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