CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20845/ S-14

Trade Name: **INOMax**

Generic Name: **Nitric Oxide**

Sponsor: **Mallinckrodt Hospital**

Approval Date: 03/04/2013

Indications:

INOMAX is a vasodilator, which in conjunction with ventilatory support and appropriate agents, is indicated for the treatment of term and near term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.

- Monitor for $Pa0_2$ methemoglobin, and inspired NO_2 during INOmax administration
- Utilize additional therapies to maximize oxygen delivery

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20845/S-14

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Other Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20845/S-14

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20845/S-014

SUPPLEMENT APPROVAL

INO Therapeutics
Attention: Mary Ellen Anderson
Senior Director, Regulatory Affairs
Perryville III Corporate Park
53 Frontage Road, Third Floor
Hampton, NJ 08827-9001

Dear Ms. Anderson:

Please refer to your Supplemental New Drug Application (sNDA) dated June 25, 2012, submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for INOmax (nitric oxide) for inhalation.

This "Prior Approval" supplemental new drug application provides for labeling revised as follows:

1. Under HIGHLIGHTS/RECENT MAJOR CHANGES, changes to Dosage and Administration have been noted.

2. Under HIGHLIGHTS/DOSAGE AND ADMINISTRATION, the first bullet under "Administration" has been changed from:

   INOmax must be delivered via a system which does not cause generation of excessive inhaled nitrogen dioxide (2.2).

   To:

   Use only with an INOmax DS_{IR}®, INOmax® DS, or INOvent® operated by trained personnel (2.2)

3. Under HIGHLIGHTS/DOSAGE AND ADMINISTRATION, the second bullet under "Administration" has been changed from:

   Do not discontinue INOmax abruptly (2.2).

   To:

   Wean from INOmax gradually (2.2).

4. Under HIGHLIGHTS/WARNING AND PRECAUTIONS, the third paragraph has been changed from:

   Elevated NO_2 Levels: NO_2 levels should be monitored (5.3)

To:

Elevated NO_2 Levels: Monitor NO_2 levels continuously with a suitable Nitric Oxide Delivery System (5.3)

5. The HIGHLIGHTS/ADVERSE REACTIONS section has been changed from:

   Methemoglobinemia and elevated NO_2 levels are dose dependent adverse events. Worsening oxygenation and increasing pulmonary artery pressure occur if INOmax is discontinued abruptly. Other adverse reactions that occurred in more than 5% of patients receiving INOmax in the CINRGI study were: thrombocytopenia, hypokalemia, bilirubinemia, atelectasis, and hypotension (6).

   To:

   Methemoglobinemia and NO_2 levels are dose dependent. The most common adverse reaction is hypotension (6).

6. FULL PRESCRIBING INFORMATION: CONTENTS has been revised in accordance with changes made to the FULL PRESCRIBING INFORMATION.

7. Under INDICATIONS AND USAGE, "with validated ventilation systems *[see Dosage and Administration (2.2)]*" has been added to the first sentence of the second paragraph.

8. Under DOSAGE AND ADMINISTRATION, the following has been added as a new first paragraph:

   To ensure safe and effective administration of INOmax to avoid adverse events associated with nitric oxide or NO_2, administration of INOmax should only be performed by a health care professional who has completed and maintained training on the safe and effective use of a Nitric Oxide Delivery System provided by the manufacturer of the delivery system and the drug.

9. Under DOSAGE AND ADMINISTRATION, the Administration section has been significantly revised and now reads as follows:

   2.2 Administration

   Methemoglobin should be measured within 4-8 hours after initiation of treatment with INOmax and periodically throughout treatment *[see Warnings and Precautions (5.2)]*.

   Nitric Oxide Delivery Systems

   INOmax must be administered using the INOmax DS_{IR}®, INOmax® DS, or INOvent® Nitric Oxide Delivery Systems, which deliver operator-determined concentrations of nitric oxide in conjunction with a ventilator or breathing gas administration system after dilution with an oxygen/air mixture. A Nitric Oxide Delivery System includes a nitric oxide administration apparatus, a nitric oxide gas analyzer and a nitrogen dioxide gas analyzer. Failure to calibrate the Nitric Oxide Delivery System could result in under- or over- dosing of nitric oxide.

   To address potential power failure, keep available a backup battery power supply. To address potential system failure, keep available an independent reserve nitric oxide delivery system. Failure to transition to a reserve nitric oxide delivery system can result in abrupt or prolonged discontinuation of nitric oxide *[see Warnings and Precautions (5.1)]*.

Training in Administration

The user of INOmax and Nitric Oxide Delivery Systems must complete a comprehensive training program for health care professionals provided by the delivery system and drug manufacturers.

Health professional staff that administers nitric oxide therapy have access to supplier-provided 24 hour/365 days per year technical support on the delivery and administration of INOmax at 1-877-566-9466.

Weaning and Discontinuation

Abrupt discontinuation of INOmax may lead to increasing pulmonary artery pressure (PAP) and worsening oxygenation even in neonates with no apparent response to nitric oxide for inhalation. To wean INOmax, downtitrate in several steps, pausing several hours at each step to monitor for hypoxemia.

10. Under WARNINGS AND PRECAUTIONS, section 5.1 has been revised from:

Rebound
Abrupt discontinuation of INOmax may lead to worsening oxygenation and increasing pulmonary artery pressure.

To:

Rebound Pulmonary Hypertension Syndrome following Abrupt Discontinuation
Wean from INOmax *[see Dosage and Administration (2.2)]*. Abrupt discontinuation of INOmax may lead to worsening oxygenation and increasing pulmonary artery pressure, i.e., Rebound Pulmonary Hypertension Syndrome. Signs and symptoms of Rebound Pulmonary Hypertension Syndrome include hypoxemia, systemic hypotension, bradycardia, and decreased cardiac output. If Rebound Pulmonary Hypertension occurs, reinstate INOmax therapy immediately.

11. Under WARNINGS AND PRECAUTIONS, section 5.2 has been revised from:

Methemoglobinemia
Methemoglobinemia increases with the dose of nitric oxide. In clinical trials, maximum methemoglobin levels usually were reached approximately 8 hours after initiation of inhalation, although methemoglobin levels have peaked as late as 40 hours following initiation of INOmax therapy. In one study, 13 of 37 (35%) of neonates treated with INOmax 80 ppm had methemoglobin levels exceeding 7%. Following discontinuation or reduction of nitric oxide, the methemoglobin levels returned to baseline over a period of hours.

To:

Hypoxia from Methemoglobinemia
Nitric oxide combines with hemoglobin to form methemoglobin, which does not transport oxygen, Methemoglobin levels increase with the dose of INOmax; it can take 8 hours or more before steady-state methemoglobin levels are attained. Monitor methemoglobin and adjust the dose of INOmax to optimize oxygenation.
If methemoglobin levels do not resolve with decrease in dose or discontinuation of INOmax, additional therapy may be warranted to treat methemoglobinemia *[see Overdosage (10)]*.

12. Under WARNINGS AND PRECAUTIONS, section 5.3 has been revised from:

Elevated NO_2 Levels
In one study, NO_2 levels were <0.5 ppm when neonates were treated with placebo, 5 ppm, and 20 ppm nitric oxide over the first 48 hours. The 80 ppm group had a mean peak NO_2 level of 2.6 ppm.

To:

Airway Injury from Nitrogen Dioxide
Nitrogen dioxide (NO_2) forms in gas mixtures containing NO and O_2. Nitrogen dioxide may cause airway inflammation and damage to lung tissues. If the concentration of NO_2 in the breathing circuit exceeds 0.5 ppm, decrease the dose of INOmax.

If there is an unexpected change in NO_2 concentration, when measured in the breathing circuit, then the delivery system should be assessed in accordance with the Nitric Oxide Delivery System O&M Manual troubleshooting section, and the NO_2 analyzer should be recalibrated. The dose of INOmax and/or FiO_2 should be adjusted as appropriate.

13. Under WARNINGS AND PRECAUTIONS, section 5.4 has been revised from:

    Patients who had pre-existing left ventricular dysfunction treated with inhaled nitric oxide, even for short durations, experienced serious adverse events (e.g., pulmonary edema).

    To:

    Patients with left ventricular dysfunction treated with INOmax may experience pulmonary edema, increased pulmonary capillary wedge pressure, worsening of left ventricular dysfunction, systemic hypotension, bradycardia and cardiac arrest. Discontinue INOmax while providing symptomatic care.

14. Under ADVERSE REACTIONS/Clinical Trials Experience, Table 1 and the paragraph preceding it have been deleted and replaced with the following text:

    In CINRGI, the only adverse reaction (>2% higher incidence on INOmax than on placebo) was hypotension (14% vs. 11%).

15. Under ADVERSE REACTIONS, the Post-Marketing Experience section has been revised and now reads as follows:

    Accidental Exposure
    Based upon post-marketing experience, accidental exposure to nitric oxide for inhalation in hospital staff has been associated with chest discomfort, dizziness, dry throat, dyspnea, and headache.

16. Under DRUG INTERACTION, the reference to tolazoline has been deleted.

17. Under CLINICAL PHARMACOLOGY/Pharmacokinetics, the numerical subheadings for 12.4, 12.5, and 12.6 have been deleted.

18. Under CLINCAL STUDIES/CINRGI Study, the following has been added to the end of the section:

    In clinical trials, reduction in the need for ECMO has not been demonstrated with the use of inhaled nitric oxide in neonates with congenital diaphragmatic hernia (CDH).

19. All REFERENCES in section 15 have been deleted.

20. Under HOW SUPPLIED/STORAGE AND HANDLING, the following text has been added:

    All regulations concerning handling of pressure vessels must be followed.

    Protect the cylinders from shocks, falls, oxidizing and flammable materials, moisture, and sources of heat or ignition.

    The cylinders should be appropriately transported to protect from risks of shocks and falls.

21. Various editorial changes and corrections have been made throughout.

22. The revision dates have been updated.

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)

5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Russell Fortney, Regulatory Project Manager, at (301) 796-1068.

Sincerely,

{See appended electronic signature page}

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

Enclosure: Content of Labeling

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

/s/

NORMAN L STOCKBRIDGE
03/04/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20845/S-14

LABELING

INOMAX - nitric oxide gas
INO Therapeutics

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use INOmax safely and effectively. See full prescribing information for INOmax.

INOmax (nitric oxide) for inhalation
Initial U.S. Approval: 1999

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.2) 3/2013

----------INDICATIONS AND USAGE----------

INOmax is a vasodilator, which, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation (1.1).

Monitor for PaO_2, methemoglobin, and inspired NO_2 during INOmax administration (1.1).

Utilize additional therapies to maximize oxygen delivery (1.1).

----------DOSAGE AND ADMINISTRATION----------

Dosage: The recommended dose of INOmax is 20 ppm, maintained for up to 14 days or until the underlying oxygen desaturation has resolved (2.1).
Administration:

- Use only with an INOmax DS_{IR}®, INOmax® DS, or INOvent® operated by trained personnel (2.2)
- Wean from INOmax gradually (2.2).

----------DOSAGE FORMS AND STRENGTHS----------

INOmax (nitric oxide) is a gas available in 100 ppm and 800 ppm concentrations (3).

----------CONTRAINDICATIONS----------

Neonates known to be dependent on right-to-left shunting of blood (4).

----------WARNINGS AND PRECAUTIONS----------

Rebound: Abrupt discontinuation of INOmax may lead to worsening oxygenation and increasing pulmonary artery pressure (5.1).

Methemoglobinemia: Methemoglobin increases with the dose of nitric oxide; following discontinuation or reduction of nitric oxide, methemoglobin levels return to baseline over a period of hours (5.2).

Elevated NO_2 Levels: Monitor NO_2 levels continuously with a suitable Nitric Oxide Delivery System (5.3).

Heart Failure: In patients with pre-existing left ventricular dysfunction, INOmax may increase pulmonary capillary wedge pressure leading to pulmonary edema (5.4).

----------ADVERSE REACTIONS----------

Methemoglobinemia and NO_2 levels are dose dependent. The most common adverse reaction is hypotension (6).

To report SUSPECTED ADVERSE REACTIONS, contact INO Therapeutics at 1-877-566-9466 and http://www.inomax.com/ or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Nitric oxide donor agents: Nitric oxide donor compounds, such as prilocaine, sodium nitroprusside, and nitroglycerin, when administered as oral, parenteral, or topical formulations, may have an additive effect with INOmax on the risk of developing methemoglobinemia (7).

Revised: 3/2013

FULL PRESCRIBING INFORMATION:
CONTENTS*

*** Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Hypoxic Respiratory Failure

INOmax® is a vasodilator, which, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.

Utilize additional therapies to maximize oxygen delivery with validated ventilation systems *[see Dosage and Administration (2.2)]*. In patients with collapsed alveoli, additional therapies might include surfactant and high-frequency oscillatory ventilation.

The safety and effectiveness of INOmax have been established in a population receiving other therapies for hypoxic respiratory failure, including vasodilators, intravenous fluids, bicarbonate therapy, and mechanical ventilation. Different dose regimens for nitric oxide were used in the clinical studies *[see Clinical Studies (14)]*.

Monitor for PaO_2, methemoglobin, and inspired NO_2 during INOmax administration.

2 DOSAGE AND ADMINISTRATION

To ensure safe and effective administration of INOmax to avoid adverse events associated with nitric oxide or NO_2, administration of INOmax should only be performed by a health care professional who has completed and maintained training on the safe and effective use of a Nitric Oxide Delivery System provided by the manufacturer of the delivery system and the drug.

2.1 Dosage

Term and near-term neonates with hypoxic respiratory failure

The recommended dose of INOmax is 20 ppm. Treatment should be maintained up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from INOmax therapy.

As the risk of methemoglobinemia and elevated NO_2 levels increases significantly when INOmax is administered at doses >20 ppm; doses above this level are not recommended.

2.2 Administration

Methemoglobin should be measured within 4-8 hours after initiation of treatment with INOmax and periodically throughout treatment *[see Warnings and Precautions (5.2)]*.

Nitric Oxide Delivery Systems

INOmax must be administered using the INOmax DS_{IR}®, INOmax® DS, or INOvent® Nitric Oxide Delivery Systems, which deliver operator-determined concentrations of nitric oxide in conjunction with a ventilator or breathing gas administration system after dilution with an oxygen/air mixture. A Nitric Oxide Delivery System includes a nitric oxide administration apparatus, a nitric oxide gas analyzer and a nitrogen dioxide gas analyzer. Failure to calibrate the Nitric Oxide Delivery System could result in under- or over- dosing of nitric oxide.

To address potential power failure, keep available a backup battery power supply. To address potential system failure, keep available an independent reserve nitric oxide delivery system. Failure to transition to a reserve nitric oxide delivery system can result in abrupt or prolonged discontinuation of nitric oxide *[see Warnings and Precautions (5.1)]*.

Training in Administration

The user of INOmax and Nitric Oxide Delivery Systems must complete a comprehensive training program for health care professionals provided by the delivery system and drug manufacturers.

Health professional staff that administers nitric oxide therapy have access to supplier-provided 24 hour/365 days per year technical support on the delivery and administration of INOmax at 1-877-566-9466.

Weaning and Discontinuation

Abrupt discontinuation of INOmax may lead to increasing pulmonary artery pressure (PAP) and worsening oxygenation even in neonates with no apparent response to nitric oxide for inhalation. To wean INOmax, downtitrate in several steps, pausing several hours at each step to monitor for hypoxemia.

3 DOSAGE FORMS AND STRENGTHS

INOmax (nitric oxide) for inhalation is a gas available in 100 ppm and 800 ppm concentrations.

4 CONTRAINDICATIONS

INOmax is contraindicated in the treatment of neonates known to be dependent on right-to-left shunting of blood.

5 WARNINGS AND PRECAUTIONS

5.1 Rebound Pulmonary Hypertension Syndrome following Abrupt Discontinuation

Wean from INOmax *[see Dosage and Administration (2.2)]*. Abrupt discontinuation of INOmax may lead to worsening oxygenation and increasing pulmonary artery pressure, i.e., Rebound Pulmonary Hypertension Syndrome. Signs and symptoms of Rebound Pulmonary Hypertension Syndrome include hypoxemia, systemic hypotension, bradycardia, and decreased cardiac output. If Rebound Pulmonary Hypertension occurs, reinstate INOmax therapy immediately.

5.2 Hypoxemia from Methemoglobinemia

Nitric oxide combines with hemoglobin to form methemoglobin, which does not transport oxygen, Methemoglobin levels increase with the dose of INOmax; it can take 8 hours or more

before steady-state methemoglobin levels are attained. Monitor methemoglobin and adjust the dose of INOmax to optimize oxygenation.

If methemoglobin levels do not resolve with decrease in dose or discontinuation of INOmax, additional therapy may be warranted to treat methemoglobinemia *[see Overdosage (10)]*.

5.3 Airway Injury from Nitrogen Dioxide

Nitrogen dioxide (NO_2) forms in gas mixtures containing NO and O_2. Nitrogen dioxide may cause airway inflammation and damage to lung tissues. If the concentration of NO_2 in the breathing circuit exceeds 0.5 ppm, decrease the dose of INOmax.

If there is an unexpected change in NO_2 concentration, when measured in the breathing circuit, then the delivery system should be assessed in accordance with the Nitric Oxide Delivery System O&M Manual troubleshooting section, and the NO_2 analyzer should be recalibrated. The dose of INOmax and/or FiO_2 should be adjusted as appropriate.

5.4 Heart Failure

Patients with left ventricular dysfunction treated with INOmax may experience pulmonary edema, increased pulmonary capillary wedge pressure, worsening of left ventricular dysfunction, systemic hypotension, bradycardia and cardiac arrest. Discontinue INOmax while providing symptomatic care.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from the clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

6.1 Clinical Trials Experience

Controlled studies have included 325 patients on INOmax doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOmax, a result adequate to exclude INOmax mortality being more than 40% worse than placebo.

In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOmax and placebo-treated groups.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOmax and 212 patients who received placebo. Among these patients, there was no evidence of an adverse effect of treatment on the need for rehospitalization, special medical services, pulmonary disease, or neurological sequelae.

In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, periventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

In CINRGI, the only adverse reaction (>2% higher incidence on INOmax than on placebo) was hypotension (14% vs. 11%).

6.2 Post-Marketing Experience

Accidental Exposure

Based upon post-marketing experience, accidental exposure to nitric oxide for inhalation in hospital staff has been associated with chest discomfort, dizziness, dry throat, dyspnea, and headache.

7 DRUG INTERACTIONS

No formal drug-interaction studies have been performed, and a clinically significant interaction with other medications used in the treatment of hypoxic respiratory failure cannot be excluded based on the available data. INOmax has been administered with dopamine, dobutamine, steroids, surfactant, and high-frequency ventilation. Although there are no study data to evaluate the possibility, nitric oxide donor compounds, including sodium nitroprusside and nitroglycerin, may have an additive effect with INOmax on the risk of developing methemoglobinemia. An association between prilocaine and an increased risk of methemoglobinemia, particularly in infants, has specifically been described in a literature case report. This risk is present whether the drugs are administered as oral, parenteral, or topical formulations.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with INOmax. It is not known if INOmax can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. INOmax is not intended for adults.

8.2 Labor and Delivery

The effect of INOmax on labor and delivery in humans is unknown.

8.3 Nursing Mothers

Nitric oxide is not indicated for use in the adult population, including nursing mothers. It is not known whether nitric oxide is excreted in human milk.

8.4 Pediatric Use

The safety and efficacy of nitric oxide for inhalation has been demonstrated in term and near-term neonates with hypoxic respiratory failure associated with evidence of pulmonary hypertension *[see Clinical Studies (14.1)]*. Additional studies conducted in premature neonates for the prevention of bronchopulmonary dysplasia have not demonstrated substantial evidence of

efficacy *[see Clinical Studies (14.3)]*. No information about its effectiveness in other age populations is available.

8.5 Geriatric Use

Nitric oxide is not indicated for use in the adult population.

10 OVERDOSAGE

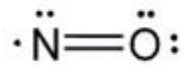
Overdosage with INOmax will be manifest by elevations in methemoglobin and pulmonary toxicities associated with inspired NO_2. Elevated NO_2 may cause acute lung injury. Elevations in methemoglobin reduce the oxygen delivery capacity of the circulation. In clinical studies, NO_2 levels >3 ppm or methemoglobin levels >7% were treated by reducing the dose of, or discontinuing, INOmax.

Methemoglobinemia that does not resolve after reduction or discontinuation of therapy can be treated with intravenous vitamin C, intravenous methylene blue, or blood transfusion, based upon the clinical situation.

11 DESCRIPTION

INOmax (nitric oxide gas) is a drug administered by inhalation. Nitric oxide, the active substance in INOmax, is a pulmonary vasodilator. INOmax is a gaseous blend of nitric oxide and nitrogen (0.08% and 99.92%, respectively for 800 ppm; 0.01% and 99.99%, respectively for 100 ppm). INOmax is supplied in aluminum cylinders as a compressed gas under high pressure (2000 pounds per square inch gauge [psig]).

The structural formula of nitric oxide (NO) is shown below:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nitric oxide is a compound produced by many cells of the body. It relaxes vascular smooth muscle by binding to the heme moiety of cytosolic guanylate cyclase, activating guanylate cyclase and increasing intracellular levels of cyclic guanosine 3',5'-monophosphate, which then leads to vasodilation. When inhaled, nitric oxide selectively dilates the pulmonary vasculature, and because of efficient scavenging by hemoglobin, has minimal effect on the systemic vasculature.

INOmax appears to increase the partial pressure of arterial oxygen (PaO_2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from lung regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios.

12.2 Pharmacodynamics

Effects on Pulmonary Vascular Tone in PPHN

Persistent pulmonary hypertension of the newborn (PPHN) occurs as a primary developmental defect or as a condition secondary to other diseases such as meconium aspiration syndrome (MAS), pneumonia, sepsis, hyaline membrane disease, congenital diaphragmatic hernia (CDH), and pulmonary hypoplasia. In these states, pulmonary vascular resistance (PVR) is high, which results in hypoxemia secondary to right-to-left shunting of blood through the patent ductus arteriosus and foramen ovale. In neonates with PPHN, INOmax improves oxygenation (as indicated by significant increases in PaO_2).

12.3 Pharmacokinetics

The pharmacokinetics of nitric oxide has been studied in adults.

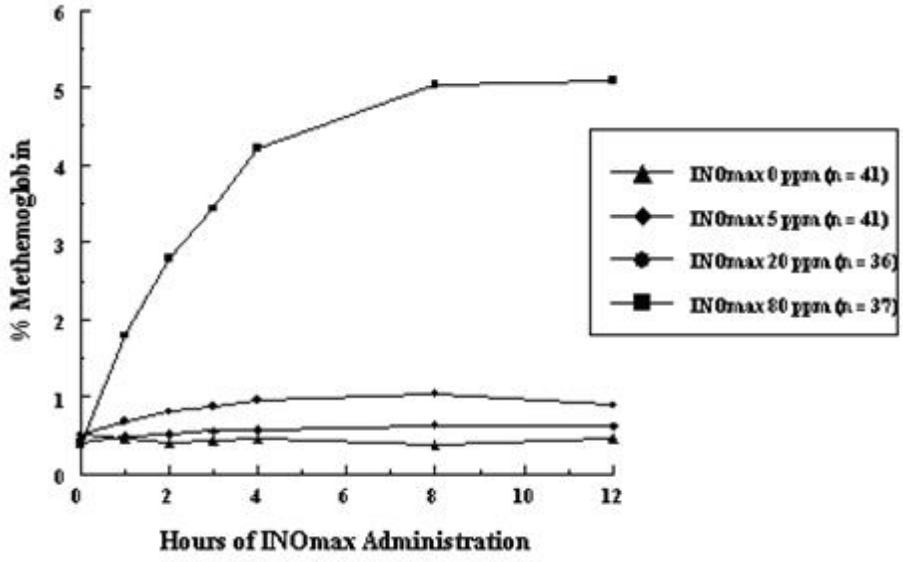
Uptake and Distribution

Nitric oxide is absorbed systemically after inhalation. Most of it traverses the pulmonary capillary bed where it combines with hemoglobin that is 60% to 100% oxygen-saturated. At this level of oxygen saturation, nitric oxide combines predominantly with oxyhemoglobin to produce methemoglobin and nitrate. At low oxygen saturation, nitric oxide can combine with deoxyhemoglobin to transiently form nitrosylhemoglobin, which is converted to nitrogen oxides and methemoglobin upon exposure to oxygen. Within the pulmonary system, nitric oxide can combine with oxygen and water to produce nitrogen dioxide and nitrite, respectively, which interact with oxyhemoglobin to produce methemoglobin and nitrate. Thus, the end products of nitric oxide that enter the systemic circulation are predominantly methemoglobin and nitrate.

Metabolism

Methemoglobin disposition has been investigated as a function of time and nitric oxide exposure concentration in neonates with respiratory failure. The methemoglobin (MetHb) concentration-time profiles during the first 12 hours of exposure to 0, 5, 20, and 80 ppm INOmax are shown in Figure 1.

Figure 1: Methemoglobin Concentration-Time Profiles Neonates Inhaling 0, 5, 20 or 80 ppm INOmax



Methemoglobin concentrations increased during the first 8 hours of nitric oxide exposure. The mean methemoglobin level remained below 1% in the placebo group and in the 5 ppm and 20 ppm INOmax groups, but reached approximately 5% in the 80 ppm INOmax group. Methemoglobin levels >7% were attained only in patients receiving 80 ppm, where they comprised 35% of the group. The average time to reach peak methemoglobin was 10 ± 9 (SD) hours (median, 8 hours) in these 13 patients, but one patient did not exceed 7% until 40 hours.

Elimination

Nitrate has been identified as the predominant nitric oxide metabolite excreted in the urine, accounting for >70% of the nitric oxide dose inhaled. Nitrate is cleared from the plasma by the kidney at rates approaching the rate of glomerular filtration.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of a carcinogenic effect was apparent, at inhalation exposures up to the recommended dose (20 ppm), in rats for 20 hr/day for up to two years. Higher exposures have not been investigated.

Nitric oxide has demonstrated genotoxicity in Salmonella (Ames Test), human lymphocytes, and after *in vivo* exposure in rats. There are no animal or human studies to evaluate nitric oxide for effects on fertility.

14 CLINICAL STUDIES

14.1 Treatment of Hypoxic Respiratory Failure (HRF)

The efficacy of INOmax has been investigated in term and near-term newborns with hypoxic respiratory failure resulting from a variety of etiologies. Inhalation of INOmax reduces the oxygenation index (OI= mean airway pressure in cm H_2O × fraction of inspired oxygen concentration [FiO_2]× 100 divided by systemic arterial concentration in mm Hg [PaO_2]) and increases PaO_2 *[see Clinical Pharmacology (12.1)]*.

NINOS Study

The Neonatal Inhaled Nitric Oxide Study (NINOS) was a double-blind, randomized, placebo-controlled, multicenter trial in 235 neonates with hypoxic respiratory failure. The objective of the study was to determine whether inhaled nitric oxide would reduce the occurrence of death and/or initiation of extracorporeal membrane oxygenation (ECMO) in a prospectively defined cohort of term or near-term neonates with hypoxic respiratory failure unresponsive to conventional therapy. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS; 49%), pneumonia/sepsis (21%), idiopathic primary pulmonary hypertension of the newborn (PPHN; 17%), or respiratory distress syndrome (RDS; 11%). Infants ≤14 days of age (mean, 1.7 days) with a mean PaO_2 of 46 mm Hg and a mean oxygenation index (OI) of 43 cm H_2O / mm Hg were initially randomized to receive 100% O_2 with (n=114) or without (n=121) 20 ppm nitric oxide for up to 14 days. Response to study drug was defined as a change from baseline in PaO_2 30 minutes after starting treatment (full response = >20 mm Hg, partial = 10–20 mm Hg, no response = <10 mm Hg). Neonates with a less than full response were evaluated for a response to 80 ppm nitric oxide or control gas. The primary results from the NINOS study are presented in Table 2.

Table 2: Summary of Clinical Results from NINOS Study

	Control (n=121)	NO (n=114)	P value
Death or ECMO[*,†]	77 (64%)	52 (46%)	0.006
Death	20 (17%)	16 (14%)	0.60
ECMO	66 (55%)	44 (39%)	0.014

[*] Extracorporeal membrane oxygenation

[†] Death or need for ECMO was the study's primary end point

Although the incidence of death by 120 days of age was similar in both groups (NO, 14%; control, 17%), significantly fewer infants in the nitric oxide group required ECMO compared with controls (39% vs. 55%, p = 0.014). The combined incidence of death and/or initiation of ECMO showed a significant advantage for the nitric oxide treated group (46% vs. 64%, p = 0.006). The nitric oxide group also had significantly greater increases in PaO_2 and greater decreases in the OI and the alveolar-arterial oxygen gradient than the control group (p<0.001 for all parameters). Significantly more patients had at least a partial response to the initial administration of study drug in the nitric oxide group (66%) than the control group (26%, p<0.001). Of the 125 infants who did not respond to 20 ppm nitric oxide or control, similar percentages of NO-treated (18%) and control (20%) patients had at least a partial response to 80

ppm nitric oxide for inhalation or control drug, suggesting a lack of additional benefit for the higher dose of nitric oxide. No infant had study drug discontinued for toxicity. Inhaled nitric oxide had no detectable effect on mortality. The adverse events collected in the NINOS trial occurred at similar incidence rates in both treatment groups *[see Adverse Reactions (6.1)]*. Follow-up exams were performed at 18–24 months for the infants enrolled in this trial. In the infants with available follow-up, the two treatment groups were similar with respect to their mental, motor, audiologic, or neurologic evaluations.

CINRGI Study

This study was a double-blind, randomized, placebo-controlled, multicenter trial of 186 term and near-term neonates with pulmonary hypertension and hypoxic respiratory failure. The primary objective of the study was to determine whether INOmax would reduce the receipt of ECMO in these patients. Hypoxic respiratory failure was caused by MAS (35%), idiopathic PPHN (30%), pneumonia/sepsis (24%), or RDS (8%). Patients with a mean PaO_2 of 54 mm Hg and a mean OI of 44 cm H_2O / mm Hg were randomly assigned to receive either 20 ppm INOmax (n=97) or nitrogen gas (placebo; n=89) in addition to their ventilatory support. Patients who exhibited a PaO_2 >60 mm Hg and a pH < 7.55 were weaned to 5 ppm INOmax or placebo. The primary results from the CINRGI study are presented in Table 3.

Table 3: Summary of Clinical Results from CINRGI Study

	Placebo	INOmax	P value
ECMO[*,†]	51/89 (57%)	30/97 (31%)	<0.001
Death	5/89 (6%)	3/97 (3%)	0.48

[*] Extracorporeal membrane oxygenation

[†] ECMO was the primary end point of this study

Significantly fewer neonates in the INOmax group required ECMO compared to the control group (31% vs. 57%, p<0.001). While the number of deaths were similar in both groups (INOmax, 3%; placebo, 6%), the combined incidence of death and/or receipt of ECMO was decreased in the INOmax group (33% vs. 58%, p<0.001).

In addition, the INOmax group had significantly improved oxygenation as measured by PaO_2, OI, and alveolar-arterial gradient (p<0.001 for all parameters). Of the 97 patients treated with INOmax, 2 (2%) were withdrawn from study drug due to methemoglobin levels >4%. The frequency and number of adverse events reported were similar in the two study groups *[see Adverse Reactions (6.1)]*.

In clinical trials, reduction in the need for ECMO has not been demonstrated with the use of inhaled nitric oxide in neonates with congenital diaphragmatic hernia (CDH).

14.2 Ineffective in Adult Respiratory Distress Syndrome (ARDS)

In a randomized, double-blind, parallel, multicenter study, 385 patients with adult respiratory distress syndrome (ARDS) associated with pneumonia (46%), surgery (33%), multiple trauma (26%), aspiration (23%), pulmonary contusion (18%), and other causes, with PaO_2/FiO_2 <250

mm Hg despite optimal oxygenation and ventilation, received placebo (n=193) or INOmax (n=192), 5 ppm, for 4 hours to 28 days or until weaned because of improvements in oxygenation. Despite acute improvements in oxygenation, there was no effect of INOmax on the primary endpoint of days alive and off ventilator support. These results were consistent with outcome data from a smaller dose ranging study of nitric oxide (1.25 to 80 ppm). INOmax is not indicated for use in ARDS.

14.3 Ineffective in Prevention of Bronchopulmonary Dysplasia (BPD)

The safety and efficacy of INOmax for the prevention of chronic lung disease [bronchopulmonary dysplasia, (BPD)] in neonates ≤ 34 weeks gestational age requiring respiratory support has been studied in three large, multi-center, double-blind, placebo-controlled clinical trials in a total of 2,149 preterm infants. Of these, 1,068 received placebo, and 1,081 received inhaled nitric oxide at doses ranging from 5-20 ppm, for treatment periods of 7-24 days duration. The primary endpoint for these studies was alive and without BPD at 36 weeks postmenstrual age (PMA). The need for supplemental oxygen at 36 weeks PMA served as a surrogate endpoint for the presence of BPD. Overall, efficacy for the prevention of bronchopulmonary dysplasia in preterm infants was not established. There were no meaningful differences between treatment groups with regard to deaths, methemoglobin levels, or adverse events commonly observed in premature infants, including intraventricular hemorrhage, patent ductus arteriosus, pulmonary hemorrhage, and retinopathy of prematurity. The use of INOmax for prevention of BPD in preterm neonates ≤ 34 weeks gestational age is not indicated.

16 HOW SUPPLIED/STORAGE AND HANDLING

INOmax (nitric oxide) is available in the following sizes:

Size D	Portable aluminum cylinders containing 353 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 344 liters) (NDC 64693-002-01)
Size D	Portable aluminum cylinders containing 353 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 344 liters) (NDC 64693-001-01)
Size 88	Aluminum cylinders containing 1963 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 1918 liters) (NDC 64693-002-02)
Size 88	Aluminum cylinders containing 1963 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 1918 liters) (NDC 64693-001-02)

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

All regulations concerning handling of pressure vessels must be followed.

Protect the cylinders from shocks, falls, oxidizing and flammable materials, moisture, and sources of heat or ignition.

The cylinders should be appropriately transported to protect from risks of shocks and falls.

Occupational Exposure

The exposure limit set by the Occupational Safety and Health Administration (OSHA) for nitric oxide is 25 ppm, and for NO_2 the limit is 5 ppm.

INO Therapeutics
Perryville III Corporate Park
53 Frontage Road, Third Floor
P.O. Box 9001
Hampton, NJ 08827-9001
USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20845/S-14

OTHER REVIEW(S)

Center for Drug Evaluation and Research

Division of Cardiovascular and Renal Products

Label Review

NDA: 20,845/S014

Name of Drug: INOmax (nitric oxide)

Sponsor/Monitors: INO Therapeutics

Date of Submission: 6/25/12

Date Review Completed: 11/26/12

Reviewer: Gail Moreschi, M.D., MPH, FACP

INOmax was originally approved by the FDA on December 23, 1999. The current INOmax label is dated July 2011. This proposed safety label supplement reflects changes that have occurred in Canada and the EU and includes updates in the following sections:

- Section 2 Dose and Administration (Strengthened emphasis on training)
- Section 2.2 Administration (Strengthened emphasis on avoiding abrupt discontinuation, provided description of the device features and components of training necessary to assure safe use.)
- Section 5.1 Warnings and Precautions. Abrupt Discontinuation of INOmax/Rebound (Added mitigation steps)
- Section 5.3 Warnings and Precautions. Elevated NO levels (add mitigation steps)
- (b) (4)
- Section 6.1 Adverse Reactions. Clinical Trial Experience (CINRGI trial adverse reactions)
- Section 6.2 Adverse Reactions. Post Marketing Experience (Most recent evaluation of post-marketing data)

CDRH will review the modifications in the Sections that pertain to the safe use of the device in the Nitric Oxide Delivery Systems (above Sections 2, 2.2, 5.1, and 5.3).

Health Canada requested the addition of a training program to their label for healthcare professionals. The EMA requested that the adverse events reported in the CINRGI clinical trial and the post-marketing section be updated and therefore changes have been made to Sections 6.1 and 6.2.

For this proposed safety label update the sponsor has submitted two volumes which include the Canadian Product Monograph, the EMA Label Justification Document, the synopsis and safety sections of the CINRGI Study and the INOT27 Study, and supporting journal articles.

(b) (4)

(b) (4)

The sponsor has reviewed the adverse events reported in the CINRGI clinical trial and the post-marketing experience with INOmax and has reviewed this data to identify adverse events that have a reasonable possibility of a causal relationship with INOmax. The sponsor determined that this newly assessed safety data warranted a label change under **Section 6: Adverse Reactions**. These label changes are:

- Section 6.1: "Clinical Trial Experience". There is a revision to the CINRGI Adverse Reactions table and the preceding paragraph to include events that have been assessed for seriousness, frequency and strength of causal association with INOmax.
- Section 6.2: "Post-Marketing Experience". There are revisions to the Post-marketing data based on an assessment of post marketing data received cumulatively through 31 March 2011 for patients < 1 year of age. Accidental Exposure is a new subsection included under Post-Marketing Experience.

Attached is the proposed finalized copy of the updated label and a comparison of the current label to the changes in the proposed label.

Recommendations:

The changes and information regarding the device in the Nitric Oxide Delivery Systems will be reviewed by CDRH. The other safety changes as proposed in the INOmax label supplement are acceptable to this medical reviewer.

28 page(s) of Draft Labeling has been withheld in Full as b4 (CCI/TS)immediately following this page

---

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

/s/

GAIL I MORESCHI
11/26/2012

RHPM Review of Labeling

Application:	NDA 20845/S-014
Sponsor:	INO Therapeutics
Product:	INOmax (nitric oxide) for inhalation
Submission Date:	June 25, 2012
Receipt Date:	June 26, 2012
Type of Submission:	Prior Approval Supplement

Background:

This supplement proposed labeling revisions to harmonize labeling with changes already made to EU and Canadian labeling, to reflect safety enhancements, and to incorporate into the label some language in the FDA guidance on Special Controls for nitric oxide delivery systems.

Proposed Changes:

The following changes were requested by the sponsor:

1. Under HIGHLIGHTS/RECENT MAJOR CHANGES, changes to Administration, Warnings and Precautions, and Adverse Reactions have been noted.

   Review: [redacted (b) (4)] "[redacted (b) (4)] changed to "Dosage and Administration (2.2)".

2. Under HIGHLIGHTS/DOSAGE AND ADMINISTRATION, a new first bullet for the Administration section has been added:

   Use only with an INOmax DSIR, INOmax DS, or INOvent operated by trained personnel (2.2)

   Review: Acceptable.

3. The revision dates have been updated.

   Review: Acceptable.

4. Various editorial changes and correction have been made throughout.

   Review: Acceptable; these are minor formatting changes.

5. Under HIGHLIGHTS/WARNING AND PRECAUTIONS, the third paragraph has been changed from:

   Elevated NO2 Levels: NO2 levels should be monitored (5.3)

To:

Elevated NO2 Levels: [redacted] (b) (4)

Review: Acceptable with slight modification (see attached label).

6. Throughout, "inhaled nitric oxide" has been changed to "INOmax" and references to "a Nitric Oxide Delivery System" have been added where appropriate.

   Review: Acceptable.

7. Under INDICATIONS AND USAGE, the "with validated ventilation systems *[see Administration (2.2)]* has been added to the first sentence of the second paragraph.

   Review: Acceptable.

8. Under DOSAGE AND ADMINISTRATION, the following has been added as a new first paragraph:

   To ensure safe and effective administration of INOmax to avoid adverse events associated with nitric oxide or NO2, administration of INOmax should only be performed by a health care professional who has completed and maintained training on the safe and effective use of a Nitric Oxide Delivery System provided by the manufacturer of the delivery system and the drug.

   Review: Acceptable.

9. Under DOSAGE AND ADMINISTRATION, the Administration section has been significantly revised and now reads as follows:

2 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

(b) (4) Abrupt discontinuation of INOmax may lead to increasing pulmonary artery pressure (PAP) and worsening oxygenation even in neonates with no apparent response to nitric oxide for inhalation.

Review: Dr. Stockbridge substantially revised this section.

10. The DOSAGE FORMS AND STRENGTHS section has been changed from:

    Nitric oxide is a gas available in 100 ppm and 800 ppm concentrations.

    To:

    INOmax (nitric oxide) for inhalation is a gas available in 100 ppm and 800 ppm concentrations (b) (4)

    Review: The blue text was deleted by Dr. Stockbridge.

11. Under WARNINGS AND PRECAUTIONS, section 5.1 has been revised from:

    Abrupt discontinuation of INOmax may lead to worsening oxygenation and increasing pulmonary artery pressure.

    To:

    (b) (4)

    Abrupt discontinuation of INOmax may lead to worsening oxygenation and increasing pulmonary artery pressure, i.e. Rebound Pulmonary Hypertension Syndrome. Signs and symptoms of Rebound Pulmonary Hypertension Syndrome include: Hypoxemia (b) (4) Systemic Hypotension, Bradycardia, and decrease in Cardiac Output.

    If Rebound Pulmonary Hypertension occurs (b) (4) reinstate INOmax therapy immediately.

    (b) (4)

    Review: Dr. Stockbridge substantially revised this section (see attached label).

12. Under WARNINGS AND PRECAUTIONS, section 5.2 has been revised from:

Methemoglobinemia increases with the dose of nitric oxide. In clinical trials, maximum methemoglobin levels usually were reached approximately 8 hours after initiation of inhalation, although methemoglobin levels have peaked as late as 40 hours following initiation of INOmax therapy. In one study, 13 of 37 (35%) of neonates treated with INOmax 80 ppm had methemoglobin levels exceeding 7%. Following discontinuation or reduction of nitric oxide, the methemoglobin levels returned to baseline over a period of hours.

To:

If methemoglobin levels do not resolve with decrease in dose or discontinuation of INOmax, additional therapy may be warranted to treat methemoglobinemia [see OVERDOSAGE (10)].

Review: Dr. Stockbridge revised this section (see attached label).

13. Under WARNINGS AND PRECAUTIONS, section 5.3 has been revised from:

In one study, NO2 levels were <0.5 ppm when neonates were treated with placebo, 5 ppm, and 20 ppm nitric oxide over the first 48 hours. The 80 ppm group had a mean peak NO2 level of 2.6 ppm.

To:

Nitrogen dioxide (NO_2) forms in gas mixtures containing NO and O_2. Nitrogen dioxide may cause airway inflammation and damage to lung tissues. Therefore, if the concentration of NO_2 in the breathing circuit exceeds 0.5 ppm, the dose of INOmax should be reduced. INOmax should only be administered with a Nitric Oxide Delivery System capable of continually monitoring NO_2. (b) (4) If there is an unexpected change in NO_2 concentration, when measured in the breathing circuit, then the delivery system should be assessed in accordance with the Nitric Oxide Delivery System O&M Manual troubleshooting section, and the NO_2 analyzer should be recalibrated. The dose of INOmax and/or FiO_2 should be adjusted as appropriate.

Review: Dr. Stockbridge revised this section (see attached label).

14. Under WARNINGS AND PRECAUTIONS, section 5.4 has been revised from:

Patients who had pre-existing left ventricular dysfunction treated with inhaled nitric oxide, even for short durations, experienced serious adverse events (e.g., pulmonary edema).

To:

Patients who have pre-existing left ventricular dysfunction treated with INOmax [redacted], may experience pulmonary edema, increased pulmonary capillary wedge pressure, worsening of left ventricular dysfunction, systemic hypotension, bradycardia and cardiac arrest. In this event [redacted] discontinue INOmax while providing symptomatic care.

Review: Drs. Karkowsky and Stockbridge revised this section (see attached label).

15. Under WARNINGS AND PRECAUTIONS, [redacted]

[redacted]

Review: Dr. Karkowsky suggested deleting this section. Dr. Stockbridge agreed.

16. Under ADVERSE REACTIONS/Clinical Trials Experience, the paragraph preceding Table 1 has been changed from:

[redacted]

To:

[redacted] (b) (4)

17. Under ADVERSE REACTIONS/Clinical Trials Experience, [redacted] (b) (4)

[redacted] (b) (4)

Review of 16 & 17: Dr. Stockbridge revised this section (see attached label).

18. Under ADVERSE REACTIONS, the Post-Marketing Experience section has been revised and now reads as follows:

[redacted] (b) (4)

Accidental Exposure
Based upon post-marketing experience, accidental exposure to nitric oxide for inhalation in hospital staff has been associated with Chest Discomfort, Dizziness, Dry Throat, Dyspnea, and Headache.

Review: Dr. Stockbridge deleted all but the Accidental Exposure information.

19. Under DESCRIPTION, "[redacted] (b) (4) had been added to the first sentence.

Review: Dr. Stockbridge deleted the new text.

20. Under CLINCAL STUDIES/CINRGI Study, the following has been added to the end of the section:

In clinical trials, reduction in the need for ECMO has not been demonstrated with the use of inhaled nitric oxide in neonates with congenital diaphragmatic hernia (CDH).[3,4]

Review: Acceptable.

21. Under REFERENCES, four new references have been added.

    Review: Dr. Stockbridge deleted all references.

22. Under HOW SUPPLIED/STORAGE AND HANDLING, the following has been added:

    All regulations concerning handling of pressure vessels must be followed.
    Protect the cylinders from shocks, falls, oxidizing and flammable materials, moisture, and sources of heat or ignition.
    The cylinders should be appropriately transported to protect from risks of shocks and falls.

    Review: Acceptable

Summary:

Dr. Moreschi's review indicated that the changes were acceptable.

Dr. Karkowsky suggested changes to section 5.4 and proposed rejecting the sponsor's proposed addition of (b) (4)

In addition, a cursory SEALD review suggested additional formatting changes.

The above suggestions were reviewed by Dr. Stockbridge. He made significant revisions to the sponsors proposed changes (see attached tracked changes version of the label). The sponsor agreed with all of these proposed changes.

An approval letter will be drafted for Dr. Stockbridge's signature.

Russell Fortney
Regulatory Project Manager
2/27/13

20 Pages(s) of Draft Labeling has been w ithheld in Full as b4 (CCI/TS) immediately following this page.

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
03/04/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20845/S-14

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

For Consulting Center Use Only:

Date Received: _____
Assigned to: _____
Date Assigned: _____
Assigned by: _____

Completed date: _____
Reviewer Initials: _____
Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center: CDRH
Division: DAGID
Mail Code: HF_-
Consulting Reviewer Name: Lex Schultheis/Albert Moyal
Building/Room #: Building 66/Room 2530
Phone #: 301-796-1289
Fax #:
Email Address:
RPM/CSO Name and Mail Code:

From (Originating Center):
Center: CDER
Division: Division of Cardio-Renal Products
Mail Code: HFD-110
Requesting Reviewer Name: Russell Fortney

Building/Room #: WO 22/4171
Phone#: 301-796-1068
Fax #:
Email Address:
RPM/CSO Name and Mail Code: Russell Fortney

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: 11/19/12
Requested Completion Date: **12/18/12**
Submission/Application Number: NDA 20-845
Submission Type: NDA
Type of Product: ☒ Drug-device combination ☐ Drug-biologic combination ☐ Device-biologic combination ☐ Drug-device-biologic combination ☐ Not a combination product
Submission Receipt Date: 6/26/12
Official Submission Due Date: N/A
Name of Product: Nitric Oxide for inhalation
Name of Firm: Ikaria/INO Therapeutics

Intended Use: treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):
This consult requests CDRH review of the sponsor's proposed labeling changes. Attached to this consult is a tracked changes version of the proposed changes. We specifically request CDRH input on section 2 DOSAGE AND ADMINISTRATION. In addition, I have added the entire supplement to an eroom which will be made available to the reviewer upon assignment. Please call me if you have any questions (301-796-1068).

Documents to be returned to Requesting Reviewer? π Yes ☐ π No ☒

Type of Request: Consultative Review ☒ π Collaborative Review ☐

20 pages(s) of Draft labeling has been withheld in Full as b4 (CCI/TS) immediately following this page

---

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
11/19/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 20845/S-014

INO Therapeutics
Attention: Ms. Mary Ellen Anderson
Sr. Director, Regulatory Affairs
Perryville III Corporate Park
53 Frontage Rd., 3rd Floor, P.O. Box 9001
Hampton, NJ 08827-9001

Dear Ms. Anderson:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA Number: 20845

Supplement Number: 014

Product Name: INOmax (nitric oxide) for Inhalation

Date of Submission: June 25, 2012

Date of Receipt: June 26, 2012

This labeling supplemental application proposes new safety warnings.

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 25, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

SUBMISSION REQUIREMENTS

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, please contact:

Russell Fortney, R.Ph.
Regulatory Health Project Manager
(301) 796-1068

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal 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 J FROMM
07/20/2012

Prior Approval Supplement

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

/s/

SANDRA P MATTHEWS
07/16/2012