CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-779

Microbiology Review(s)
REQUEST FOR CONSULTATION

TO (Division/Office):
Microbiology (HFD-805) for Microbiology Consult
Attn: Dr. Peter Cooney

FROM:
Monica Cooper, Ph.D. (HFD-110)

<table>
<thead>
<tr>
<th>DATE</th>
<th>IND NO.</th>
<th>NDA NO.</th>
<th>TYPE OF DOCUMENT</th>
<th>DATE OF DOCUMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>August 12, 2004</td>
<td></td>
<td>21-779</td>
<td>NDA</td>
<td>June 30, 2004</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NAME OF DRUG</th>
<th>PRIORITY CONSIDERATION</th>
<th>CLASSIFICATION OF DRUG</th>
<th>DESIRED COMPLETION DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventavis (iloprost) Inhalation Solution</td>
<td>Standard</td>
<td>Treatment of Pulmonary Arterial Hypertension</td>
<td>February 15, 2005</td>
</tr>
</tbody>
</table>

| NAME OF FIRM. | CoTherix, Inc. |

REASON FOR REQUEST

I. GENERAL

- NEW PROTOCOL
- PROGRESS REPORT
- NEW CORRESPONDENCE
- DRUG ADVERTISING
- ADVERSE REACTION REPORT
- MANUFACTURING CHANGE/ADDITION
- MEETING PLANNED BY
- PRE-NDA MEETING
- END OF PHASE II MEETING
- RESUBMISSION
- SAFETY/EFFICACY
- PAPER NDA
- CONTROL SUPPLEMENT
- RESPONSE TO DEFICIENCY LETTER
- FINAL PRINTED LABELING
- LABELING REVISION
- ORIGINAL NEW CORRESPONDENCE
- FORMATIVE REVIEW
- OTHER (SPECIFY BELOW):

II. BIOMETRICS

<table>
<thead>
<tr>
<th>STATISTICAL EVALUATION BRANCH</th>
<th>STATISTICAL APPLICATION BRANCH</th>
</tr>
</thead>
<tbody>
<tr>
<td>TYPE A OR B NDA REVIEW</td>
<td>CHEMISTRY REVIEW</td>
</tr>
<tr>
<td>END OF PHASE II MEETING</td>
<td>PHARMACOLOGY</td>
</tr>
<tr>
<td>CONTROLLED STUDIES</td>
<td>BIOPHARMACEUTICS</td>
</tr>
<tr>
<td>PROTOCOL REVIEW</td>
<td>OTHER (SPECIFY BELOW):</td>
</tr>
<tr>
<td>OTHER (SPECIFY BELOW):</td>
<td></td>
</tr>
</tbody>
</table>

III. BIOPHARMACEUTICS

- DISSOLUTION
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES
- DEFICIENCY LETTER RESPONSE
- PROTOCOL-BIOPHARMACEUTICS
- IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMILOGY PROTOCOL
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- CLINICAL
- PRECLINICAL

COMMENT/SPECIAL INSTRUCTIONS:

Ventavis is a sterile, aqueous solution formulated for inhalation via a nebulizer. Please review the microbiology. This NDA was submitted as an electronic document and is available through the Electronic Document Room (EDR).
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

---------------------
Monica Cooper
8/12/04 10:50:32 AM
Product Quality Microbiology Review
Review for HFD-110
16 December 2004

NDA: 21-779 Response Amendment

Drug Product Name
Proprietary: Ventavis Inhalation Solution
Non-proprietary: iloprost
Drug Product Classification: Treatment of pulmonary arterial hypertension.

Review Number: 2

Subject of this Review
Submission Date: 15 December 2004
Receipt Date: 15 December 2004 (e-mail)
Consult Date: 15 December 2004
Date Assigned for Review: 15 December 2004

Submission History (for amendments only)

Applicant/Sponsor
Name: CoTherix, Inc.
Address: 5000 Shoreline Court, Suite 101
South San Francisco, CA 94080
Representative: Ms Klara Dickinson
Director, Regulatory Affairs
Email: kdickinson@cotherix.com

Telephone: (650) 808-6518
Fax: (650) 808-6899

Name of Reviewer: James L. McVey

Conclusion: The information provided supports the sterility claim from a product quality microbiology perspective.
Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION:** Original.

2. **SUPPLEMENT PROVIDES FOR:** Manufacture and distribution for sale of a sterile inhalation solution.

3. **MANUFACTURING SITE:** Iloprost inhalation solution is manufactured for CoTherix by [Company Name]. The manufacturing facility address is:

   [Address]

   The contact person at [Company Name] for preapproval inspection related activities is:

   [Contact Name]

   The U.S. Agent for [Company Name], Schering AG is:

   [Agent Name]

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Iloprost Inhalation Solution is packaged in mL clear, type I glass ampules. Each ampule has a net content of mL of μg/mL Iloprost.

5. **METHOD(S) OF STERILIZATION:** [Method]

6. **PHARMACOLOGICAL CATEGORY:** Treatment of pulmonary hypertension.

B. **SUPPORTING/RELATED DOCUMENTS:** N.A.

C. **REMARKS:** See Section 3 for reviewers comments.

*filename: N21779r2*
Executive Summary

I. Recommendations

A. Recommendation on Approvability – Approve.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N.A.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The product is formulated and...

B. Brief Description of Microbiology Deficiencies – N.A.

C. Assessment of Risk Due to Microbiology Deficiencies – N.A.

III. Administrative

A. Reviewer's Signature $\checkmark$

B. Endorsement Block
   Microbiologist: James L. McVey
   Microbiology Supervisor: David Hussong

C. CC Block
   cc: DFS
Redacted 2

page(s) of trade secret

and/or confidential

commercial information

(b4)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

James McVey
12/20/04 11:09:25 AM
MICROBIOLOGIST

David Hussong
12/21/04 09:42:20 AM
MICROBIOLOGIST
Product Quality Microbiology Review
Review for HFD-110
9 December 2004

NDA: 21779 N000

Drug Product Name
Proprietary: Ventavis Inhalation Solution
Non-proprietary: iloprost
Drug Product Classification: Treatment of pulmonary arterial hypertension.

Review Number: 1

Subject of this Review
Submission Date: 30 Jun 2004
Receipt Date:
Consult Date: 12 Aug 2004
Date Assigned for Review: 19 Aug 2004

Submission History (for amendments only)
Date(s) of Previous Submission(s):
Date(s) of Previous Micro Review(s):

Applicant/Sponsor
Name: CoTherix, Inc.
Address: 5000 Shoreline Court, Suite 101
South San Francisco, CA 94080
Representative: Ms Klara Dickinson
Director, Regulatory Affairs
Email: kdickinson@cotherix.com

Telephone: (650) 808-6518
Fax: (650) 808-6899

Name of Reviewer: James L. McVey

Conclusion: Approvable pending the resolution of product quality microbiology issues.
Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original.

2. SUPPLEMENT PROVIDES FOR: Manufacture and distribution for sale of a sterile inhalation solution.

3. MANUFACTURING SITE: Iloprost inhalation solution is manufactured for CoTherix by manufacturers. The manufacturing facility address is:

   
   The contact person at for preapproval inspection related activities is:

   
   The U.S. Agent for is Schering AG is:

   

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Iloprost Inhalation Solution is packaged in mL clear, type I glass ampules. Each ampule has a net content of mL of μg/mL Iloprost.

5. METHOD(S) OF STERILIZATION: 

6. PHARMACOLOGICAL CATEGORY: Treatment of pulmonary hypertension.

B. SUPPORTING/RELATED DOCUMENTS: N.A.

C. REMARKS: See Section 3 for reviewers comments.

filename: N21779r1
Executive Summary

I. Recommendations

A. Recommendation on Approvability – Approvable.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N.A.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – Product is formulation

B. Brief Description of Microbiology Deficiencies –

3 The impact of the drug product on the potential contaminant should be assessed in order to assure adequate lethality is administered.

C. Assessment of Risk Due to Microbiology Deficiencies – The risk to human health cannot be assessed until the data requested is provided.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block
   Microbiologist: James L. McVey
   Microbiology Supervisor: David Hussong

C. CC Block
   cc: DFS
Redacted 6

page(s) of trade secret

and/or confidential

commercial information

(b4)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
-------------------
James McVey
12/9/04 03:36:02 PM
MICROBIOLOGIST

David Hussong
12/9/04 03:55:24 PM
MICROBIOLOGIST
microbiology review with moderate risk deficiencies noted - APPROVABLE