in hospitals. Therefore, DMETS reiterates our concern for potential confusion if this product is distributed outside of the restricted distribution program.

2. The sponsor also indicated that Ventavis is currently marketed in three countries (Finland, Austria, and United Kingdom) [redacted] The sponsor notes that there has not been any postmarketing evidence of confusion between Ventolin and Ventavis in countries that the two products are marketed. Additionally, these countries do not use a specialized distribution program for Ventavis, therefore, both Ventolin and Ventavis are distributed in retail pharmacies.

DMETS Response: *DMETS acknowledges that the firm has not identified any postmarketing medication errors in other countries between Ventavis and Ventolin. However, we question whether there are medication error reporting programs in these countries that would capture this information. Thus, a lack of postmarketing evidence of confusion does not necessarily indicate that confusion does not occur. Additionally, based on the sponsor's statement that no confusion has occurred in Finland, Austria, and United Kingdom, DMETS assumes that the sponsor is confirming that the proprietary name 'Ventolin' is a marketed product in all of these countries. Finally, DMETS notes that differences in healthcare scenarios, dispensing, and administration of drug products in these foreign countries may make it difficult to extrapolate these results to the U.S. market.*

3. DMETS concurs with the changes made to the container label and carton labeling. However, we recommend the following additional revisions.

- 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:

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.

In summary, DMETS has no objection to the use of the proprietary name, Ventavis, as long as this product is a component of the proposed restricted distribution program. This distribution program alleviates our concern of the potential for orthographic confusion between Ventavis and Ventolin and the established name Iloprost and Alupent. However, if Ventavis is marketed via the normal distribution process (e.g., retail pharmacies, hospital pharmacies) DMETS continues to have concern that there is a potential for confusion and would not recommend use of this proprietary name. We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Sammie Beam at 301-827-2102.

**Appears This Way
On Original**

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

/s/

Carol Holquist
12/15/04 04:17:52 PM
DRUG SAFETY OFFICE REVIEWER
Signing for Denise Toyer

**Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Building Room 6-34
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: September 14, 2004

NDA NUMBER: 21-779

NAME OF PRODUCT: Ventavis
(Iloprost Inhalation Solution)
10 mcg/mL

NDA SPONSOR: CoTherix, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Cardio-Renal Drug Products for an assessment of the proposed proprietary name, Ventavis. A draft container label, carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Ventavis is a sterile solution of iloprost formulated for inhalation via a nebulizer. The pharmacological effects of iloprost after inhalation are due to the preferential vasodilatation of the pulmonary arterial bed with improvement of pulmonary artery pressure, pulmonary vascular resistance, cardiac output, and mixed venous oxygen saturation. The sponsor is seeking an indication for the treatment of pulmonary arterial hypertension in patients with NYHA Class III or IV symptoms. A maintenance dose of 5 mcg should be administered via a nebulizer system with a dosing frequency of up to 6 to 9 times a day according to the individuals' need and tolerability. The maximum daily dose evaluated in clinical studies was 45 mcg.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1, 2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to "Ventavis" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark electronic search system (TESS)

¹ MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, 2004, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the DMETS database of proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

was conducted.⁴ The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted prescription analysis studies, involving health care practitioners within FDA. These exercises were conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the names.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Ventavis". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Ventavis acceptable from a promotional perspective.
2. The Expert Panel identified two proprietary names that were thought to have the potential for confusion with the proposed proprietary name "Ventavis", and one proprietary name that was thought to have the potential for confusion with the established name "Iloprost". These products are listed in Table 1 (see below), along with the dosage form available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Proprietary Name	Established name, Dosage Form(s), and Strength(s)	Usual adult dose*	Other**
Iloprost	Iloprost, Inhalation Solution, 10 mcg/ml	Inhale 5 mcg via a nebulizer system 6 to 9 times per day during waking hours. (Maximum daily dose evaluated was 45 mcg) Use contents of one ampule for each inhalation session.	
Ventolin	Albuterol, Aerosol, Metered, Inhalation, 90 mcg/inhalation Inhalation Solution, 0.083% and 0.5%	Aerosol: Inhale 2 puffs every 4 to 6 hours. Inhalation Solution: Administer 2.5 mg 3 to 4 times a day via a nebulizer. (Ventolin Inhalation Solution has been discontinued)	SA/LA
Restasis	Cyclosporine, Emulsion, Ophthalmic, 0.05%	Instill 1 drop every 12 hours.	SA/LA
Alupent	Metaproterenol Sulfate, Aerosol, Metered, Inhalation, 0.65 mg/inhalation, Inhalation Solution, 0.4%, 0.6% and 5%	Aerosol: Inhale 2 to 3 puffs every 3 to 4 hours. Do not exceed 12 inhalations/day. Inhalation Solution: Use 0.2 mL or 0.3 mL of the 5% solution via IPPB or nebulizer 3 to 4 times a day. Dilute with 2.5 mL of saline or other diluent.	LA to established name Iloprost

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

⁴ WWW location <http://www.uspto.gov/main/trademarks.htm>

⁵ Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

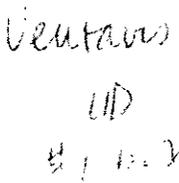
B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names identified in POCA that were considered to have significant phonetic or orthographic similarities to Ventavis were discussed by the Expert Panel.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of "Ventavis" with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses) for each proposed proprietary name. These exercises were conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for "Ventavis". These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via email. In addition, outpatient orders were recorded on voice mail and included an order for "Ventavis". The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTIONS:	VERBAL PRESCRIPTION:
<p><i>Outpatient:</i></p>  <p>Ventavis UD #1000</p>	<p><i>Outpatient:</i></p> <p>Ventavis 1 box Use as directed With 3 refills</p>
<p><i>Inpatient:</i></p>  <p>Start Ventavis on the following days. The physician should start the following</p>	

2. Results:

None of the interpretations of the proposed name was an exact match with any currently marketed U.S. product. However, two respondents in the handwritten prescription studies interpreted the names as "Ventarin", which may look similar to Ventolin. See Attachment A for the complete listing of interpretations from the verbal and written prescription studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proposed proprietary name "Ventavis", the primary concerns related to the potential for look-alike and sound-alike confusion with Ventolin and Restasis. Additionally, in reviewing the proposed established name "Iloprost", the primary concern related to the potential for look-alike confusion with Alupent.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Ventavis.

1. Ventolin was identified to have sound and look-alike similarities to the proposed name, Ventavis. Ventolin contains the active ingredient albuterol and is indicated for the relief and prevention of bronchospasm in patients with reversible obstructive airway disease. Both names consist of three syllables and each syllable can be enunciated with a similar phonetic length. The first syllable of each name consists of exactly the same letters and therefore the first syllable can be enunciated in exactly the same manner. The second syllable of each name only consists of either the vowel "o" or "a", and the short vowel sound in this syllable could easily be misinterpreted. Therefore, when spoken the last syllable of each name must be clearly enunciated to differentiate the names. Also, each name consists of 8 letters, and five of the eight letters are the same and appear in the same corresponding positions. Therefore, when scripted the letters that appear in the fifth, sixth, and eighth positions must be clearly written to differentiate the names. The proprietary name Ventolin has been used to market an inhalation aerosol, inhalation solution, inhalation capsule, syrup, and tablet dosage formulations of albuterol sulfate. However, the proprietary name Ventolin is currently only used to market the aerosol dosage formulations of albuterol sulfate. Even though Ventolin inhalation solution is no longer marketed, physicians can still write orders for Ventolin inhalation solution. It is a well known proprietary name, and healthcare professionals would normally interpret an order for Ventolin inhalation solution as an order for albuterol sulfate inhalation solution. Many healthcare professionals may not even be aware that Ventolin inhalation solution has been discontinued, since these orders would normally be dispensed with a generic albuterol sulfate inhalation solution. Therefore, DMETS has decided it would be prudent to not only evaluate the potential for confusion between Ventavis inhalation solution and Ventolin inhalation aerosol, but also the potential for confusion between Ventavis inhalation solution and Ventolin inhalation solution. An evaluation of Ventavis inhalation solution and Ventolin inhalation aerosol indicates the products differ in their product strength (10 mcg/mL vs. 90 mcg/activation), usual dose (5 mcg vs. 2 inhalations or puffs), frequency of administration (up to 6 to 9 times a day vs. every 4 to 6 hours),

dosage formulation (solution vs. aerosol) and packaging configuration (ampule vs. inhaler). An order for a Ventolin inhalation aerosol may also include the abbreviation MDI to indicate a "multi-dose inhaler" or the modifier HFA to identify an inhaler with a non-chlorofluorocarbon propellant. However, if a nonspecific outpatient prescription is communicated as,

"Vent---,
Use as directed,
1 box",

then a pharmacist could interpret the order for 1 box of Ventavis inhalation solution, or 1 box containing a Ventolin inhaler. Orders that only consist of nonspecific information and initially seem acceptable, could be interpreted differently by pharmacists, and therefore increase the risk of confusion and medication errors involving Ventavis and Ventolin.

An evaluation of Ventavis inhalation solution and Ventolin inhalation solution indicates the products can share similar characteristics in the dosage (initial dose 2.5 mcg vs. 2.5 mg) or (1 ampule vs. 1 vial), the route of administration (oral, via nebulizer), dosage formulation (inhalation solution), and packaging configuration (unit dose ampules or vials). Although the maintenance dose of Ventavis should be 5 mcg, the initial dose should be only 2.5 mcg. Therefore, if the initial dosage is communicated on an order, then the dosage may not aid in differentiating the products, because of the overlapping numerals, 2.5, and similarity between the abbreviations for the units, microgram versus milligram, (mcg vs. mg). On outpatient prescriptions, physicians could communicate the dosage as 1 ampule/vial, without actually indicating the dose in milligrams or micrograms. Healthcare professionals commonly use the terms, ampule and vial interchangeably when prescribing inhalation solution products. Thus, the incorrect use of either term to identify a unit of medication per the manufacturer's labeling would normally not aid healthcare professionals to differentiate products. Albuterol sulfate inhalation solution is available in two concentrations, 0.083% and 0.5%. If the concentration is included on orders for albuterol sulfate inhalation solution, then the concentration should aid in differentiating the products Ventavis and Ventolin. However, if the concentration is not included on an order for Ventolin, then a pharmacist can safely dispense the medication without contacting the physician. A pharmacist can decide which concentration to dispense based upon the patient's age. The pharmacist is also assured that each product contains the same amount of medication, 2.5 mg of albuterol. This is because the different concentrations, 0.083% and 0.5%, of albuterol sulfate inhalation solution are in unit dose vials containing different volumes of solution, 3 mL vs. 0.5 mL, respectively. The most distinguishing characteristic that may aid in differentiating the products is the frequency of administration. Ventavis may be administered more frequently than Ventolin (6 to 9 times a day vs. 3 to 4 times a day). However, if Ventavis is only ordered with a frequency of as needed, or as directed, then the frequency of administration may not aid in differentiating the products. Therefore, DMETS is concerned if outpatient prescriptions are communicated as,

"Vent---
Use 1 ampule/vial as directed or
as needed via nebulizer
Dispense 120 vials",

then there is an increased risk of confusion and medication errors involving Ventavis and Ventolin inhalation solutions. In conclusion, DMETS believes that the sound and look-alike similarities in the names, in addition to the aforementioned product and outpatient prescription similarities increase the potential risk of a medication error involving Ventavis and Ventolin.

avis
olin

Ventavis Inh. Sol.
Ventolin Inh. Sol.

2. Restasis was identified to have sound and look-alike similarities to the proposed name, Ventavis. Restasis is a cyclosporine ophthalmic emulsion product, and is indicated to increase tear production in patients whose tear production has been suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. When spoken the second and third syllable of each name, "stasis" and "tavis", can sound similar and possess a rhyming quality. However, when spoken the first syllable of each name, "Re" vs. "Ven" can sound different and aid in differentiating the names. Each name consists of 8 letters, and five of the eight letters that appear in corresponding positions are exactly the same. Therefore, when scripted the letters that appear in the first, third, and sixth positions must be clearly written to differentiate the names. However, these medications have differentiating product characteristics. Restasis and Ventavis have different product strengths (0.05% vs. 10 mcg/mL), indication for use (tear production vs. pulmonary arterial hypertension), usual dose (one drop vs. 5 mcg), frequency of administration (twice a day –approximately 12 hours apart vs. up to 6 to 9 times a day), route of administration (topical vs. oral via a nebulizer), and the dosage formulation (ophthalmic emulsion vs. inhalation solution). The different product characteristics of the medications should decrease the potential risk of a medication error involving these two products.

Ventavis
Restasis

restasis
ventavis

3. Alupent was identified to have look-alike similarities to the proposed established name, Iloprost. Alupent contains the active ingredient metaproterenol sulfate, and is indicated for bronchial asthma and reversible bronchospasm that may occur in association with bronchitis and emphysema. When scripted both names possess a similar length even though the name Iloprost contains one more letter than the name Alupent. Also each name contains the letters, "l", "p" and "t", and these letters which can appear either above or below the other lower case letters are located at similar positions within the

two names. Therefore, the other lower case letters must be clearly scripted to differentiate the names. Alupent and Iloprost inhalation solutions could share similar or overlapping characteristics in the dosage (1 ampule vs. 1 vial), dosage formulation (inhalation solution), route of administration (oral, via a nebulizer), and packaging configuration (unit dose ampules or vials). Both products could share similar directions of use (Use 1 vial x times a day as needed via a nebulizer) and the quantity to be dispensed (#120 vials/ampules). However, Alupent and Iloprost inhalation solutions have different product strengths (0.4%, 0.6%, and 5% vs. 10 mcg/mL), and frequency of administration (3 to 4 times vs. up to 9 times). These two product characteristics could aid in differentiating the products on an outpatient prescription. However, DMETS is concerned if the product strength is omitted on a written prescription for Alupent, then healthcare professionals may misinterpret the name of the medication. For example, if an outpatient prescription is scripted as,

“Alupent inhalation solution
Use 1 ampule/vial as directed
as needed via nebulizer
120 vials”,

then a pharmacist could misinterpret the name as Iloprost. Additionally, practitioners may commonly script Iloprost inhalation solution prescriptions without the product strength, since practitioners may not feel this information is necessary to identify the product. DMETS is also concerned if a nonspecific outpatient prescription is scripted as,

“Alupent/Iloprost,
Use as directed,
1 box”,

then a pharmacist could interpret the order for 1 box of Iloprost inhalation solution, or 1 box containing a Alupent inhaler. An Alupent inhaler prescription may also not include the product strength, since practitioners may not feel this information is necessary to correctly identify the product. Orders that only consist of nonspecific information and initially seem acceptable, could be interpreted differently by pharmacists, and therefore increase the risk of confusion and medication errors involving Iloprost and Alupent. Thus, DMETS believes that the look-alike similarities between the established name Iloprost and proprietary name Alupent, increase the potential risk for medication errors involving Iloprost inhalation solution and both Alupent inhalation solution and Alupent inhalers.

Alupent
Iloprost



III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary name Ventavis. In reviewing the proprietary name, the primary concerns related to sound and look-alike potential for confusion with the proprietary name, Ventolin.

A. Sound-alike and Look-alike Concerns:

Ventolin was identified to have sound and look-alike similarities to the proposed name, Ventavis. Ventolin contains the active ingredient albuterol and is indicated for the relief and prevention of bronchospasm in patients with reversible obstructive airway disease. Both names consist of three syllables and each syllable can be enunciated with a similar phonetic length. The first syllable of each name consists of exactly the same letters and therefore the first syllable can be enunciated in exactly the same manner. The second syllable of each name only consists of either the vowel "o" or "a", and the short vowel sound in this syllable could easily be misinterpreted. Therefore, when spoken the last syllable of each name must be clearly enunciated to differentiate the names. Also, each name consists of 8 letters, and five of the eight letters are the same and appear in the same corresponding positions. Therefore, when scripted the letters that appear in the fifth, sixth, and eighth positions must be clearly written to differentiate the names. The proprietary name Ventolin has been used to market an inhalation aerosol, inhalation solution, inhalation capsule, syrup, and tablet dosage formulations of albuterol sulfate. However, the proprietary name Ventolin is currently only used to market the aerosol dosage formulations of albuterol sulfate. Even though Ventolin inhalation solution is no longer marketed, physicians can still write orders for Ventolin inhalation solution. It is a well known proprietary name, and healthcare professionals would normally interpret an order for Ventolin inhalation solution as an order for albuterol sulfate inhalation solution. Many healthcare professionals may not even be aware that Ventolin inhalation solution has been discontinued, since these orders would normally be dispensed with a generic albuterol sulfate inhalation solution. Therefore, DMETS has decided it would be prudent to not only evaluate the potential for confusion between Ventavis inhalation solution and Ventolin inhalation aerosol, but also the potential for confusion between Ventavis inhalation solution and Ventolin inhalation solution. An evaluation of Ventavis inhalation solution and Ventolin inhalation aerosol indicates the products differ in their product strength (10 mcg/mL vs. 90 mcg/activation), usual dose (5 mcg vs. 2 inhalations or puffs), frequency of administration (up to 6 to 9 times a day vs. every 4 to 6 hours), dosage formulation (solution vs. aerosol) and packaging configuration (ampule vs. inhaler). An order for a Ventolin inhalation aerosol may also include the abbreviation MDI to indicate a "multi-dose inhaler" or the modifier HFA to identify an inhaler with a non-chlorofluorocarbon propellant. However, if a nonspecific outpatient prescription is communicated as,

"Vent---,
Use as directed,
1 box",

then a pharmacist could interpret the order for 1 box of Ventavis inhalation solution, or 1 box containing a Ventolin inhaler. Orders that only consist of nonspecific information and initially seem acceptable, could be interpreted differently by pharmacists, and therefore increase the risk of confusion and medication errors involving Ventavis and Ventolin.

An evaluation of Ventavis inhalation solution and Ventolin inhalation solution indicates the products can share similar characteristics in the dosage (initial dose 2.5 mcg vs. 2.5 mg) or (1 ampule vs. 1 vial), the route of administration (oral, via nebulizer), dosage formulation (inhalation solution), and packaging configuration (unit dose ampules or vials). Although the maintenance dose of Ventavis should be 5 mcg, the initial dose should be only 2.5 mcg. Therefore, if the initial dosage is communicated on an order, then the dosage may not aid in differentiating the products, because of the overlapping numerals, 2.5, and similarity between the abbreviations for the units, microgram versus milligram, (mcg vs. mg). On outpatient prescriptions, physicians could communicate the dosage as 1 ampule/vial, without actually indicating the dose in milligrams or micrograms. Healthcare professionals commonly use the terms, ampule and vial interchangeably when prescribing inhalation solution products. Thus, the incorrect use of either term to identify a unit of medication per the manufacturer's labeling would normally not aid healthcare professionals to differentiate products. Albuterol sulfate inhalation solution is available in two concentrations, 0.083% and 0.5%. If the concentration is included on orders for albuterol sulfate inhalation solution, then the concentration should aid in differentiating the products Ventavis and Ventolin. However, if the concentration is not included on an order for Ventolin, then a pharmacist can safely dispense the medication without contacting the physician. A pharmacist can decide which concentration to dispense based upon the patient's age. The pharmacist is also assured that each product contains the same amount of medication, 2.5 mg of albuterol. This is because the different concentrations, 0.083% and 0.5%, of albuterol sulfate inhalation solution are in unit dose vials containing different volumes of solution, 3 mL vs. 0.5 mL, respectively. The most distinguishing characteristic that may aid in differentiating the products is the frequency of administration. Ventavis may be administered more frequently than Ventolin (6 to 9 times a day vs. 3 to 4 times a day). However, if Ventavis is only ordered with a frequency of as needed, or as directed, then the frequency of administration may not aid in differentiating the products. Therefore, DMETS is concerned if outpatient prescriptions are communicated as,

"Vent---
Use 1 ampule/vial as directed or
as needed via nebulizer
Dispense 120 vials",

then there is an increased risk of confusion and medication errors involving Ventavis and Ventolin inhalation solutions. In conclusion, DMETS believes that the sound and look-alike similarities in the names, in addition to the aforementioned product and outpatient prescription similarities increase the potential risk of a medication error involving Ventavis and Ventolin.

Ventavis
Ventolin

Ventavis Lab. Sol.
Ventolin Lab. Sol.

B. Labeling, Packaging, and Safety Related Issues:

In the review of the container label, carton and insert labeling of Ventavis, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following improvements, which might minimize potential user error.

1. CONTAINER LABEL (Ampule)

- a. DMETS suggests that the dosage formulation should appear in the parentheses as part of the established name to read "Iloprost Inhalation Solution".
- b. Please ensure that the established name appears with at least half the prominence as the proprietary name after accounting for differences such as font style, size, and print color.
- c. DMETS suggests that the total drug content and the product strength should be presented directly under the established name utilizing two different lines and within a box or border with the same color background. DMETS suggests the total drug content be the primary expression of strength followed immediately by the concentration per mL. For example,

20 mcg/2 mL (10 mcg/mL)
--

Expressing the total drug content and product strength in this manner may help prevent practitioners from misinterpreting the total drug content of a drug product. Medication errors can occur when a user or practitioner reads the product strength (e.g., 10 mcg/mL), but fails to read or calculate the total drug content.

2. CARTON LABEL

- a. See comments 1a. – 1c.

b. []

c. []

- d. In the "Storage" section, DMETS recommends that the present wording should be revised to include an actual storage temperature range for the product in both degrees Celsius and Fahrenheit.

3. INSERT LABELING

- a. DMETS recommends increasing the prominence of the proprietary and established names. Please ensure that the established name appears with at least half the prominence as the proprietary name.

- b. DMETS recommends replacing the abbreviation “ μg ” with the abbreviation “mcg” for micrograms. Post-marketing error reports have shown the abbreviation “ μg ” has been misinterpreted as an abbreviation for “mg” or milligrams.
- c. The first sentence in the “Description” section presents the product strength as an expression of the salt, 10 mcg/mL iloprost tromethamine, but the rest of the labeling indicates the product strength is expressed based on the active moiety, 10 mcg/mL iloprost. Please revise accordingly.
- d. The following comments pertain to the “Dosage and Administration” section:
 - i. DMETS recommends that guidance should be provide on the minimum dosing interval in which a patient may be able to safely repeat their dose (e.g., every 30 minutes, or every hour).
 - ii. DMETS recommends that directions should be included for the user concerning the proper technique and procedure that should be followed to safely open, empty and discard the glass ampules of iloprost inhalation solution.
- e. In the “Description” and “How Supplied” sections, DMETS suggests removing the reference to the actual size of the glass ampule, 3 mL. Removal of this reference should aid in decreasing the risk of confusion between the size of the ampule, (3 mL), and the total volume in the vial, (2 mL).
- f. In the “Stability and Storage” section, DMETS recommends that the present wording should be revised to include an actual storage temperature range for the product in both degrees Celsius and Fahrenheit.

**Appears This Way
On Original**

IV. RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name "Ventavis". In addition, DMETS is concerned with the potential risk of confusion and medication errors involving the established name, Iloprost.
2. DMETS recommends consulting David B. Lewis, FDA representative to the USAN council concerning the potential risk of confusion and medication errors involving the established name, Iloprost, and the proprietary name, Alupent.
3. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review that might lead to safer use of the product.
4. DDMAC finds the proprietary name, "Ventavis" acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

/S/

Scott Dallas, R.Ph.
Safety Evaluator
Office of Drug Safety (DMETS)

Attachment A:

Prescription Study Results for the proposed name "Ventavis"

Inpatient Written Prescription	Outpatient Written Prescription	Outpatient Verbal Prescription
Ventanis	Ventabiz	Fentavix
Ventarin	Ventarin	Ventabis
Ventaris	Ventavis	Venta-bis
Ventaris	Ventavis	Ventahist
Ventaris	Ventavis	Ventanist
Ventaris	Ventavis	Ventavis
Ventaris	Ventavis	Ventifis
Ventarus	Ventavis	Ventivist
Ventarus	Ventavis	Ventobids
Ventavis	Ventavis	Ventobis
Ventavis	Ventavis	Ventolix
Ventavis	Ventavis	Zenazbis
Ventavis	Ventavis	Zentabis or Ventalis or Ventabis
Ventavis	Ventavis	Zentavis
Ventavis	Ventavis	Zentaviss
Vintaris	Ventavis	
Vintavis	Veutavis	

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

/s/

Scott Dallas
10/28/04 09:04:16 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
10/28/04 09:59:58 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
10/28/04 10:06:04 AM
DRUG SAFETY OFFICE REVIEWER

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION**



US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to: CDER, DCRDP (HFD-110); 5600 Fishers Lane; Rockville, MD 20857

Transmitted to FAX Number: 650-808-6899

Attention: Klara Dickinson

Company Name: CoTherix, Inc.

Phone: 650-808-6518

Subject: Confirmation of 12/2/04 Teleconference

Date: 10/28/04

Pages including this sheet: 2

From: Melissa Robb

Phone: 301-594-5313

Fax: 301-594-5494

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

Confirmation of Teleconference

Drug: Ventavis (Iloprost) Inhalation Solution
NDA: 21-779
Sponsor: CoTherix, Inc.

Date Requested: October 25, 2004
Date Confirmation Faxed: October 28, 2004

Type: Guidance
Classification: C

Teleconference Date: December 2, 2004
Teleconference Time: 1:30 PM

FDA Participants:

Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardio-Renal Drug Products, HFD-110
Thomas Marciniak, M.D.	Acting Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Clinical, HFD-110
Maryann Gordon, M.D.	Medical Officer, HFD-110
Melissa Robb	Regulatory Health Project Manager, HFD-110

- **PLEASE SUBMIT 5 DESK COPIES OF YOUR BRIEFING DOCUMENT (IN ADDITION TO THE ARCHIVAL COPY)**
- **PLEASE PROVIDE ME WITH A LIST OF ATTENDEES AND A CALL IN NUMBER, NO LATER THAN ONE DAY BEFORE THE MEETING**

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

/s/

Melissa Robb
10/28/04 08:04:34 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

9/10/04

FILING COMMUNICATION

NDA 21-779

CoTherix, Inc.
Attention: Ms. Klara A. Dickinson
5000 Shoreline Court, Suite 101
South San Francisco, CA 94080

Dear Ms. Dickinson:

Please refer to your June 30, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ventavis® (iloprost) Inhalation Solution.

We also refer to your submissions dated July 15, 20, August 6, 10, 18, and September 8, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on August 29, 2004 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, please contact:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 594-5313

Sincerely,


{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Edward Fromm

9/10/04 01:30:24 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

8/16/04

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-779

CoTherix, Inc.
Attention: Ms. Klara A. Dickinson
5000 Shoreline Court, Suite 101
South San Francisco, CA 94080

Dear Ms. Dickinson:

Please refer to your pending new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ventavis (iloprost) Inhalation Solution.

We also refer to our acknowledgment letter dated July 14, 2004, that stated the drug review priority classification for this application would be standard (S).

Our policy regarding determination of priority or standard review status is based on the proposed indication and alternative treatment marketed for the proposed indication. Upon further consideration of your application, we have concluded that this application should receive a priority (P) review. The new user fee goal date is December 31, 2004.

If you have any questions, please call:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

{See ^{ES/}appended electronic signature page}

Edward Fromm
Acting Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Edward Fromm

8/16/04 08:49:03 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

7/14/04
Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-779

CoTherix, Inc.
Attention: Ms. Klara A. Dickinson
5000 Shoreline Court, Suite 101
South San Francisco, CA 94080

Dear Ms. Dickinson:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Ventavis® (iloprost) Inhalation Solution
Review Priority Classification:	Standard (S)
Date of Application:	June 30, 2004
Date of Receipt:	June 30, 2004
Our Reference Number:	NDA 21-779

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 29, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 30, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application. Accordingly, pediatric studies are deferred for your application under 21 CFR 314.55 until 3 years from the date of this letter. However, agreement with the Division on a plan to study Ventavis in pediatric patients must be reached within 6 months from the date of this letter.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please call:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 594-5313

Sincerely,


{See appended electronic signature page}

Edward Fromm
Acting Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Edward Fromm
7/14/04 02:53:43 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA #: 21,779

Trade Name: Ventavis
Generic Name: Iloprost
Strengths: 10 mcg/mL Inhalation solution

Applicant: CoTherix, Inc.

Date of Application: June 30, 2004
Date of Receipt: June 30, 2004
Date clock started after UN: N/A
Date of Filing Meeting: August 13, 2004
Filing Date: August 29, 2004
Action Goal Date (optional): User Fee Goal Date: April 30, 2005

Indication(s) requested: treatment of pulmonary arterial hypertension in patients with New York Heart Association (NYHA) Class III or IV symptoms . 1

Type of Original NDA: (b)(1) (b)(2)
OR
Type of Supplement: (b)(1) (b)(2)

NOTE:

- (1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.
- (2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:
 NDA is a (b)(1) application OR NDA is a (b)(2) application

Therapeutic Classification: S P
Resubmission after withdrawal? N/A Resubmission after refuse to file? N/A
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.) applicant, review pending

Form 3397 (User Fee Cover Sheet) submitted: YES

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health): applied, review pending for small business

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx to OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the

product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? NO
If yes, explain:
- Does another drug have orphan drug exclusivity for the same indication? YES
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? NO
If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).
- Is the application affected by the Application Integrity Policy (AIP)? NO
If yes, explain.
- If yes, has OC/DMPQ been notified of the submission? N/A
- Does the submission contain an accurate comprehensive index? YES
- Was form 356h included with an authorized signature? YES
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES
If no, explain:
- If an electronic NDA, does it follow the Guidance? YES
If an electronic NDA, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?
Entire application
- Additional comments:
- If in Common Technical Document format, does it follow the guidance? YES
- Is it an electronic CTD? NO
If an electronic CTD, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?
Additional comments:
- Patent information submitted on form FDA 3542a? YES
- Exclusivity requested? YES, 5 years

NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Financial Disclosure forms included with authorized signature? YES
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? YES
If not, have the Document Room make the corrections.
- List referenced IND numbers: 65,820
- End-of-Phase 2 Meeting(s)? NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? May 12, 2004, CMC
If yes, distribute minutes before filing meeting. May 13, 2004

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A
- Has DOTCDP been notified of the OTC switch application? N/A

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES
If no, did applicant submit a complete environmental assessment? N/A
If EA submitted, consulted to Florian Zielinski (HFD-357)? N/A
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? N/A

**Appears This Way
On Original**

ATTACHMENT

MEMO OF FILING MEETING

NDA: 21,779; Ventavis (Iloprost) Inhalation Solution

DATE: August 13, 2004

BACKGROUND:

Iloprost, a prostacyclin analog, is currently approved as Ilomedin for intravenous administration in approximately 30 countries worldwide for the treatment of occlusive arterial disease. Ventavis is an inhalation solution developed by Schering AG, Germany, for the treatment of pulmonary hypertension. The rationale for the inhaled route of administration is to provide high local concentrations, while minimizing the systemic side effects of prostacyclin therapy and avoiding the complications of chronic indwelling catheters. Ventavis was approved in the European Union in September 2003. The sponsor submitted a NDA on June 30, 2004 requesting approval for the treatment of Pulmonary Arterial Hypertension (PAH) in patients with New York Heart Association (NYHA) Class III or IV symptoms. □ □

ATTENDEES:

Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardio-Renal Drug Products
Tom Marciniak, M.D.	Acting Deputy Director, Division of Cardio-Renal Drug Products
Abraham Karkowsky, M.D., Ph.D.	Medical Team Leader
Maryann Gordon, M.D.	Medical Officer
Valeria Freidlin, Ph.D.	Statistician
Kasturi Srinivasachar, Ph.D.	Chemistry Team Leader
Monica Cooper, Ph.D.	Chemist
Jim Willard, Ph.D.	Pharmacologist
Nhi Beasley, Pharm.D.	Clinical Pharmacology and Biopharmaceutics Reviewer
Robert Shibuya, Ph.D.	DSI

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>	<u>Review Due</u>
Medical:	Maryann Gordon, M.D.	15-Nov-04
Statistical:	Valeria Freidlin, Ph.D.	1-Nov-04
Pharmacology:	Jim Willard, Ph.D.	1-Nov-04
Chemistry:	Monica Cooper, Ph.D.	15-Nov-04
Biopharmaceutical:	Nhi Beasley, Pharm.D.	15-Nov-04
Regulatory Health Project Management:	Melissa Robb	

Per reviewers, are all parts in English or English translation? YES
If no, explain:

CLINICAL FILE X _____ REFUSE TO FILE _____

• Clinical site inspection needed: YES

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

/s/

Russell Fortney
8/18/04 11:06:28 AM

6/12/04

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST		
NDA 21-779	Efficacy Supplement Type SE-	Supplement Number
Drug: Ventavis (iloprost) Inhalation Solution		Applicant: CoTherix, Inc.
RPM: Melissa Robb		HFD-110 Phone # 301-594-5313
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
❖ Application Classifications:		
• Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
• Chem class (NDAs only)		1
• Other (e.g., orphan, OTC)		Orphan
❖ User Fee Goal Dates		December 31, 2004
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
• User Fee		<input type="checkbox"/> Paid UF ID number N/A
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify) N/A
• User Fee exception		<input checked="" type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated	() None (X) Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	X DDMAC 11/18/04; 12/21/04 DMETS 10/28/04; 12/15/04 DSRCS 12/16/04
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	X
• Reviews	CMC 12/3/04; 12/17/04 DMETS 10/28/04; 12/15/04
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	X 5/12/04(CMC) 5/13/04
• Pre-Approval Safety Conference (indicate date; approvals only)	X 11/18/04
• Other	N/A
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	Office Director 12/28/04 Medical Team Leader 12/23/04
CMC Information	
❖ Clinical review(s) (indicate date for each review)	X 11/12/04
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	X See Clinical Review 11/12/04
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	N/A- Orphan
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	X 10/27/04
❖ Biopharmaceutical review(s) (indicate date for each review)	X 12/1/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X 12/20/04
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	X 12/3/04, 12/17/04
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	12/3/04
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	X 12/9/04
❖ Facilities inspection (provide EER report)	Date completed: 12/13/04 (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed (X) Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	X 12/14/04
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	X 11/9/04
❖ CAC/ECAC report	X 10/26/04

May 13, 2004

Sponsor: CoTherix, Inc.
Drug: Ventavis (Iloprost) Inhalation Solution
Pre-IND: 65, 820

Date Requested: March 15, 2004
Date Confirmation Faxed: March 19, 2004

Type: Pre-NDA
Classification: B

FDA Participants:

Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardio-Renal Drug Products, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Acting Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Thomas Marciniak, M.D.	Team Leader, Clinical, HFD-110
Maryann Gordon, M.D.	Medical Officer, HFD-110
Elena Mishina, Ph.D.	Pharmacokineticist, HFD-860
Albert DeFelice, Ph.D.	Team Leader, Pharmacology, HFD-110
James Willard, Ph.D.	Pharmacologist, HFD-110
John Lawrence, Ph.D.	Statistician, HFD-710
Melissa Robb	Regulatory Health Project Manager, HFD-110

CoTherix Participants:

James Pennington, M.D.	Chief Medical Officer
Henry Hsu, M.D.	Vice President, Clinical Research
Curtis Ruegg, Ph.D.	Senior Vice President, Technical Operations
Robert Van Dyke, M.S.	Senior Director, Technical Operations
Klara Dickinson	Director, Regulatory Affairs
Daven Mody, Pharm.D., MBA	Senior Associate, Regulatory Affairs
Crystal Browning	Associate, Regulatory Affairs
Keith Nolop, M.D.	Vice President, Clinical Research

Background:

Iloprost, a prostacyclin analog, is currently approved as Ilomedin for intravenous administration in approximately 30 countries worldwide for the treatment of occlusive arterial disease. Ventavis is an inhalation solution developed by Schering AG, Germany, for the treatment of pulmonary hypertension. The rationale for the inhaled route of administration is to provide high local concentrations, while minimizing the systemic side effects of prostacyclin therapy and avoiding the complications of chronic indwelling catheters. Ventavis was approved in the European Union in September 2003. The sponsor and the Division had a pre-IND meeting on November 20, 2003. The sponsor requested this meeting to discuss and agree upon the content and format of the New Drug Application (NDA) for Ventavis (iloprost) inhalation solution.

Meeting:

Questions:

Efficacy:

1. A summary of efficacy will be provided in Module 2.7.3. Because there is a single, pivotal trial supporting efficacy, a formal Integrated Summary of Efficacy will not be provided in Module 5. Does the FDA concur with this approach?

The Division agreed.

2. Will the plan for the Efficacy Summary (Module 2.7.3), as outlined in Section 8.2.2 and Appendix 3 of this briefing package, support the proposed indication statement "the treatment of pulmonary arterial hypertension in patients with New York Heart Association Class III and IV symptoms. [

]]

The Division believes that based on the nature of the trial performed and dependent on the data reviewed, the proposed indication is possible.

3. Our intent is to provide additional analyses of the 6-minute walk test results (see Appendix 3) since this is a key variable used in similar applications. Is this approach acceptable?

The Division agreed.

Safety:

1. As discussed and previously agreed with the Division, in addition to providing the data from the inhaled clinical trials, CoTherix will provide safety data from controlled clinical trials conducted with the oral and IV iloprost formulations. As summarized in Section 8.2.3 of this briefing package, the Integrated Summary of Safety (ISS) will be composed of subjects receiving inhaled iloprost and oral iloprost. Due to CoTherix's inability to obtain complete study reports and/or case report forms for some of the IV clinical trials, the IV clinical studies will not be integrated into the ISS; rather the serious adverse events from these studies will be summarized. For each, CoTherix will provide the study synopsis and relevant publication, if any, rather than the study reports. Is this approach acceptable?

Dr. Stockbridge inquired if the sponsor plans on analyzing the data separately by mode of delivery. The sponsor confirmed this is their intent. Dr. Stockbridge requested clarification of what information will be provided on the intravenous formulation. The sponsor stated they planned only to include data collected from controlled studies of 4 weeks or greater duration. This would include data from approximately 450 patients receiving the drug. The shorter term exposures the sponsor does not plan to include. Dr. Stockbridge expressed concern that this may include information not available in other places, such as special patient populations or dose ranges not evaluated elsewhere. The sponsor stated that most of the short term intravenous trials were early Phase 2 trials in the patient population (occlusive arterial disease). The sponsor added that data on similar populations is available in the oral database. Dr. Stockbridge concluded by stating that he will defer answering this question until he is aware of what data would be excluded from the application. The sponsor will submit a summary of these short term intravenous studies for the Division to review. Dr. Karkowsky added that sometimes better monitoring, i.e. ECG, is performed in shorter trials. The sponsor stated their definitive QTc trial is ongoing.

2. Is the ISS Statistical Analysis Plan (SAP) (See Appendix 4) appropriate and sufficient to support the proposed label for the treatment of pulmonary arterial hypertension in patients with New York Heart Association Class III and IV symptoms. [

]]

The Division agreed.

3. Does the FDA agree with the overall ISS pooling strategy, as outlined in the SAP in Appendix 4?

The Division agreed.

4. A summary of safety will be provided in Module 2.7.4 and the ISS will be provided in Module 5, Section 5.3.5.3 *Reports of Analyses of Data from More than One Study*. Is this an acceptable approach?

The Division agreed.

Case Report Forms and Case Report Tabulations:

1. Case Report Forms (CRFs) will be provided for the deaths, SAEs, and discontinuations due to adverse events (AEs). CoTherix proposes to file CRFs from the three inhaled clinical trials and make available upon request, the CRFs from the 15 oral clinical trials being filed to support safety. Is this approach acceptable?

The Division inquired about the CRFs from the intravenous trials. The sponsor stated that not all of the CRFs are available from the intravenous trials. The sponsor can try to locate as many as possible. Dr. Stockbridge stated the Division would like to know up front which CRFs the sponsor would not be able to provide. In addition, the Division would like the sponsor to commit to a time frame for submitting CRFs when requested for review. The sponsor stated that CRFs would be provided within 30 days of the request from the Division. Dr. Stockbridge stated that would be acceptable.

2. The CRFs will be provided electronically, and bookmarked according to the Guidance for Industry: Providing Regulatory Submissions in Electronic Format-NDAs. The CRFs are in English. However, there are selected pages of the CRF that are in a foreign language. For CRF pages that are in a foreign language, the link will be made back to an English sample CRF or a translated page will be provided. Is this approach acceptable?

The Division agreed.

3. Section 8.3.3.2 of this briefing package outlines the SAS datasets that will be provided electronically. Are the proposed datasets, their format, and content acceptable?

The sponsor clarified that this table was located on page 63 of the briefing package. The sponsor confirmed that the oral and inhaled safety databases will be identical in structure. The other databases will be as similar as possible, depending on data collected. The sponsor also confirmed that no safety data will be included with the individual study reports. The Division believed this plan was acceptable.

4. References will be provided in Module 5, Section 5.4 Literature References. CoTherix proposes to provide copies of important references cited in the Clinical Summary, or individual technical reports supporting the inhaled studies, or studies supporting the PK/PD sections. References cited in the oral clinical study reports and IV synopsis will be available upon request. Is this approach acceptable?

The Division agreed. Dr. Mishina inquired if the sponsor is planning on submitting PK/PD data electronically for review. The sponsor is unsure if all that data is available electronically, but will try to get it for the submission. Dr. Mishina agreed that only the data from pivotal PK and PK/PD studies will be required.

Nonclinical:

1. Schering has created separate toxicokinetics reports with individual study report numbers that are distinct from the numbers used for the toxicology studies that they support. These toxicokinetics reports are cross-referenced to the appropriate toxicity studies in the Toxicology Narrative Summary and in the appropriate toxicity table in the CTD Nonclinical Tabulated Summaries. These toxicokinetics studies are also listed in the Pharmacokinetics Overview Table, with cross-reference information to the related toxicity studies. We propose to include the full reports of the toxicokinetics studies in the Pharmacokinetics Section of the CTD. Is this approach acceptable?

The Division agreed.

2. Discussion of the nonclinical work that has been conducted with the individual diastereoisomers of iloprost is included as a separate section near the end of each of the nonclinical narrative summaries. The supporting full reports will be included in the "Other Studies" section of each discipline (pharmacology, pharmacokinetics, or toxicology), rather than being mixed in among the studies that were conducted with iloprost drug substance. Is this approach acceptable?

The Division agreed.

3. The nonclinical narrative summaries cite references to over 50 publications. Most of these citations occur in the animal pharmacology summary. We propose to submit full copies of referenced publications from the

nonclinical summaries only. References cited in individual study reports will be available upon request. Is this approach acceptable?

The Division agreed.

The sponsor stated they did not plan on submitting datasets for the carcinogenicity studies, but would make them available, if needed, for the Division to review. The Division agreed.

Procedural:

1. In the March 9, 2004 meeting, the FDA referenced the possibility that the Ventavis® NDA could be granted priority review. CoTherix is now requesting a priority review classification for the Ventavis® NDA. Ventavis® is indicated for the treatment of pulmonary arterial hypertension (PAH), a life-threatening disease for which the life expectancy is 2.8 to 4 years. Although the current prostanoid therapies (Flolan® and Remodulin®) are safe and effective in the treatment of PAH, they do exhibit safety limitations. Intravenous therapy has been associated with a lack of pulmonary selectivity, tolerance leading to progressive increase in dose, recurrent infections of the IV catheter, and life-threatening rebound pulmonary hypertension. Subcutaneous therapy frequently causes significant pain at the catheter infusion site. The oral endothelin receptor antagonist bosentan has been associated with 3-fold liver transaminase elevations in 11% of patients and cannot be given to women during pregnancy. The inhaled route of administration of Ventavis® (iloprost) provides high local concentrations while minimizing the systemic side effects of prostacyclin therapy and avoiding the complications of indwelling catheters. Will the FDA grant priority review for the Ventavis® NDA?

Dr. Stockbridge stated that without comparator data to available therapies showing increased safety and a purely theoretical argument, it is unlikely that a priority review status would be granted. The sponsor stated that side effects seen with other treatments are not seen in their database. Additionally, since Ventavis does not use an invasive delivery mode, it does not involve the possibility of pain or infection that can be found with other prostanoid therapies currently approved. The sponsor also referred to the literature which states that due to the selective pulmonary delivery of Ventavis, no shunting occurs. The sponsor also believes that Ventavis has a better safety profile than bosentan, which has liver side effects and can not be used in pregnant patients. Dr. Stockbridge stated that the limited safety profile included with this submission makes it difficult for the Division to find rare risks. The sponsor stated they have data on approximately 1,000 patients taking the oral formulation for over one year, and 100 patients using the inhaled formulation for over one year. Dr. Stockbridge stated the Division would consider this issue at the time of filing if further arguments were included in the submission.

2. As discussed in the March 9, 2004 meeting, CoTherix will be providing the data from the definitive QTc study as a safety update following the submission of the NDA. The data will be submitted approximately 2 months following the filing of the NDA application. In addition, an update to the long-term follow-up surveillance study (ME303045) will be provided. Is the timing of the filing of this safety data acceptable?

The Division asked for clarification of the statement "approximately 2 months". The sponsor stated they would provide this data \pm 1 week. The Division stated this is acceptable.

Electronic NDA:

1. The Ventavis NDA will be filed in a CTD format as an electronic NDA, per the January 1999 Guidance for Industry: Providing Regulatory Submissions in Electronic Format-NDAs. Does the FDA find the structure of the eNDA, as provided in Appendix 2 of this briefing package acceptable?

The Division agreed.

The sponsor stated at the Pre-NDA CMC meeting held on May 12, 2004, it was decided that the information on the nebulizers, including the in vitro comparisons, would be located in the Appendix of Module 3. Dr. Stockbridge agreed with this plan.

The sponsor inquired about the status of their submission requesting a waiver for pediatric studies. Dr. Stockbridge stated that at this time, a decision has not yet been made. Dr. Stockbridge stated he is not inclined to waive a commitment for pediatric studies for drugs for which there may be some interest in pediatric use. Alternatively, according to the new Act, a deferral would require establishing a Phase 4 commitment to conduct pediatric studies, including a date for completion of studies. C

¶ Dr. Stockbridge stated that if the sponsor has not received comment back from the Division prior to submission of their NDA, they should inquire about it in the cover letter of their submission.

The final topic discussed was the Division's letter dated April 8, 2004 conveying comments on CoTherix's protocol C200-002 and the sponsor's response dated April 30, 2004. The Division had inquired about dose selection and dosing interval. The sponsor stated the dose was chosen because the main objective of this trial was safety. Therefore, they did not want to use a higher dose than that of which was used in their Phase 3 trial. Dr. Stockbridge stated the Division's concern was not with this particular study, but with the entire development program. The Division believes it is important to know what limits dose and to understand the time course of effects following dosing. Measurements at peak will not contribute to the understanding of the dosing interval. The sponsor stated that the application will include data at trough levels, including data following the overnight period without dosing.

Addendum to Minutes from the Office of Drug Safety:

- If the sponsor and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then the Sponsor is encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).
- If the NDA/BLA application includes RiskMAPs or pharmacovigilance plans and will be submitted in the Common Technical Document format, please submit as follows:
 - RiskMAPs**
 - 2.5.5 Overview of Safety with appropriate cross references to section
 - 2.7.4 Summary of Clinical Safety
 - and any other relevant sections of the Common Technical Document for the NDA/BLA application.
 - Pharmacovigilance plans**
 - 2.5.5 Overview of Safety, with any protocols for specific studies provided in 5.3.5.4 Other Clinical Study Reports or other sections as appropriate
 - (e.g., module 4 if the study is a nonclinical study).

If the application is not being submitted as a Common Technical Document, include proposed RiskMAPs in the NDA Clinical Data Section (21 CFR 314.50 (d)(5)) or BLA Clinical Data Section (21 CFR 601.25(b)(3)) and clearly label and index them.

- For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the Draft Guidance for Industry Development and Use of Risk Minimization Action Plans and the Draft Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment which can be located electronically at <http://www.fda.gov/cder/guidance/5766dft.pdf> and <http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0189-gdl0001-5767dft.doc>.
- If there is any information on product medication errors from the premarketing clinical experience, ODS requests that this information be submitted with the NDA/BLA application.
- The sponsor is encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.

Signature, minutes preparer: *{See appended electronic signature page}*

Concurrence Chair: *{See appended electronic signature page}*

Drafted: 5/14/04

Finalized: 5/25/04

RD:

Stockbridge	5/25/04
Karkowsky	5/25/04
Marciniak	5/21/04
Gordon	5/19/04
Mishina	5/19/04
DeFelice	5/18/04
Willard	5/14/04
Lawrence	5/14/04

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

/s/

Melissa Robb
5/25/04 03:28:29 PM

Norman Stockbridge
5/25/04 04:13:34 PM

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

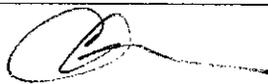
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Chris Gray-Smith	TITLE Chief Financial Officer
FIRM / ORGANIZATION CoTherix, Inc 5000 Shoreline Court, South San Francisco, CA 94080	
SIGNATURE 	DATE 6/14/04

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Withheld

6

**page(s) of trade
secret
and/or confidential
commercial
information**

(b4)

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated as a clinical investigator in the submitted study _____, is submitted in accordance with 21 CFR part _____.

Name of clinical investigator

Name of clinical study

_____ is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

any proprietary interest in the product tested in the covered study held by the clinical investigator;

any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Chris Gray-Smith	TITLE Chief Financial Officer
FIRM/ORGANIZATION CoTherix, Inc. 5000 Shoreline Court, Suite 101, South San Francisco, CA 94080	
SIGNATURE 	DATE 06/14/2004

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

**DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF
CLINICAL INVESTIGATORS**

Attachment for Form FDA 3455

[
]]
Dr. L [a co-investigator [] disclosed that
received \$30,000.00 to support a clinical research nurse to conduct]

[] r

This information is being disclosed because the \$30,000.00 payment to the site for a study nurse, exceeds the \$25,000.00 defined in 21 CFR 54.2(f). This payment was not felt to have biased the study. The study was monitored by Schering as part of Schering's Good Clinical Practice (GCP) to assure compliance with the study protocol and GCP regulations.

**Appears This Way
On Original**

PRESCRIPTION DRUG USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS

CoTherix, Inc
5000 Shoreline Court, Suite 101
South San Francisco, CA 94080

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

21,779

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

21,779

(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

(650) 808-6518

3. PRODUCT NAME

Ventavis (iloprost) Inhalation Solution

6. USER FEE I.D. NUMBER

4769

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
and 12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

ATUSE OF AUTHORIZED COMPANY REPRESENTATIVE

TITLE
Director Regulatory Affairs

DATE
6/30/2004

Withheld

1

**page(s) of trade
secret
and/or confidential
commercial
information**

(b4)

Minutes of a Meeting
May 12, 2004

Sponsor: CoTherix, Inc.
Drug: Ventavis (Iloprost) Inhalation Solution
Pre-IND: 65, 820

Date Requested: March 15, 2004
Date Confirmation Faxed: March 19, 2004

Type: Pre-NDA, CMC
Classification: B

FDA Participants:

Hasmukh Patel, Ph.D.	Deputy Director, Division of New Drug Chemistry I, HFD-810
Kasturi Srinivasachar, Ph.D.	Team Leader, Chemistry, HFD-810
Javher Advani, Ph.D.	Chemist, HFD-810
Melissa Robb	Regulatory Health Project Manager, HFD-110

CoTherix Participants:

Curtis Ruegg, Ph.D.	Senior Vice President, Technical Operations
Robert Van Dyke, M.S.	Senior Director, Technical Operations
Thomas Fuerst, Ph.D.	Chemist, Schering AG
Christoph Stephan Hilger, Ph.D.	Chemist, Schering AG
Klara Dickinson	Director, Regulatory Affairs
Crystal Browning	Associate, Regulatory Affairs

Background:

Iloprost, a prostacyclin analog, is currently approved as Ilomedin for intravenous administration in approximately 30 countries worldwide for the treatment of occlusive arterial disease. Ventavis is an inhalation solution developed by Schering AG, Germany, for the treatment of pulmonary hypertension. The rationale for the inhaled route of administration is to provide high local concentrations, while minimizing the systemic side effects of prostacyclin therapy and avoiding the complications of chronic indwelling catheters. Ventavis was approved in the European Union in September 2003. The sponsor and the Division had a pre-IND meeting on November 20, 2003. The sponsor requested this meeting to discuss and agree upon the content and format of the Chemistry, Manufacturing and Controls (CMC) sections of the New Drug Application (NDA) for Ventavis (iloprost) inhalation solution.

Meeting:

Questions:

Drug Substance:

1. The defined starting materials for the iloprost drug substance are []
iloprost [] Does the FDA concur that these starting materials are acceptable? 1

The Division has difficulty accepting [] as a starting material. Since it is not commercially available and currently made in house, the Division does not believe it meets the criteria described in the Draft Guidance for Industry entitled Drug Substance: Chemistry,

Manufacturing, and Controls Information (Issued 1/2004, Posted 1/6/2004). Specifically, Dr. Srinivasachar believes that [] does not meet the criteria due to the complexity of the structure. According to the draft guidance, proposed starting materials "should be readily distinguishable from potential isomers and analogs so that adequate controls can be established..." The draft guidance also states that "if advanced techniques suitable for complex structures (¹H-NMR, ¹³C-NMR, 2D NMR, mass spectrometry, elemental analysis, X-ray crystallography, chiral HPLC) are needed to distinguish the proposed starting material from potential isomers and analogs, the chemical is not an appropriate candidate for designation as a starting material".

The Division stated that since they do not have the DMF number, they have not been able to access the file for review. The sponsor stated this number has been assigned and they will provide it to the Division. The DMF includes information on the synthesis and a flow diagram.

The Division inquired if the sponsor was planning to [] and that is why they wanted it designated as a starting material. The sponsor stated there is no plan [] The Division believes in that case there is no reason not to call it an intermediate. The Division added that if the sponsor wished [] they could request it to be a starting material post approval. The Division added [] manufacturing of the product would not result in it being considered commercially available.

The sponsor believes that [] designated as a starting material would result in decreased monitoring and reporting requirements since cGMP would not apply. The Division noted that since all steps are done at one facility, when FDA inspected the process, they would review the entire process and would not start in the middle of the synthetic scheme.

The Division believes that even though there is currently only one way [] if the Agency were to designate it as a starting material, then there would be no assurance that the same method would be used [] The Agency would have no way of ensuring that no new impurities resulted from a new manufacturing process.

The sponsor believes [] [] does qualify to be designated as a starting material. The Division agreed to review the scheme to see if any of the compounds in the preceding steps would be appropriate to designate as a starting material. The Division would like this issue resolved prior to submission of the NDA. The Division stated they would review the synthesis included in the DMF and discuss this issue further via teleconference.

The sponsor provided a short presentation [] The Division reiterated its concern that if this was designated a starting material, the Agency would no longer have any control over the manufacturing process. New impurities could be formed which may not be controlled by the agreed upon specifications. The Division believes this issue needs to be discussed further internally. The Division added [] is chosen as a starting material, the Division would need to review the specifications. The Division requested the sponsor provide further justifications outlining why the Division should [] an acceptable starting material.

The Division agreed with defining iloprost [] as a starting material. The Division noted that the sponsor will control the [] impurity level at ().

2. — years of real time stability data will be provided on — lots of drug substance to support a — month re-test date. Is this approach acceptable?

The Division stated that this is a review issue based on data submitted with the NDA. Dr. Srinivasachar noted that in the briefing package there are 2 different sets of specifications for the drug substance, release and stability. Dr. Srinivasachar stated the only specifications that should be included are shelf life specifications. The sponsor stated this was done to be consistent with specifications provided in Europe and that it will be corrected to shelf life specifications when the NDA is submitted.

3. CoTherix will cross reference a majority of the information addressing the details of the drug substance chemistry, manufacturing, and controls to the Schering DMF, submitted to the FDA on February 18, 2004. The drug substance information summarized in the NDA is based on the January 2004 Draft Guidance: Drug Substance Chemistry Manufacturing and Controls Information, and is highlighted in section 9.4.1 of the briefing package. Is this approach acceptable?

The Division agreed.

4. Drug substance batch records (master batch record and executed batch record) will not be provided in the NDA. This information is provided in the Schering DMF. Is this acceptable?

The Division agreed and added that batch records are not required for the drug substance. The sponsor added that a detailed description is included in the DMF.

The Division stated the sponsor should follow the established ICH guidelines for impurities. [

this limit in their NDA submission.

] The sponsor will provide justification for

Drug Product:

1. The components of the Ventavis formulations are defined in Table 7.2.1 of the briefing package. All excipients meet the USP or National Formulary specifications except ethanol 96%; this excipient meets the European Pharmacopea (Ph.Eur.) specification. In order for Schering to maintain a standard set of excipients for the world wide market of Ventavis and other Schering products, CoTherix proposes to test ethanol 96% to the Ph. Eur. Specification. Is this approach acceptable?

The Division agreed.

2. The Phase 3 clinical trial was performed using Ilomedin 20, diluted at the time of administration with isotonic saline (1:1) and nebulized for study in patients with pulmonary hypertension. An equivalent amount of iloprost (10µg/mL) is administered by this procedure as compared to that using Ventavis; the differences in the administered formulations can be regarded as insignificant and not expected to influence the clinical profile for Ventavis. Ventavis differs from the commercially available Ilomedin preparations only in the active ingredient content. Does the FDA agree that drug product used in Phase 3 supports the intended commercial product?

Dr. Srinivasachar stated that from a CMC point of view, this is acceptable.

3. Facility Transfer: Clinical trial drug product and the three lots to supply registration stability data were produced at the Berlin facility. These — registration lots were produced in Berlin at — of the intended commercial scale and are intended to serve as the primary stability data for drug product in the NDA. Following these development activities in Berlin, the same process and equipment were transferred to the [] facility, which is the facility that will manufacture commercial product for the European Union and the United States. In support of the site transfer, a comparison of batch data for pivotal, registration, and [] lots will be provided in the NDA. Is this approach acceptable?

The Division agreed.

4. Shelf Life: Both primary and supportive stability data will be filed in the NDA to support the requested expiration date. The primary stability data will include — years of real time stability and — months of accelerated stability data from — lots produced at the Berlin facility at — intended commercial scale. The supportive stability data will include — months of real time stability from lots produced at the [] facility and up to — years of real time stability data for the Ilomedin 20 product. Collectively, CoTherix believes this data will support an expiration date of —. Does the FDA agree that a three year expiration date is reasonable?

The Division stated that expiration date determination will be based on data using the Ventavis drug product. The determination of an expiration date is a review issue. The sponsor confirmed that the process being used for the commercially marketed product was also used in the batch that was — of the commercial scale.

The Division noted that the same issue exists with regard to stated specifications of the drug product that was discussed earlier for the drug substance. The sponsor should use established ICH guidelines or provide justifications why they are not following those guidelines.

The Division inquired why the sponsor did — testing only at baseline. The sponsor stated since the drug product is inhaled it was not needed. It was done at baseline because it was following the guidelines for an intravenous formulation. The Division believed this was acceptable, but will confirm with microbiology.

The Division stated that [] The Division asked if the sponsor is planning on marketing a 2mL/20 mcg single use solution vial. The sponsor confirmed this. The Division inquired why they were planning on marketing it in such a way since patients are to take doses of 2.5-5mcg at a time. The sponsor stated this was done because when the drug was administered using a jet nebulizer there were large amounts of waste.

Nebulizer:

1. CoTherix proposes to place the nebulizer information and *in vitro* characterization data in Module 3 Regional Information, as Module 3.2.R.4 (see section 9.4.4 of this briefing packet). Is this approach acceptable?

It was agreed that this information should be located in the Appendix of Module 3.

2. Does CoTherix need to provide a letter of authorization to reference the ProDose 510K in support of the Ventavis NDA?

The sponsor stated that the 510K for the ProDose has been approved by the Center for Devices and Radiological Health (CDRH). The Division stated since the device was approved, no letter of

authorization would be needed. However, the sponsor was asked to include a copy of the approval letter in their NDA submission.

Procedural:

1. Does the Division of New Drug Chemistry find the overall content and format of Module 2.3 and Module 3 acceptable?

The Division agreed.

2. The manufacturing and release testing for both the drug substance and drug product are performed in Europe. CoTherix will review the batch records and release data and issue the release of U.S. marketed product. Based on this information, CoTherix proposes to file the Field Copy to the Office of Compliance rather than a District Office. Is this approach acceptable?

The Division stated since an electronic submission is planned, the sponsor will not need to file the Field Copy with the Office of Compliance.

Batch Analyses:

1. We will supply detailed batch information (Date of mfg, process, site, scale, etc.), batch analysis data and batch analysis reports (CoA's) for all batches used in preclinical studies as well as stability batches and batches supportive of manufacturing consistency. For clinical batches, we will provide full batch data for clinical inhalation studies. For IV and oral clinical studies, only batch # and study # will be supplied. Does the Agency find this to be acceptable?

The Division stated that no information will be needed for the oral and IV formulations. The sponsor plans to submit ~executed batch records. One would be for the Ilomedin 20 which was used in the Phase 3 trials. The second batch would be from a stability lot manufactured at the Berlin facility. The final batch would be from the — facility and would be from a commercial lot. The Division agreed with this plan.

Signature, minutes preparer: *{See appended electronic signature page}*

Concurrence Chair: *{See appended electronic signature page}*

Drafted: 5/14/04

Finalized: 6/3/04

RD:

Patel 6/3/04

Srinivasachar 5/17/04

Advani 5/14/04

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

/s/

Melissa Robb
6/3/04 12:55:26 PM

Kasturi Srinivasachar
6/4/04 04:45:39 PM

March 9, 2004

Sponsor: CoTherix, Inc.
Drug: Ventavis (Iloprost) Inhalation Solution
Pre-IND: 65, 820

Date Requested: February 4, 2004
Date Confirmation Faxed: February 6, 2004

Type: Guidance
Classification: C

FDA Participants:

Robert Temple, M.D.	Director, Office of Drug Evaluation 1, HFD-101
Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Thomas Marciniak, M.D.	Medical Team Leader, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Medical Team Leader, HFD-110
Maryann Gordon, M.D.	Medical Officer, HFD-110
Albert DeFelice, Ph.D.	Pharmacology Team Leader, HFD-110
Elena Mishina, Ph.D.	Pharmacokineticist, HFD-860
Kasturi Srinivasachar, Ph.D.	Chemistry Team Leader, HFD-110
Javher Advani, Ph.D.	Chemist, HFD-110
Melissa Robb	Regulatory Health Project Manager, HFD-110

CoTherix Participants:

Scott Harkonen, M.D.	Chairman and CEO
Don Santel	President and COO
James Pennington, M.D.	Chief Medical Officer
Keith Nolop, M.D.	Vice President, Drug Development
Curtis Ruegg, Ph.D.	Sr. Vice President, Technical Operations
Thomas Fuerst, Ph.D.	Chemist, Schering AG
ChristophStephen Hiler, Ph.D.	Chemist, Schering AG
Orlin Petrov, Ph.D.	Chemist, Schering AG
⌋	
	Consulting Pulmonologist
Klara Dickinson	Director, Regulatory Affairs

Background:

Iloprost, a prostacyclin analog, is currently approved as Ilomedin for intravenous administration in approximately 30 countries worldwide for the treatment of occlusive arterial disease. Ventavis is an inhalation solution developed by Schering AG, Germany, for the treatment of pulmonary hypertension. The rationale for the inhaled route of administration is to provide high local concentrations, while minimizing the systemic side effects of prostacyclin therapy and avoiding the complications of chronic indwelling catheters. Ventavis was approved in the European Union in September 2003. The sponsor and the Division had a pre-IND meeting on November 20, 2003. The sponsor requested this meeting to discuss the development of iloprost as a diastereoisomeric mixture.

Meeting:

The sponsor began by presenting their justifications for the continued development of iloprost as a diastereoisomeric mixture. Dr. Temple commented that the FDA's Policy Statement for the Development of New Stereoisomeric Drugs suggests that diastereoisomers usually differ greatly in their physicochemical properties, thus making separation relatively simple. The sponsor stated that in this mixture the stereoisomers act more like enantiomers. The sponsor confirmed that there was, however, no interconversion.

Dr. Throckmorton inquired how the sponsor was able to ensure that the exact ratio of each stereoisomer was always present. The sponsor stated that the current process, which has been in use by Schering for the past six years, is able to control the ratio. The sponsor confirmed that they have release specifications that control the ratio of the two diastereoisomers.

Dr. Throckmorton commented that sponsor believes they have "extensive" screening data on the properties of the diastereoisomers available for review. However, they have data only in one species that looks only at anticipated pharmacological concerns and safety. From this information, the sponsor believed these data demonstrated that the two isomers differ only in potency. Dr. Throckmorton noted that the sponsor had not looked at other issues like receptor binding. Dr. Throckmorton said that the Division and Office were satisfied that no additional human data would be needed for the development of iloprost, provided we had a fuller understanding of the receptor binding properties of both isomers. To obtain this, Dr. Throckmorton said that the sponsor should perform in vitro testing looking at a standard panel of receptor binding properties in each isomer in order to better understand the pharmacology. The sponsor had no further questions or clarifications on this issue.

The next issue discussed was that of the clinical development of iloprost. The sponsor stated they are planning to perform [] The sponsor believes this will provide valuable information for labeling, but do not believe this information is needed to establish the safety and/or efficacy of the drug. The sponsor believes the data they currently have are sufficient to establish the safe and effective use of the drug. Dr. Throckmorton stated that the Agency is unable to comment on the robustness of the currently available data, as that is a review issue. However, Dr. Throckmorton was concerned that the primary endpoint of the trial from the completed clinical study relied on only approximately 22 patients. Dr. Throckmorton inquired about the timing of the walk testing in relation to dosing. The sponsor stated that the walk test was performed 15-30 minutes following dosing (thus, it was close to a peak measure). Dr. Throckmorton stated this could make labeling the drug to describe how often it should be administered more difficult and that typically we looked at trough measures for a drug with a short half-life. The sponsor said that their data showed an effect at both peak and trough, although the effect was much less prominent at trough. Patients in the trial were started at either 2.5 or 5 mcg, 6 times daily and were up-titrated to 9 times daily as tolerated. Such symptoms as headache and flushing were reasons patients had not tolerated the increased dosages. Dr. Throckmorton stated that all these data would be examined during the review.

Dr. Throckmorton noted another issue that needed further discussion. The sponsor had proposed that labeling suggest use with a nebulizer different from the one used in the clinical trials. After discussions with both the Center for Devices and Radiological Health (CDRH) and the Division of Pulmonary and Allergy Drug Products within the Center for Drug Evaluation and Research, we do not believe that in vitro testing would be sufficient for bridging data from one nebulizer to another. Dr. Throckmorton said that clinical data should be available from a nebulizer which is available for sale in the United States. The sponsor stated that the HaloLite, which was used in the Phase 3 trial, and the ProDose, currently under review by CDRH, are essentially the same machine. Both rely on the same nebulization principle for delivery of the drug. The only difference is that the ProDose allows for a more flexible user interface. The Agency agreed that this was encouraging but would also be a review issue. The Agency believes that an additional trial would not only provide useful information for labeling [] but also provide additional clinical data with the ProDose nebulizer. It would also be a confirmatory trial of the existing single study the sponsor is proposing to file.

Dr. Throckmorton inquired about the proposed timing of the New Drug Application (NDA) filing. The sponsor stated they are planning to submit the iloprost NDA in June 2004. Dr. Throckmorton stated the receptor-binding data discussed earlier would need to be available at the time of submission. The sponsor stated they would have the data : [] available at the end of this year. Dr. Throckmorton stated that there would not be enough time to review those data within the initial review cycle. Dr. Throckmorton added that it had not yet been decided if this would be a priority or standard review, but a priority review only allows 6 months for data to be reviewed.

The sponsor stated that they had been advised by their consultants [] [] The sponsor stated they have decided to perform their QT trial using healthy volunteers. The sponsor inquired about submitting this data during the review cycle. Dr. Throckmorton stated that this information could be submitted at the 4 month safety update for a standard review cycle. It was noted that if this were reviewed as a priority submission, the data would need to be submitted 2 months after the NDA was initially submitted.

Signature, minutes preparer: _____ /S/

Concurrence Chair: _____ /S/

Drafted: 3/10/04 Finaled: 3/23/04

- RD:
- Temple 3/23/04
 - Throckmorton 3/19/04
 - Stockbridge 3/19/04
 - Marciniak 3/17/04
 - Karkowsky 3/18/04
 - Gordon 3/17/04
 - DeFelice 3/16/04
 - Mishina 3/16/04
 - Srinivasachar 3/15/04
 - Advani 3/15/04

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

/s/

Melissa Robb
3/23/04 11:02:05 AM

Robert Temple
3/29/04 02:43:29 PM

January 29, 2004

Sponsor: CoTherix, Inc.
Drug: Ventavis (Iloprost) Inhalation Solution
Pre-IND: 65, 820

Date Requested: December 16, 2003
Date Confirmation Faxed: December 30, 2003

Type: Guidance
Classification: C

FDA Participants:

Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Thomas Marciniak, M.D.	Medical Team Leader, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Medical Team Leader, HFD-110
Maryann Gordon, M.D.	Medical Officer, HFD-110
Albert DeFelice, Ph.D.	Pharmacology Team Leader, HFD-110
Elena Mishina, Ph.D.	Pharmacokineticist, HFD-860
Kasturi Srinivasachar, Ph.D.	Chemistry Team Leader, HFD-110
Melissa Robb	Regulatory Health Project Manager, HFD-110

CoTherix Participants:

Scott Harkonen, M.D.	Chairman and CEO, CoTherix
Jim Pennington, M.D.	Chief Medical Officer, CoTherix
Keith Nolop, M.D.	Vice President, Drug Development, CoTherix
Karen Mosher, R.N.	Director Clinical Operations, CoTherix
Curtis Ruegg, Ph.D.	Sr. Vice President, Technical Operations, CoTherix
Robert Van Dyke, M.S.	Sr. Director, Technical Operations, CoTherix
Klara Dickinson	Director, Regulatory Affairs, CoTherix
Sylvia Nikkho, M.D.	Core Clinician, Schering AG
Fred Sigmund, M.D.	Senior Pathologist, Schering AG
Thomas Fuerst, Ph.D.	Schering, AG
Gabriele Kapfer	Global Regulatory Affairs, Schering AG

Background:

Iloprost, a prostacyclin analog, is currently approved as Ilomedin for intravenous administration in approximately 30 countries worldwide for the treatment of occlusive arterial disease. Ventavis is an inhalation solution developed by Schering AG, Germany, for the treatment of pulmonary hypertension. The rationale for the inhaled route of administration is to provide high local concentrations, while minimizing the systemic side effects of prostacyclin therapy and avoiding the complications of chronic indwelling catheters. Ventavis was approved in the European Union in September 2003. The sponsor and the Division had a pre-IND meeting on November 20, 2003. The sponsor requested this meeting to discuss with the Division how to proceed to a New Drug Application (NDA).

Questions:

1. Does the information submitted to the Agency on December 15, 2003 provide justification to develop iloprost as a diastereoisomeric mixture?

The Division does not agree. Dr. Throckmorton stated that this is a very difficult issue. Dr. Throckmorton believes that in order to evaluate this question, the Division must look at both the population being served and the safety of the compound. Dr. Throckmorton acknowledged that this compound does have safety data available from the oral, intravenous, and inhaled formulations. Dr. Throckmorton believes that one could argue that since the available data seems to show the products is safe, there should be less concern that the product is a diastereoisomeric mixture. However, without any data it is impossible to know whether each diastereoisomer contributes to the product's efficacy, and the Agency guidance on this issue seems clearly to call for that information for developing diastereoisomers. Therefore, the Division believes it is important to understand the individual diastereoisomers.

Dr. Throckmorton was unsure of how easy it would be to separate the diastereoisomers, but assuming it was not difficult, as is the case with many diastereoisomeric mixtures, he suggested conducting a trial similar in structure to that which the sponsor has already proposed, placebo-controlled looking at each diastereoisomer independently. Dr. Throckmorton believed the primary endpoint could look at the results of one of the diastereoisomers or a combination of the two. Safety data would be derived from both studies of the diastereoisomeric mixture and from the diastereoisomer studied individually. Dr. Throckmorton viewed this as a possible solution, but was open to other alternatives. Dr. Throckmorton believed it is important to describe the compound in order to better serve the population.

The sponsor inquired if they were to submit a NDA with only the one efficacy trial, would the Division refuse to file it. Dr. Throckmorton was unsure of what the outcome would be at the time of filing. He would need to discuss the situation with Dr. Temple.

The sponsor ☐

3 Dr. Srinivasachar suggested the sponsor make an argument for the Division to review outlining attempts at separation and difficulties encountered.

The sponsor inquired if the seriousness of the indication (pulmonary hypertension) would outweigh the isomer issue. Dr. Throckmorton stated that the Division does not want to delay drug development unnecessarily in this disease. However, the Division believes it is important to resolve the isomer issue. Dr. Throckmorton added that he would invite the sponsor to present their argument to the Office if they believed that producing single diastereoisomers was technically challenging and that other information might suffice.

The sponsor noted that the FDA's Policy Statement for the Development of New Stereoisomeric Drugs states that consideration should be given to the safety of the product. Dr. Throckmorton agreed that if there were identified safety concerns, it would only make the need for separating the diastereoisomers stronger. Even absent this concern, however, he believes that determining which of the two components (actually, two drugs) contributes to clinical efficacy is needed.

2. Are the data provided to the Agency on December 15, 2003 sufficient to establish that the HaloLite and ProDose nebulizers deliver a comparable dose?

Dr. Throckmorton stated that this issue has been discussed at length with reviewers in the Center for Devices and Radiological Health. They had advised the Division that it is the therapeutic window of the drug that is important when evaluating nebulizers. They also suggested further consultation with other Division's that regulate inhaled drugs more often. Dr. Throckmorton stated he plans to discuss this issue further with the Director of the Division of Pulmonary and Allergy Drug Products. Dr. Throckmorton will follow-up with the sponsor on this issue after further discussions within the Agency have taken place.

3. The NDA will be filed with safety exposure from 204 patients receiving inhaled iloprost, and approximately 3000 patients who received iloprost in controlled clinical trials using either intravenous or oral formulations. Will this total of approximately 3200 patients exposed to iloprost be adequate for assessing the safety of the product?

The Agency agrees, especially with regard to the IV data. Dr. Throckmorton noted that the oral data may be more complicated, since the drug was a cyclodextrin clathrate capsule. More information would be required to characterize the systemic absorption.

4. Does the proposed clinical study address the Division's request for additional clinical data, including safety, efficacy and QT interval measurements?

Dr. Throckmorton noted that paired ECGs were to be collected at four weeks at end inhalation, 5 minutes, 10 minutes, 20 minutes and 60 minutes post-inhalation. It was noted that C_{max} would be achieved by 5 minutes. Dr. Throckmorton believed that on face this appears to be an adequate evaluation, but stated he would need more information outlining how much change the sponsor thought they would be able to detect using a protocol like this in order to comment definitively. In particular, how the study will show that it is sensitive enough to detect changes in QT should be addressed by the sponsor.

5. CoTherix would like to discuss potential outcomes of this study and the impact on approval.

CoTherix plan is to file the NDA based on the Schering Marketing Authorization Application (MAA), as defined in the pre-IND meeting on November 20, 2003. The NDA will be supplemented with the data from the study proposed in the meeting package. If the proposed study results in a trend in favor of active drug but not statistical significance, what would be the implication for NDA approval?

Dr. Throckmorton stated the sponsor's first trial was In these cases, the Division believes it important for reproducibility to be shown. Dr. Throckmorton stated that if the second trial showed a trend and the first trial was robust, it would be possible for the sponsor to present an argument explaining the shortcomings of the second trial, underpowered, etc. Dr. Throckmorton stated the outcome would be dependent on the data available.

6. Assuming the Diastereoisomer issue is resolved, would the NDA be accepted for filing based on the clinical plan described?

This issue was discussed previously.

The sponsor added

The sponsor was concerned

1. The sponsor inquired about using

non US sites for clinical trials. Dr. Throckmorton stated the Agency has no issues with accepting data from non US trials as long as the sites were available for inspection.

The sponsor stated they will discuss the diastereoisomer issue further internally and submit further data and arguments for review by the Division. Dr. Throckmorton agreed and encouraged the sponsor to contact the Division for further discussion if needed and to set up a meeting with Dr. Temple if desired.

/S/

Signature, minutes preparer: _____

Concurrence Chair: **/S/** _____

Drafted: 1/30/04

Finaled: 2/10/04

RD:

Throckmorton	2/10/04
Stockbridge	2/9/04
Marciniak	2/2/04
Karkowsky	2/3/04
Gordon	2/2/04
DeFelice	2/2/04
Mishina	2/2/04
Srinivasachar	1/30/04

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

/s/

Melissa Robb
2/10/04 03:54:37 PM

Doug Throckmorton
2/10/04 04:03:06 PM

Minutes of a Meeting
November 20, 2003

Sponsor: CoTherix, Inc.
Drug: Ventavis (Iloprost) Inhalation Solution
Pre-IND: 65, 820

Type: Pre-IND
Classification: B

Date Requested: October 3, 2003
Date Confirmation Faxed: October 3, 2003
Briefing Package Received: October 21, 2003

FDA Participants:

Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Thomas Marciniak, M.D.	Medical Team Leader, HFD-110
Albert DeFelice, Ph.D.	Pharmacology Team Leader, HFD-110
Elena Mishina, Ph.D.	Pharmacokineticist, HFD-860
Kasturi Srinivasachar, Ph.D.	Chemistry Team Leader, HFD-110
Javher Advani, Ph.D.	Chemist, HFD-110
John Lawrence, Ph.D.	Statistician, HFD-710
Melissa Robb	Regulatory Health Project Manager, HFD-110

CoTherix Participants:

Robert Van Dyke, M.S.	Senior Director, Technical Operations, CoTherix
Karen Mosher, R.N.	Director, Clinical Operations, CoTherix
Keith Nolop, M.D.	Vice President, Drug Development, CoTherix
⌊	⌋
⌊	⌋ Consultant
Don Santel	President and COO, CoTherix
Scott Harkonen, M.D.	Chairman and CEO, CoTherix
⌊	Consultant, ⌊
Sylvia Nikkho, M.D.	Core Clinician, Schering AG
Fred Sigmund, M.D.	Senior Pathologist, Schering AG
Gabriele Kapfer	Global Regulatory Affairs, Schering AG

Background:

Iloprost, a prostacyclin analog, is currently approved as Ilomedin for intravenous administration in approximately 30 countries worldwide for the treatment of occlusive arterial disease. Ventavis is an inhalation solution developed by Schering AG, Germany, for the treatment of pulmonary hypertension. The rationale for the inhaled route of administration is to provide high local concentrations, while minimizing the systemic side effects of prostacyclin therapy and avoiding the complications of chronic indwelling catheters. Ventavis was approved in the European Union in September 2003. The sponsor requested this meeting to discuss with the Division how to proceed to a New Drug Application.

Meeting:

Dr. Throckmorton began by requesting the sponsor give further details about the fact that Iloprost is a mixture of two diastereoisomers. The sponsor stated the substance is controlled in synthesis and is in a fixed 55:45 ratio. The sponsor added they have good data available on the certificate of analysis and plan to file a Drug Master File in the first quarter of 2004. The sponsor stated the fact that the drug product is a mixture of two diastereoisomers was not an issue that was discussed with the EMEA.

Dr. Throckmorton informed the sponsor that the Agency had a policy entitled, "FDA'S POLICY STATEMENT FOR THE DEVELOPMENT OF NEW STEREOISOMERIC DRUGS". The policy states that since diastereoisomers "are both chemically distinct and pharmacologically different (unless they are interconverted *in vivo*)... [they] should...be treated as separate drugs and developed accordingly". Therefore, the Agency would view Iloprost as a combination product. Dr. Throckmorton stated he brought this topic up for discussion because he believes it could have broad implications for the future of this drug's development program. The sponsor confirmed that there is no interconversion *in vivo*. Dr. Throckmorton encouraged the sponsor to review the policy and determine if it applies to their drug and how it will affect their planned submission. Dr. Throckmorton stated he did not see why the Agency would ignore this policy, even in a population of patients with pulmonary arterial hypertension, but was open to discussions around this point.

The sponsor stated that they were not aware of any clinical experience with the individual diastereoisomers, but there may be some data available from the intravenous formulation. The sponsor inquired if the fact that the drug product is in a fixed ratio would matter to the Agency. The Agency stated that is not the concern. Rather, the Agency would want to be assured that both components of the drug provided efficacy. Clinical testing may determine that one of the diastereoisomers is not needed for efficacy or negatively impacts safety.

Dr. Throckmorton briefly discussed three possible options the sponsor could explore to address this issue. In his first option, Dr. Throckmorton believed the sponsor could develop the drug as if it were a combination product. The sponsor could show that the two components both contribute to efficacy by testing various doses. Thus, they would be able to establish that both diastereoisomers are needed. This would also allow for the collection of additional safety data. Another option would be to gain greater understanding of the hemodynamic characteristics of both diastereoisomers and then link them to clinical efficacy. Dr. Throckmorton said that for this option, the sponsor would need to convince the Agency that hemodynamic effects would inform efficacy, perhaps by referencing other clinical trials linking such changes to recognized clinical outcomes. This option would also rely on preclinical data as supportive data. The final option would rely strictly on preclinical data. Dr. Throckmorton suggested that he felt this last option would be a difficult argument to make but that he was open to arguments from the sponsor.

The sponsor provided some information that is known about the diastereoisomers through preclinical data. The sponsor stated that the two diastereoisomers, 4R and 4S, exhibit similar specificity, with 4S being 4-12 times more potent. The sponsor reported no differences in toxicities in either of the two diastereoisomers or the combination product.

Dr. Throckmorton provided the sponsor with a copy of the policy discussed and invited the sponsor to meet with the Agency in the future, after discussing it further internally, before making any final decisions on how to pursue this issue.

Questions:

1. Will the preclinical, toxicology data package as listed in the Table of Contents of the MAA (Section 4.2) with numerous studies conducted in several species be sufficient in support of an NDA?

The Agency stated subject to review, it appears adequate. Dr. DeFelice noted that, pending resolution of the R,S issue, the sponsor seems to have a very comprehensive preclinical package. The sponsor confirmed that they would be able to provide all datasets correctly formatted for review.

2. Are the rat inhalation studies (4 weeks and 6 months) and the experience with inhaled iloprost in patients sufficient to assess local tolerance and adequate for the NDA?

The Agency agreed. Dr. DeFelice stated that the Agency policy required inhalation studies in 1 species for 6 months.

3. Pharmacokinetic and pharmacodynamic analyses were conducted for the systemic and inhaled route of administration of iloprost. Will the existing pharmacokinetic data be sufficient for the NDA?

After the sponsor confirmed that the pharmacokinetic trials were conducted in a diseased population, the Agency agreed. Dr. Mishina added that there were no concerns with multiple dosing due to the drug's short half-life and administration only six times daily. Dr. Mishina also confirmed no further testing evaluating hepatic or renal function would be required.

4. In the pivotal Phase III study conducted in Europe, HaloLite was used as the nebulizer. Will in vitro data on the characteristics of the iloprost aerosol delivered by the ProDose and HaloLite nebulizers be sufficient to establish equivalence between the two nebulizers? These characteristics include the amount of iloprost delivered at the mouthpiece of the nebulizer and distribution of the aerosol droplet size. Furthermore, ProDose is currently under review by CDRH. Does the FDA concur with this approach to establish equivalence of nebulizers?

Dr. Throckmorton began by inquiring about the different nebulizers used in the clinical development program. The sponsor stated that the Ilo-Neb was used in the Phase II trials. A phase I trial was also conducted to compare the HaloLite, Ilo-Neb and an additional nebulizer. This trial evaluated the pharmacokinetics of Iloprost after inhalation with all three devices using a 95% confidence interval. The trial provided data on pulmonary and systemic hemodynamic effects and pharmacokinetics, C_{max} and AUC, of inhaled Iloprost. In addition, the study provided a bridge between the Phase II study in which the Ilo-Neb nebulizer was used and the Phase III study which used the HaloLite nebulizer.

Dr. Throckmorton inquired about how the currently approved Iloprost labeling, marketed in the European Union, addressed the use of specific nebulizers. The sponsor stated it was labeled for use with the ProDose and HaloLite nebulizers. After further discussion, it was agreed that the ProDose and HaloLite nebulizers were merely listed as nebulizers that could be used. The sponsor also explained that the EMEA required only in vitro data on the ProDose and the HaloLite nebulizers in order to show equivalency. The sponsor stated in this trial they had included other nebulizers, but they were unable to show equivalency. The sponsor stated some of the failures were due to inappropriate dose at mouthpiece and delivery rate. Dr. Throckmorton inquired why the sponsor wanted Iloprost to be labeled for the ProDose nebulizer specifically. He explained that when drugs are labeled for a specific nebulizer it is often due to a narrow therapeutic index, as is the case with insulin, as opposed to a shallow dose response which is seen with bronchodilators. The sponsor believes it is important to be labeled for the ProDose because it would allow for dose consistency and assurances since the trials were performed with that nebulizer. It was noted that the ProDose was not used in the clinical trials. The sponsor believes in vitro testing would be sufficient to bridge from the ProDose to the HaloLite as the two are basically the same device, with the same manufacturer, same aerosol generation and same particle size. Dr. Throckmorton said that sounded reasonable, but that it would be a case the sponsor would have to make that in vitro data is sufficient and in vivo data should not be required. The sponsor plans to submit data collected by Schering on the various nebulizers tested. Dr. Throckmorton acknowledged that the device standards on nebulizers are very broad. Additionally, the trial, which compared HaloLite and Ilo-Neb nebulizers assessed the bioequivalence based on the 95% confidence interval. The US requirement for the bioequivalence is more stringent and based on the 90% confidence interval comparison.

5. We would like to discuss and obtain clarification of the potential need to conduct a separate QT interval study.

The sponsor believes they have shown a lack of effect on QT. They cited the fact that the drug class is not associated with QT prolongation, they have large amounts of preclinical data, both in vivo and in vitro and no arrhythmias reported in clinical trials. The sponsor is proposing to evaluate ECGs done prior to the study and following completion of the study. The sponsor states they have ECGs available from the Phase III trial that they would be able to look at which would provide 12 week data. In addition, the sponsor stated they have ECGs available from a Phase I trial after oral and intravenous administration. They would like to use pharmacokinetic data to bridge. Dr. Throckmorton stated that this would not be sufficient. If nothing were to be found, it would be impossible to know if that was due to trough levels of the drug. Additionally, the numbers that the sponsor would be evaluating are very small. Dr. Throckmorton also stated that the absence of QT prolongation in preclinical data does not exclude that there will be issues in humans. Dr. Throckmorton stated additional data would likely be needed, but that the sponsor should make a case as to what they could provide. The Agency has clearly indicated that while this is an important issue, precisely how to meet it has to be discussed for each drug in the context of its clinical development.

6. Given the severity of the disease, the unmet need for an alternative prostacyclin delivery route, and robustness of data contained in the clinical data available for Ventavis, under which circumstances would the European clinical data package be insufficient for a filing of a NDA?

Dr. Throckmorton began by stating he favored the collection of additional clinical data, but that is if the sponsor chose to submit the current package he couldn't predict the outcome of the review. Dr. Throckmorton then inquired about total patient exposures. The sponsor stated they had 203 patients enrolled in clinical trials with the inhaled Iloprost. In addition, approximately 100 patients were taking the drug enrolled with individual physician investigators. The sponsor added that they have up to two years of follow-up data available for some patients. In the intravenous formulation, more than 7000 patients received Iloprost in clinical trials, 155 of them with pulmonary hypertension. The sponsor added that the 155 pulmonary hypertension patients that received intravenous Iloprost were part of an uncontrolled trial. Dr. Throckmorton stated that controlled data is more helpful when analyzing safety data. Dr. Throckmorton requested the sponsor submit a summary of all available controlled patient exposure data. This information should include dose, duration and length of exposure. The sponsor agreed.

Dr. Throckmorton noted that the sponsor has only a single pivotal trial and supportive open-label and investigator data. He agreed that the trial does look robust, as the sponsor measured efficacy in various ways, and the sponsor is reporting a nominal p-value, 0.007. This makes the single trial more substantial than 'one trial' potentially. Information on multiple doses is another way that single trials have been viewed as more robust, although those data are not present here. He acknowledged that the sponsor does have hemodynamic data available, but added that pharmacokinetic data are not a surrogate for efficacy. Dr. Throckmorton stated he wasn't sure if the data the sponsor has available would be sufficient for approval. Dr. Throckmorton did believe it would likely be sufficient for filing of a NDA. Dr. Throckmorton stated he would prefer to have additional data to review. He suggested a trial similar to that which was done for bosentan. Dr. Throckmorton believed that would provide the sponsor with the needed QT data, additional safety data and efficacy data. Dr. Throckmorton added that he would even be satisfied if the sponsor chooses an endpoint looking at only something like six minute walk. The sponsor stated they do have a 3-month open, randomized parallel-group trial with a long-term uncontrolled follow-up. Dr. Throckmorton stated that if the sponsor was looking at endpoints that could not be influenced by unblinding, such as mortality, that this trial may be beneficial. However, if the trial evaluated endpoints that could be influenced by unblinding it would not be helpful in establishing efficacy. The sponsor stated in this trial the endpoint was walk distance. Dr. Throckmorton believed this is a parameter that could be influenced by unblinding.

The sponsor wanted to clarify that the intravenous data would be useful in determining safety and patient exposures. Dr. Throckmorton agreed that the intravenous data could aid in establishing the safety of inhaled Iloprost if the data was collected for relevant concentrations. Dr. Throckmorton stated there are many things that they are looking at with patient exposures. The Agency would want to ensure that they had data available to show that there are no safety concerns with the interaction of the disease, for example an inhaled drug in a population with diseased lungs. Dr. Throckmorton agreed it is difficult to collect large amounts of long term

data due to the nature of the disease. Dr. Throckmorton stated that controlled data provides information for labeling that can instruct physicians what to monitor during initiation of treatment and during follow-up. Dr. Throckmorton stated that although post-marketing reports are helpful, they usually only identify rare events. Dr. Throckmorton stated it would be an argument for the sponsor to make that they have sufficient amounts of safety data available.

The sponsor also requested clarification about the additional trial Dr. Throckmorton discussed previously. Dr. Throckmorton stated he would like to see reproducibility. He agreed that the trial the sponsor has already performed does seem robust and internally consistent, but were reviewers to find anything wrong with that trial, it could be fatal for a NDA with no other pivotal trials. The sponsor expressed concern with gaining approval from an IRB for a placebo-controlled trial. Dr. Throckmorton suggested either a withdrawal trial or a trial using Iloprost as an add-on to existing therapies. Dr. Throckmorton noted that an add-on trial would also provide information about drug interactions.

7. CoTherix believes that the clinical efficacy trials provide sufficient data package for an NDA, and therefore, CoTherix would like to move into NDA discussions soon. Does the Division think this approach is reasonable?

Dr. Throckmorton stated that he believes the package the sponsor has is very small, including both low patient exposure numbers and only one pivotal trial. Dr. Throckmorton believes submitting the package without performing an additional efficacy trial is risky.

[]

8. How do we assure that the NDA we plan to submit will be assigned to the Division of Cardio-Renal Drug Products?

The Agency assigns applications based on indication. Dr. Throckmorton agrees that this application should be reviewed by the Division of Cardio-Renal Drug Products. Dr. Throckmorton requested the sponsor notify the Division prior to submitting the NDA.

9. The Schering development program did not address the treatment of pediatric patients. Will the Division grant a waiver for the clinical evaluation of pediatric patients?

Dr. Throckmorton stated that at this time the Pediatric Rule is stayed. Dr. Throckmorton stated if that were to change, the Division would grant a deferral and allow for pediatric trials to be conducted as a phase 4 commitment.

/S/

Signature, minutes preparer: _____

/S/

Concurrence Chair: _____

Drafted: 11/21/03

Finaled: 12/11/03

RD:

Throckmorton	12/11/03
Stockbridge	12/10/03
Marciniak	12/10/03
DeFelice	12/9/03
Mishina	12/08/03
Srinivasachar	12/5/03
Advani	12/2/03
Lawrence	11/24/03

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

/s/

Melissa Robb
12/11/03 10:02:56 AM
Faxed to sponsor 12/11/03

Doug Throckmorton
12/11/03 09:55:01 AM