

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-779

Chemistry Review(s)

NDA 21-779

Ventavis® (iloprost) Inhalation Solution

CoTherix, Inc.

**Monica D. Cooper, Ph.D.
and
William C. Timmer, Ph.D.**

Division of Cardio-Renal Drug Products

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CHEMISTRY REVIEW

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 21-779

2. REVIEW NUMBER: #2

3. REVIEW DATE: 17-December-2004

4. REVIEWERS: Monica D. Cooper, Ph.D.: Drug Substance
William C. Timmer, Ph.D.: Drug Product

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
NDA 21-779 (N000)	30-JUN-2004
Amendment (N000 BC)	06-AUG-2004
Amendment (N000 BL)	28-OCT-2004

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (N000 BL)	18-NOV-2004
Amendment (N000 BC)	24-NOV-2004
Amendment (N000 BL)	01-DEC-2004
Amendment (N000 BC)	10-DEC-2004

CHEMISTRY REVIEW

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: CoTherix, Inc.
Address: 5000 Shoreline Court, Suite 101
South San Francisco, CA 94080
Representative: Klara Dickinson
Telephone: 650-808-6518

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: Ventavis®
Non-Proprietary Name (USAN): Iloprost
Code Name: ZK 36374
Chemistry Type: 1
Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 21 U.S.C. § 355

10. PHARMACOL. CATEGORY: Pulmonary arterial hypertension

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 20 µg in 2 mL (10 µg/mL)

13. ROUTE OF ADMINISTRATION: Inhalation via Nebulizer

14. Rx/OTC DISPENSED: _Rx _OTC

CHEMISTRY REVIEW

Chemistry Review Data Sheet

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

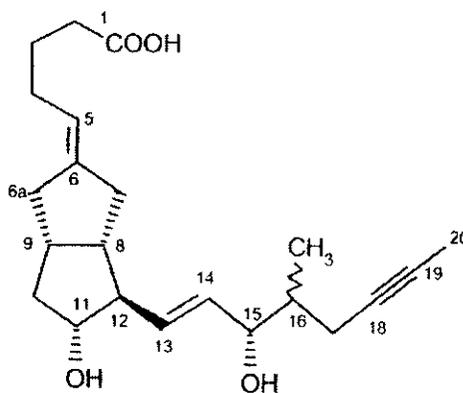
___ SPOTS product – Form Completed

___ Not a SPOTS product

16. CHEMICAL INFORMATION:

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

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



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

Chemical Formula: C₂₂H₃₂O₄
Mol. Wt.: 360.49
CAS No.: 78919-13-8

CHEMISTRY REVIEW

Chemistry Review Data Sheet

17. RELATED / SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED
1	II	Schering AG	Iloprost drug substance	1	Inadequate	28-October-2004
2	II	\	\	7	N/A	not used in commercial DP
3	III	\	\	4	N/A	---

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

- 2 – Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	65,820	Iloprost Inhalation Solution

CHEMISTRY REVIEW

Chemistry Review Data Sheet

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	13-DEC-04	S. Adams
LNC	N/A	----	----
Methods Validation	<i>to be initiated post approval</i>		----
ODS DMETS	'Ventavis' acceptable	15-DEC-04	D.P. Toyer, Pharm. D.
EA	Acceptable	03-DEC-04	W.C. Timmer, Ph.D.
Microbiology	Acceptable	16-DEC-04	James McVey, Ph.D.

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The Chemistry Review for NDA 21-779

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval. This new drug application (21-779) is recommended for approval from the perspective of chemistry, manufacturing, and controls. All deficiencies identified in the DMF for the drug substance and in the NDA have been resolved. Deficiencies identified in the microbiology review (J. McVey, 09-Dec-2004) were also resolved (see 2nd microbiology review, J. McVey).

The Office of Compliance has given an overall acceptable recommendation for the facilities.

The action letter should state --

- Based on the drug substance stability data, an expiration date of not more than 36 months and a retest date of not more than 12 months are recommended for the drug substance, when stored frozen (-20 to -25°C)
- An expiration date of 36 months is granted for the drug product when stored at 20 – 25°C.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no Phase 4 commitments.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substance

The drug substance is iloprost, a synthetic analog of the natural, highly unstable prostacyclin PGI₂.

Iloprost drug substance consists of a fixed mixture (approximately 47:53, 4S:4R) of two diastereoisomers that are controlled by the manufacturing process. The diastereoisomers do not interconvert during storage. The Agency has a policy entitled,

Chemistry Assessment Section

“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.” This issue was discussed extensively in several pre-NDA meetings with the applicant. The applicant argued that it would be technically difficult to separate the diastereoisomeric mixture on a large scale and that the process would be costly in both time and resources. The applicant also noted that the two diastereoisomers, 4R and 4S, exhibit similar specificity, with 4S being 4 – 12 times more potent. No differences in toxicities were observed. The Division recommended that the applicant perform *in vitro* testing looking at a standard panel of receptor binding properties in each isomer in order to better understand the pharmacology.

Physically, the drug substance is an oily substance, which is very slightly soluble in distilled water, buffer pH 3, and buffer pH 5. It is soluble in ethanol, methanol, ethyl acetate, acetone, and buffer pH 7 and sparingly soluble in buffer pH 9.

Iloprost is a

information for the drug substance was referenced to DMF

1 CMC

Long-term stability testing has been conducted on iloprost drug substance at the recommended storage conditions (— uncontrolled humidity). The applicant proposed a — expiration date based on available data. However, an out-of-specification result was obtained for one batch at — for assay (using the revised limits of — An informal consult to statistics (Roswitha Kelly, 09-Dec-2004) indicated the data support only a 36-month expiration date. Thus, a 36-month expiration date is recommended for the drug substance stored —

A retest date for the bulk drug substance of approximately — years was proposed in the DMF. However, given that the drug substance is unstable at temperatures above — a retest date of NMT —months is recommended.

2. Drug Product

The drug product is a ready-to-use solution for oral inhalation via a nebulizer.

Ventavis®(iloprost) Inhalation Solution is a clear, colorless, aqueous solution containing 10 µg/mL of iloprost drug substance. Drug product formulation studies were based on the commercial European formulation, marketed as Ilomedin® (available in 100 µg/mL and 20 µg/mL solutions for IV use). In particular, the formulation for the inhalation solution is identical to the 20 µg/mL solution (diluted 1:1) for IV use. In other words, the formulation of the two drug products is identical;

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

what is different is that the European approval was based on a clinical trial that dosed the drug via IV, while the clinical trial in the current submission dosed the drug via oral inhalation with a nebulizer. (This is a subtle difference that matters in the clinical review only; there are no CMC issues involved). Marketing of Ventavis® in the European Union (EU) was granted to Schering AG on September 16, 2003. CoTherix has signed a licensing agreement for the commercialization of Ventavis® in the United States.

The drug product contains two principal excipients. Iloprost bulk drug substance, which is slightly soluble in water but is freely soluble in ethanol, is manufactured in _____

There were no unique manufacturing issues, especially since the manufacturer has been producing iloprost solution in Europe for 10 or more years. The manufacturing process, which is fairly simple, consists of mixing solutions. Batch sizes are _____ L.

The drug product is terminally sterilized as required by 21 CFR 200.51.

All excipients used in the manufacture of iloprost solution are compendial¹.

Specifications were developed to evaluate appropriate physico-chemical properties of iloprost inhalation solution in order to assure its suitability for its intended use upon release and upon shelf-life. These specifications consist of critical quality control standards that are intended to assure that all batches of the drug product maintain the same batch-to-batch consistency.

Finally, the applicant has submitted _____ stability batches – all using different drug substance lots. The _____ lots were produced at a scale of at least _____ of the intended commercial batch. Real time stability data is available through 36 months. _____ additional stability batches were submitted by the commercial European supplier, who, upon NDA approval, will become the US supplier. These supportive stability lots were produced using the same lots of drug substance. At present, _____ months of real time stability data have been collected (for these stability lots).

Analysis of the supportive stability data for all _____ batches indicated that iloprost drug product remains within specification. In particular, there were no downward trends in iloprost concentration. Minimal increases in impurities were found. No changes were noted in solution appearance or color. Solution pH remained within the

¹ The excipient 96% ethanol is referenced to the European Pharmacopeia.

Chemistry Assessment Section

range of the specification with no apparent trends. In sum, the stability data support a shelf life of 36 months when stored at room temperature.

Finally, it is noted that the drug product solution is to be dosed via a nebulizer. In particular, a ProDose nebulizer is referenced in the submission. The ProDose nebulizer has received 510(k) approval on 22-APR-04 (K030747). The Center for Devices and Radiological Health (CDRH) was consulted regarding the equivalence of the ProDose nebulizer with the Halolite nebulizer, which was the nebulizer used in the clinical trials. CDRH (Ann Graham) responded that the ProDose delivery was substantially equivalent. The ProDose system is further discussed in Appendix A.4.

B. Description of How the Drug Product is Intended to be Used

Ventavis®(iloprost) Inhalation Solution is indicated for pulmonary arterial hypertension.

Pulmonary arterial hypertension (PAH) is defined as a sustained elevation of pulmonary arterial pressure. Generally, the average blood pressure (BP) in a pulmonary artery is about 14 mmHg (at rest). In PAH, the average BP is usually greater than 25 mmHg.

The main vascular changes due to PAH are vasoconstriction, smooth-muscle cell and endothelial-cell proliferation, and thrombosis. These effects suggest an imbalance between vasodilators and vasoconstrictors, growth inhibitors and mitogenic factors, and antithrombotic and prothrombotic functions.

In particular, prostacyclin, a vasodilator, inhibits platelet activation and has anti-proliferative properties; in contrast, thromboxane A₂ is a potent vasoconstrictor and platelet agonist. In PAH the imbalance between these two molecules is shifted toward thromboxane A₂. Hence, intervention with prostacyclin, or the prostacyclin analogue iloprost (the subject of this submission) should restore this balance.

Iloprost is delivered by inhalation via a nebulizer to patients with PAH. The proposed treatment regimen is an initial dose of 2.5 mcg (as delivered at the mouthpiece of the nebulizer). If this dose is well tolerated, the dose should be increased and maintained at 5 mcg. The administration frequency should be 6 – 9 times per day during waking hours and according to individual need and tolerability. *Note:* There will be residual solution remaining in the medication chamber of the nebulizer at the end of each treatment. This residual solution should be discarded after each use.

The rationale for the inhalation route of administration is to provide high local concentrations while minimizing the systemic side effects of prostacyclin therapy. Importantly, delivery of iloprost by inhalation avoids complications of the chronic

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

indwelling catheters required for delivery of the i.v. or subcutaneous formulations of the prostacyclin analogues currently available.

C. Basis for Approvability or Not-Approval Recommendation

This new drug application (21-779) is recommended for **APPROVAL**. There are no outstanding issues with regard to chemistry, manufacturing, and controls.

III. Administrative

A. Reviewer's Signature

/s/ M.D. Cooper, Ph.D. and /s/ W.C. Timmer, Ph.D.

B. Endorsement Block

Chemistry Reviewers:	Monica D. Cooper, Ph.D.; Drug Substance William C. Timmer, Ph.D.; Drug Product
Chemistry Team Leader:	Kasturi Srinivasachar, Ph.D.
Project Manager:	Melissa Robb

C. CC Block

Orig. NDA 21-779
HFD-110/Division File
HFD-110/Team Leader/K. Srinivasachar
HFD-110/Review Chemist/M.D. Cooper
HFD-110/Review Chemist/W.C. Timmer
HFD-110/Project Manager/M. Robb

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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/

Monica Cooper
12/17/04 01:27:24 PM
CHEMIST

William Timmer
12/17/04 03:28:27 PM
CHEMIST

Kasturi Srinivasachar
12/17/04 03:53:17 PM
CHEMIST

NDA 21-779

Ventavis® (iloprost) Inhalation Solution

CoTherix, Inc.

Monica D. Cooper, Ph.D.

and

William C. Timmer, Ph.D.

Division of Cardio-Renal Drug Products

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Chemistry Review Data Sheet

1. NDA 21-779

2. REVIEW NUMBER: #1

3. REVIEW DATE: 03-December-2004

4. REVIEWERS: Monica D. Cooper, Ph.D.: Drug Substance
William C. Timmer, Ph.D.: Drug Product

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

NDA 21-779 (N000)

30-JUN-2004

Amendment (N000 BC)

06-AUG-2004

Amendment (N000 BL)

28-OCT-2004

CHEMISTRY REVIEW

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: CoTherix, Inc.
Address: 5000 Shoreline Court, Suite 101
South San Francisco, CA 94080
Representative: Klara Dickinson
Telephone: 650-808-6518

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: Ventavis®
Non-Proprietary Name (USAN): Iloprost
Code Name: ZK 36374
Chemistry Type: 1
Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 21 U.S.C. § 355

10. PHARMACOL. CATEGORY: Pulmonary arterial hypertension

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 20 µg in 2 mL (10 µg/mL)

13. ROUTE OF ADMINISTRATION: Inhalation via Nebulizer

14. Rx/OTC DISPENSED: Rx OTC

CHEMISTRY REVIEW

Chemistry Review Data Sheet

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

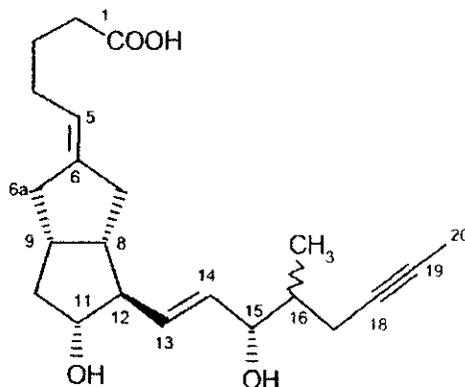
____ SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL INFORMATION:

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

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



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

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

CHEMISTRY REVIEW

Chemistry Review Data Sheet

17: RELATED / SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED
	II	Schering AG	Iloprost drug substance	1	Inadequate	28-October-2004
	II	\	\	7	N/A	not used in commercial DP
	III	\	\	4	N/A	----

¹ Action codes for DMF Table:

1 -- DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

- 2 --Type 1 DMF
- 3 -- Reviewed previously and no revision since last review
- 4 -- Sufficient information in application
- 5 -- Authority to reference not granted
- 6 -- DMF not available
- 7 -- Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	65,820	Iloprost Inhalation Solution

CHEMISTRY REVIEW

Chemistry Review Data Sheet

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending	15-NOV-04	N/A
LNC	N/A	----	----
Methods Validation	<i>to be initiated post approval</i>	15-NOV-04	----
ODS DMETS	'Ventavis' not acceptable	28-OCT-04	S. Dallas, R.Ph.
EA	Acceptable (CE to EA)	15-NOV-04	W.C. Timmer, Ph.D.
Microbiology	Pending	----	----

Appears This Way
On Original

The Chemistry Review for NDA 21-779

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

None. No recommendation is made regarding the approvability of the drug product Ventavis® (iloprost) Inhalation Solution. A final recommendation can only be provided when the Office of Compliance has given their recommendation and when the pending issues identified within the DMF for the drug substance and within the NDA are resolved. At present, the overall evaluation from the Office of Compliance for cGMP compliance is pending. A deficiency letter has been sent to the DMF holder for the drug substance outlining the information that is needed to complete this application.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no Phase 4 commitments.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substance

The drug substance is iloprost, a synthetic analog of the natural, highly unstable prostacyclin PGI₂.

Iloprost drug substance consists of a fixed mixture (approximately 47:53, 4S:4R) of two diastereoisomers that are controlled by the manufacturing process. The diastereoisomers do not interconvert during storage. The Agency has 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." This issue was discussed extensively in several pre-NDA meetings with the applicant. The applicant argued that it would be technically difficult to separate the diastereoisomeric mixture on a large scale and that the process would be costly in both time and resources. The applicant also noted that the two diastereoisomers, 4R and 4S, exhibit similar specificity, with 4S being 4 – 12 times more potent. No differences in toxicities were observed. The Division recommended that the applicant perform *in vitro* testing looking at a standard

Chemistry Assessment Section

panel of receptor binding properties in each isomer in order to better understand the pharmacology.

Physically, the drug substance is an oily substance, which is very slightly soluble in distilled water, buffer pH 3, and buffer pH 5. It is soluble in ethanol, methanol, ethyl acetate, acetone, and buffer pH 7 and sparingly soluble in buffer pH 9.

Iloprost is [

] CMC

information for the drug substance was referenced to DMF []

Long-term stability testing has been conducted on iloprost drug substance at the recommended storage conditions (— uncontrolled humidity). The applicant proposed a — expiration date based on available data. However, an out-of-specification result was obtained for — batch at — for assay (using the revised limits of —). Given that the last time-point when all — batches remained within specification for assay — was — months, a —-month expiration date is recommended for the drug substance stored at —.

A retest date for the bulk drug substance of approximately — years was proposed in the DMF. However, given that the drug substance is unstable at temperatures above — a retest date of NMT — months is recommended.

2. Drug Product

The drug product is a ready-to-use solution for oral inhalation via a nebulizer.

Ventavis®(iloprost) Inhalation Solution is a clear, colorless, aqueous solution containing 10 µg/mL of iloprost drug substance. Drug product formulation studies were based on the commercial European formulation, marketed as Ilomedin® (available in 100 µg/mL and 20 µg/mL solutions for IV use). In particular, the formulation for the inhalation solution is identical to the 20 µg/mL solution (diluted 1:1) for IV use. In other words, the formulation of the two drug products is identical; what is different is that the European approval was based on a clinical trial that dosed the drug via IV, while the clinical trial in the current submission dosed the drug via oral inhalation with a nebulizer. (This is a subtle difference that matters in the clinical review only; there are no CMC issues involved). Marketing of Ventavis® in the European Union (EU) was granted to Schering AG on September 16, 2003. CoTherix has signed a licensing agreement for the commercialization of Ventavis® in the United States.

The drug product contains two principal excipients. Iloprost bulk drug substance, which is slightly soluble in water but is freely soluble in ethanol, is manufactured in []

Chemistry Assessment Section

7

There were no unique manufacturing issues, especially since the manufacturer has been producing iloprost solution in Europe for 10 or more years. The manufacturing process, which is fairly simple, consists of mixing solutions. Batch sizes are 1 L and 3 L.

The drug product is terminally sterilized as required by 21 CFR 200.51.

All excipients used in the manufacture of iloprost solution are compendial¹.

Specifications were developed to evaluate appropriate physico-chemical properties of iloprost inhalation solution in order to assure its suitability for its intended use upon release and upon shelf-life. These specifications consist of critical quality control standards that are intended to assure that all batches of the drug product maintain the same batch-to-batch consistency.

Finally, the applicant has submitted 10 stability batches – all using different drug substance lots. The 10 lots were produced at a scale of at least 10% of the intended commercial batch. Real time stability data is available through 36 months. 10 additional stability batches were submitted by the commercial European supplier, who, upon NDA approval, will become the US supplier. These supportive stability lots were produced using the same lots of drug substance. At present, 10 months of real time stability data have been collected (for these stability lots).

Analysis of the supportive stability data for all 10 batches indicated that iloprost drug product remains within specification. In particular, there were no downward trends in iloprost concentration. Minimal increases in impurities were found. No changes were noted in solution appearance or color. Solution pH remained within the range of the specification with no apparent trends. In sum, the stability data support a shelf life of 36 months when stored at room temperature.

Finally, it is noted that the drug product solution is to be dosed via a nebulizer. In particular, a ProDose nebulizer is referenced in the submission. The ProDose nebulizer has received 510(k) approval on 22-APR-04 (K030747). The Center for Devices and Radiological Health (CDRH) was consulted regarding the equivalence of the ProDose nebulizer with the Halolite nebulizer, which was the nebulizer used in the clinical trials. CDRH (Ann Graham) responded that the ProDose delivery was substantially equivalent. The ProDose system is further discussed in Appendix A.4.

B. Description of How the Drug Product is Intended to be Used

Ventavis®(iloprost) Inhalation Solution is indicated for pulmonary arterial hypertension.

¹ The excipient 96% ethanol is referenced to the European Pharmacopeia.

Pulmonary arterial hypertension (PAH) is defined as a sustained elevation of pulmonary arterial pressure. Generally, the average blood pressure (BP) in a pulmonary artery is about 14 mmHg (at rest). In PAH, the average BP is usually greater than 25 mmHg.

The main vascular changes due to PAH are vasoconstriction, smooth-muscle cell and endothelial-cell proliferation, and thrombosis. These effects suggest an imbalance between vasodilators and vasoconstrictors, growth inhibitors and mitogenic factors, and antithrombotic and prothrombotic functions.

In particular, prostacyclin, a vasodilator, inhibits platelet activation and has anti-proliferative properties; in contrast, thromboxane A_2 is a potent vasoconstrictor and platelet agonist. In PAH the imbalance between these two molecules is shifted toward thromboxane A_2 . Hence, intervention with prostacyclin, or the prostacyclin analogue iloprost (the subject of this submission) should restore this balance.

Iloprost is delivered by inhalation via a nebulizer to patients with PAH. The proposed treatment regimen is an initial dose of 2.5 mcg (as delivered at the mouthpiece of the nebulizer). If this dose is well tolerated, the dose should be increased and maintained at 5 mcg. The administration frequency should be 6 – 9 times per day during waking hours and according to individual need and tolerability. *Note:* There will be residual solution remaining in the medication chamber of the nebulizer at the end of each treatment. This residual solution should be discarded after each use.

The rationale for the inhalation route of administration is to provide high local concentrations while minimizing the systemic side effects of prostacyclin therapy. Importantly, delivery of iloprost by inhalation avoids complications of the chronic indwelling catheters required for delivery of the i.v. or subcutaneous formulations of the prostacyclin analogues currently available.

C. Basis for Approvability or Not-Approval Recommendation

A final recommendation will be made when:

- a) the Office of Compliance has made their recommendation regarding the cGMP inspection, and
- b) the pending CMC issues have been resolved. A deficiency letter has been sent to the DMF holder detailing concerns and deficiencies that should be addressed. The DMF holder has promised an expeditious response.

III. Administrative

A. Reviewer's Signature

/s/ M.D. Cooper, Ph.D. and /s/ W.C. Timmer, Ph.D.

B. Endorsement Block

Chemistry Reviewers:	Monica D. Cooper, Ph.D.; Drug Substance William C. Timmer, Ph.D.; Drug Product
Chemistry Team Leader:	Kasturi Srinivasachar, Ph.D.
Project Manager:	Melissa Robb

C. CC Block

Orig. NDA 21-779
HFD-110/Division File
HFD-110/Team Leader/K. Srinivasachar
HFD-110/Review Chemist/M.D. Cooper
HFD-110/Review Chemist/W.C. Timmer
HFD-110/Project Manager/M. Robb

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/s/

Monica Cooper
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William Timmer
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Kasturi Srinivasachar
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