

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 29845

CHEMISTRY REVIEW(S)

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-845

DATE REVIEWED: 10-Nov-99

REVIEW #: 4

REVIEWER: JV Advani

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	26-Feb-97	27-Feb-97	03-Mar-97
AMENDMENT (BC)	28-Aug-97	02-Sep-97	04-Sep-97
AMENDMENT (BC)	17-Jun-97	19-Jun-97	24-Jun-97
AMENDMENT (BC)	16-Sep-97	17-Sep-97	18-Sep-97
Resubmission (INO Therapeutics)	25-May-99	26-May-99	04-Jun-99
AMENDMENT (BC)	13-Aug-99	17-Aug-99	20-Aug-99
AMENDMENT (BC)	27-Sep-99	28-Sep-99	30-Sep-99
AMENDMENT (BL)	06-Nov-99	08-Nov-99	10-Nov-99

NAME & ADDRESS OF APPLICANT:

INO Therapeutics, Inc.
54 Old Highway 22
Clinton, NJ 08809
(formerly Ohmeda PPD)

DRUG PRODUCT NAME

Proprietary:

Inhaled Nitric Oxide (INOMax)
This trade name was approved by LNC
Committee on 08/25/97
Nitric oxide
CAS 10102-43-9
I P

Established:

Code Name/#:

Chem.Type/Ther.Class:

PHARMACOL. CATEGORY/INDICATION:

Hypoxemic Respiratory Failure in the Term and
near-Term Newborn
Inhaled nitric oxide mixtures (nitric oxide in nitrogen)

DOSAGE FORM:

STRENGTHS:

100 ppm and 800 ppm

ROUTE OF ADMINISTRATION:

Inhaled

Rx/OTC:

Rx OTC

SPECIAL PRODUCTS:

Yes No

(If yes, fill out the form for special products and
deliver to TIA through team leader for data entry)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name:

Nitric oxide
Nitrogen (II) oxide

Molecular Formula: NO

Molecular Weight: 30.006

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
DMF	Seamless, high pressure steel Cylinders (Vol. 1.1 p0104-0106)		*Adequate	---	
DMF	High pressure, diaphragm seal, stainless steel valve. (Vol. 1.1, p. 0107-01088)		*Adequate	---	
DMF	O-rings		*Adequate	---	

* Firm has provided the necessary information in the submission.

RELATED DOCUMENTS (if applicable):

IND (Inhaled Nitric oxide - INO)
 IND Inhaled - INO

CONSULTS:

None

REMARKS/COMMENTS:

INOMax is a potent selective pulmonary vasodilator with minimal systemic cardiovascular effects. The drug product is composed of Nitric Oxide (NO) in Nitrogen (N2) at concentration of either 100 ppm or 800 ppm. It is packaged in aluminum cylinders fitted with a stainless steel valve seated with a Teflon O-ring. An EER for the establishment of Port Allen, LA, site was requested on 6/15/99 and it is acceptable. Expiration date: 36 months is proposed. 24 months stability data is provided and 30 months expiration date is acceptable. Methods validation will be requested to be performed by district laboratories. Amendment of 11/06/99- Firm has submitted on our request the proposed draft labels for cylinders, and for cardboard cylinder box. Also has included the pictures of size 88 cylinders and shrink wrap plastic which will be placed around each cylinder.

CONCLUSIONS & RECOMMENDATIONS:

The information on the draft copies of the labels for drug packages and product is reviewed and is satisfactory. However, we recommend the following storage statement in the labels. Store at 25°C (77° F) with excursions permitted between 15-30°C (59-86°F) (see USP Controlled Room Temperature). Container labels (gas cylinders) have now been provided and reviewed. The NDA may be approved from a chemistry viewpoint. The firm should be informed in the action letter that a 30 month expiration date can be granted for the drug product stored at 25° C temperature. And recommended storage statements should be included in the package insert and labels

/S/

JM Advani, Review Chemist

cc:
 Orig. NDA 20845
 HFD-110/Division File
 HFD-110/JADVANI /
 HFD-110/PM
 HFD-810/TEAM LEADER
 HFD-810/DIVISION DIRECTOR (JSimmons)
 R/D init by: KSrinivasachar
 Filename: NDA20854BC2.Doc

/S/
 11-18-99

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NOV - 5 1999

NDA #: 20-845

DATE REVIEWED: 21-Oct-99

REVIEW #: 3

REVIEWER: JV Advani

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	26-Feb-97	27-Feb-97	03-Mar-97
AMENDMENT (BC)	28-Aug-97	02-Sep-97	04-Sep-97
AMENDMENT (BC)	17-Jun-97	19-Jun-97	24-Jun-97
AMENDMENT (BC)	16-Sep-97	17-Sep-97	18-Sep-97
Resubmission (INO Therapeutics)	25-May-99	26-May-99	04-Jun-99
AMENDMENT (BC)	13-Aug-99	17-Aug-99	20-Aug-99
AMENDMENT (BC)	27-Sep-99	28-Sep-99	30-Sep-99

NAME & ADDRESS OF APPLICANT:

INO Therapeutics, Inc.
54 Old Highway 22
Clinton, NJ 08809
(formerly Ohmeda PPD)

DRUG PRODUCT NAME

Proprietary:

Inhaled Nitric Oxide (INOMax)
This trade name was approved by LNC
Committee on 08/25/97

Established:

Nitric oxide
CAS 10102-43-9
I P

Code Name/#:

Chem.Type/Ther.Class:

PHARMACOL. CATEGORY/INDICATION:

Hypoxemic Respiratory Failure in the Term and near-Term Newborn

DOSAGE FORM:

Inhaled nitric oxide mixtures (nitric oxide in nitrogen).

STRENGTHS:

100 ppm and 800 ppm

ROUTE OF ADMINISTRATION:

Inhaled

Rx/OTC:

Rx OTC

SPECIAL PRODUCTS:

Yes No

(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name:

Nitric oxide
Nitrogen (II) oxide

Molecular Formula: NO

Molecular Weight: 30.006

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
DMF	Seamless, high pressure steel Cylinders (Vol. 1.1 p0104-0106)		*Adequate	_____	
DMF	High pressure, diaphragm seal, stainless steel valve. (Vol. 1.1, p. 0107-01088)		*Adequate	_____	
DMF	O-rings		*Adequate	_____	

* Firm has provided the necessary information in the submission.

RELATED DOCUMENTS (if applicable):

IND (Inhaled Nitric oxide - INO)
IND (Inhaled - INO)

CONSULTS:

None

REMARKS/COMMENTS:

INOMax is a potent selective pulmonary vasodilator with minimal systemic cardiovascular effects. The drug product is composed of Nitric Oxide (NO) in Nitrogen (N2) at concentration of either 100 ppm or 800 ppm. It is packaged in aluminum cylinders fitted with a stainless steel valve seated with a Teflon O-ring.

An EER for the establishment of Port Allen, LA, site was requested on 6/15/99 and it is acceptable.

Expiration date: 36 months is proposed. 24 months stability data is provided and 30 months expiration date is acceptable.

Methods validation will be requested to be performed by district laboratories.

CONCLUSIONS & RECOMMENDATIONS:

The information submitted in this resubmission has been previously reviewed (refer to my 2 reviews). The firm has addressed our recommendations that were made during the 1997 submission (refer to review #2 of 10/07/97).

We recommend the following storage statement in the package insert:

Store at 25°C (77° F) with excursions permitted between 15-30°C (59-86°F) (see USP Controlled Room Temperature)..

The NDA may be approved from a chemistry viewpoint. The firm should be informed in the action letter that a 30 month expiration date can be granted for the drug product stored at 25° C temperature. Also Container labels (gas cylinder) should be provided.

TSI

Jy Advani, Review Chemist

cc:

Orig. NDA 20845
HFD-110/Division File
HFD-110/JADVANI/
HFD-110/PM
HFD-810/TEAM LEADER
HFD-810/DIVISION DIRECTOR (JSimmons)
R/D init by: KSrinivasachar
Filename: NDA20854BC

TSI
11-5-99

Z. McDonald

OCT 7 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-845 CHEM.REVIEW #: 2 REVIEW DATE: 2-Oct-97

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	26-Feb-97	27-Feb-97	03-Mar-97
Amendment (BC)	28-Aug-97	02-Sep-97	04-Sep-97
Amendment (BC)	17-Jun-97	19-Jun-97	24-Jun-97
Amendment (BC)	16-Sep-97	17-Sep-97	18-Sep-97

NAME & ADDRESS OF APPLICANT:

OHMEDA Inc.
Pharmaceutical Products Division
110 Allen Road
P.O. Box 804
Liberty Corner, NJ 07938-0804

DRUG PRODUCT NAME

Proprietary:

Inhaled Nitric Oxide (INOMax™)
This new trade name was approved
by LN committee on 8/25/97.

Nonproprietary/USAN:

Nitric Oxide

Code Name/#:

CAS 10102-43-9

Chem.Type/Ther.Class:

1 P

PHARMACOL.CATEGORY/INDICATION:

Selective respiratory hypoxia for
treatment of persistent pulmonary
hypertension and respiratory distress
syndrome in the new born.

STRENGTHS:

100 and 800 ppm

ROUTE OF ADMINISTRATION:

Inhaled

DISPENSED:

Rx OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:

NO

Chemical name(s):

Nitric oxide
Nitrogen (II) oxide

Molecular Formula:

NO

Molecular Weight: 30.006

SUPPORTING DOCUMENTS:

IND (Inhaled Nitric Oxide - INO)
IND (Inhaled - INO)

Drug Master Files:

DMF
DMF
DMF

* provided on our request (refer amendment of 6/17/97).

RELATED DOCUMENTS (if applicable):

Literature references are provided

CONSULTS: None.

REMARKS/COMMENTS:

Firm has submitted original NDA (under section 505 (b)(2) of the act for an orphan drug), for I-NO (Nitric Oxide) for Inhalation, 400 ppm (in nitrogen), packaged in size 88 (960 cu. in.) and size (172 cu. in.) seamless aluminum compressed gas cylinder with stainless steel valve and Teflon gasket. The drug product is administered using an inhalation system, at a recommended concentration of 20 ppm by dilution with air/oxygen for treatment of hypoxic respiratory failure in term and near-term infants.

Amendment of 8/28/97 provides for the 100 ppm (packaged in size D) and 800 ppm nitric oxide (packaged in sizes D and 88) cylinders in place of the 400 ppm cylinders submitted in original NDA package of 2/26/97.

Amendment of 6/17/97 is the response to the CMC deficiencies of our letter of 4/28/97.

Amendment of 09/16/97 is in response to my telephone conference with the firm on 09/15/97. Accordingly they have provided updated respond to comment #3 from the deficiency letter of 4/28/97. Also Firm will correct the oxygen concentration values (FiO2) shown in the package insert.

Inhaled nitric oxide has not been marketed or withdrawn from any country. Drug substance nitric oxide and drug product - inhaled nitric oxide mixtures will be manufactured, packaged, tested, and labeled at BOC Gases, Port Allen, LA.

CONCLUSIONS & RECOMMENDATIONS:

Deficiencies noted in the review #1, have been addressed in firm's letter of 6/17/97.

Firm in separate submission will correct the FiO2 values in the package insert. Firm will be asked to include chemical name next to the structure formula and also include all inactive ingredients (N2).

All other issues in CMC are resolved.

Methods validation package was send out to district laboratory on 7/17/97.

Firm has withdrawn this NDA (letter of 9/16/97) and intend to file again within 6 to 9 months.

cc:

Orig. NDA 20-845
HFD-110/Division File
HFD-110/JV Advani/10/02/97
HFD-110/CSO
HFD-810/C Hoiberg

R/D Init. by: SUPERVISOR

151
JV Advani, Review Chemist
filename: 20-845.2.NDA

151
1767

Z. McDonald
APR 16 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-845 CHEM.REVIEW #: 1 REVIEW DATE: 10-April-97

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	26-Feb-97	27-Feb-97	03-Mar-97

NAME & ADDRESS OF APPLICANT:
OHMEDA Inc.
Pharmaceutical Products Division
110 Allen Road
P.O. Box 804
Liberty Corner, NJ 07938-0804

DRUG PRODUCT NAME
Proprietary: Inhaled Nitric Oxide (I-NO)
Nonproprietary/USAN: Nitric Oxide
Code Name/#: CAS 10102-43-9
Chem.Type/Ther.Class: 1 P

PHARMACOL.CATEGORY/INDICATION: Selective respiratory hypoxia for treatment of persistent pulmonary hypertension and respiratory distress syndrome in the new born.
STRENGTHS: 400 ± 20 ppm

ROUTE OF ADMINISTRATION: Inhaled

DISPENSED: Rx OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:

NO

Chemical name(s): Nitric oxide
Nitrogen (II) oxide

Molecular Formula: NO Molecular Weight: 30.006

SUPPORTING DOCUMENTS:

IND (Inhaled Nitric Oxide - INO)
IND (Inhaled - INO)

Drug Master Files:

DMF
DMF
DMF

RELATED DOCUMENTS (if applicable):

Literature references are provided

CONSULTS: None.

REMARKS/COMMENTS:

Firm has submitted this NDA (under section 505 (b)(2) of the act for an orphan drug), for I-NO (Nitric Oxide) for Inhalation, 400 ppm (in nitrogen), packaged in size 88 (960 cu. in.) and size (172 cu. in.) seamless aluminum compressed gas cylinder with stainless steel valve and Teflon gasket. The drug product is administered using an inhalation system, at a recommended concentration of 20 ppm by dilution with air/oxygen for treatment of hypoxic respiratory failure in term and near-term infants.

Inhaled nitric oxide has not been marketed or withdrawn from any country. Drug substance nitric oxide and drug product - inhaled nitric oxide mixtures will be manufactured, packaged, tested, and labeled at BOC Gases, Port Allen, LA.

CONCLUSIONS & RECOMMENDATIONS:

Deficiencies noted in the review, have been summarized in the draft of the controls portion of the letter to the applicant.

cc:
Orig. NDA 20-845
HFD-110/Division File
HFD-110/JV Advani/4/14/97
HFD-110/CSO
HFD-810/C. Heiberg

R/D Init. by: SUPERVISOR

Q /S/

JV Advani, Review Chemist
filename: 20-845.NDA

4 /S/ 4/16/97