CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 207141

Name: Noxivent (Nitric Oxide Inhalation, Gas), 100PPM & 800 PPM

Sponsor: Linde Gas Equip.

Approval Date: October 02, 2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 207141Orig1s000

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA207141Orig1s000

APPROVAL LETTER

ANDA 207141

ANDA APPROVAL

ICON Clinical Research LLC
U.S. Agent for Praxair Distribution, Inc.
79 TW Alexander Dr.
4401 Research Commons, Suite 300
Durham, NC 27709
Attention: Amy Kneifel
Director, Regulatory Affairs

Dear Madam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on May 20, 2014, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Noxivent (Nitric Oxide Gas for Inhalation, 100 ppm and 800 ppm).[1]

Reference is also made to any amendments submitted prior to the issuance of this letter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is **approved**, effective on the date of this letter. We have determined your Noxivent (Nitric Oxide Gas for Inhalation, 100 ppm and 800 ppm), to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Inomax Gas for Inhalation, 100 ppm and 800 ppm, of Mallinckrodt Hospital Products IP Limited (Mallinckrodt).

The RLD upon which you have based your ANDA, Mallinckrodt's Inomax Gas for Inhalation, 100 ppm and 800 ppm, is subject to periods of patent protection. The following patents and expiration dates (with pediatric exclusivity added) are currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

U.S. Patent Number	Expiration Date
8,282,966 (the '966 patent)	December 30, 2029
8,291,904 (the '904 patent)	July 6, 2031
8,293,284 (the '284 patent)	December 30, 2029
8,431,163 (the '163 patent)	December 30, 2029
8,573,209 (the '209 patent)	July 6, 2031
8,573,210 (the '210 patent)	July 6, 2031
8,776,794 (the '6,794 patent)	July 6, 2031
8,776,795 (the '795 patent)	July 6, 2031
8,795,741 (the '741 patent)	December 30, 2029
8,846,112 (the '112 patent)	December 30, 2029
9,265,911 (the '911 patent)	July 6, 2031 (for 800 ppm strength only)
9,279,794 (the '9,794 patent)	August 19, 2034 (for 800 ppm strength only)
9,295,802 (the '802 patent)	July 6, 2031 (for 800 ppm strength only)

9,408,993 (the '993 patent)	July 6, 2031 (for 800 ppm strength only)
9,770,570 (the '570 patent)	November 3, 2036 (for 800 ppm strength only)

With respect to the '966, '284, '163, '209, '741, and '112 patents, and the drug product claims associated with the '904, '210, '6,794, '795, '911, '9,794, '802, and '993 patents,[2] your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Noxivent (Nitric Oxide Gas for Inhalation, 100 ppm and 800 ppm), under this ANDA. You have notified the Agency that Praxair Distribution, Inc. (Praxair) complied with the requirements of section 505(j)(2)(B) of the FD&C Act and that litigation was initiated against Praxair for infringement of the '996, '904, '284, '163, '209, '210, '6,794, '795, '741, '112, '911, '9,794, and '802 patents in the United States District Court for the District of Delaware [Mallinckrodt Hospital Products IP Ltd., INO Therapeutics LLC and Ikaria, Inc., v. Praxair Distribution, Inc. and Praxair, Inc., Civil Action No. 15-00170]. You have also notified the Agency that on September 5, 2017, the court decided that the '966, '284, '163, '741, and '112 patents are invalid, and that the '209, '6,794, '795, '911, '9,794, and '802 patents are not infringed.

With respect to the '570 patent, and the method of use claims associated with the '904, '210, '6,794, '795, '911, '9,794, 802, and '993 patents, your ANDA contains statements under section 505(j)(2)(A)(viii) of the FD&C Act that these are method-of-use patents that do not claim any indication or other conditions of use for which you are seeking approval under your ANDA.

With respect to 180-day generic drug exclusivity, we note that Praxair was the first ANDA applicant for Nitric Oxide Gas for Inhalation, 100 ppm and 800 ppm, to submit a substantially complete ANDA with a paragraph IV certification. Therefore, with this approval, Praxair may be eligible for 180 days of generic drug exclusivity for Nitric Oxide Gas for Inhalation, 100 ppm and 800 ppm. This exclusivity, which is provided for under 505(j)(5)(B)(iv) of the FD&C Act, would begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). The Agency notes that Praxair failed to obtain tentative approval of this ANDA within 30 months after the date of which the ANDA was filed. See section 505(j)(5)(D)(i)(IV) of the FD&C Act (forfeiture of exclusivity for failure to obtain tentative approval). The Agency is not, however, making a formal determination at this time of Praxair's eligibility for 180-day generic drug exclusivity. It will do so only if a subsequent paragraph IV applicant becomes eligible for full approval (a) within 180 days after Praxair begins commercial marketing of Nitric Oxide Gas for Inhalation, 100 ppm and 800 ppm, or (b) at any time prior to the expiration of the '209, '210, '966, '904, '284, and '163 patents if Praxair has not begun commercial marketing. Please submit correspondence to this ANDA notifying the Agency within 30 days of the date of the first commercial marketing of this drug product or the RLD. If you do not notify the Agency within 30 days, the date of first commercial marketing will be deemed to be the date of the drug product's approval. See 21 CFR 314.107(c)(2).

Under section 506A of the FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must also 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/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. 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.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[3] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts.

All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at: http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). 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 via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Vincent Sansone, PharmD
Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

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[1] We note that the reference listed drug (RLD) upon which you have based this ANDA, Mallinckrodt Hospital Products IP Limited's (Mallinckrodt's) Inomax for Inhalation, 100 ppm, is no longer being marketed in the United States and is currently listed in the discontinued section of FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"). The Agency has determined that Mallinckrodt's Inomax for Inhalation, 100 ppm, was not withdrawn from sale for reasons of safety or effectiveness. FDA published this determination in the *Federal Register* (81 FR 3430; Jan. 21, 2016). This determination allows the Agency to approve ANDAs for the discontinued drug product.

[2] The Agency notes that the '6,794, '795, '741, '112, '911, '9,794, '802, '993, and '570 patents were submitted to the Agency after submission of your ANDA. Litigation, if any, with respect to these patents would not create a statutory stay of approval.

[3] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Vincent Sansone

Digitally signed by Vincent Sansone
Date: 10/02/2018 09:01:18AM
GUID: 508da7410002ba5d796f23a69ef57f39

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA207141Orig1s000

LABELING

NDC 59579-101-02

Noxivent™

nitric oxide for inhalation

100 PPM

Rx only

CAUTION: HIGH PRESSURE GAS. CAN CAUSE RAPID SUFFOCATION WITHOUT WARNING. Use equipment rated for cylinder pressure. Store and use with adequate ventilation. Secure cylinder in use and storage. Close valve after each use and when empty. **USE IN ACCORDANCE WITH APPROPRIATE SDS.**

WARNING: Administration of this gas mixture may be hazardous or contraindicated. For use only by or under the supervision of a licensed practitioner who is experienced in the use and administration of gas mixtures, and is familiar with the indications, effects, dosages, methods, and frequency and duration of administration, and with the hazards, contraindications, and side effects and precautions to be taken.

(b) (4)

FIRST AID: IF INHALED, remove person to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical help.

RETURN WITH 25 PSIG.
TO BE REFILLED ONLY BY A LICENSED FACILITY
AUTHORIZED BY PRAXAIR DISTRIBUTION, INC.

DO NOT REMOVE THIS PRODUCT LABEL.
Store at 25°C (77°F) with excursions permitted between 15-30°C (59-86°F).
Volume: 323 Liters

PRAXAIR DISTRIBUTION, INC.
145 Shimersville Road
Bethlehem, PA 18015

UN1956
COMPRESSED GAS, N.O.S.
(NITRIC OXIDE, NITROGEN)
2.2
Net Weight: 0.5 kg

59579-101-02

PRAXAIR
Medipure
Medical Gases

MMG-100-AD (09/2018)

NDC 59579-101-01

Noxivent™

nitric oxide for inhalation

100 PPM

Rx only

CAUTION: HIGH PRESSURE GAS. CAN CAUSE RAPID SUFFOCATION WITHOUT WARNING. Use equipment rated for cylinder pressure. Store and use with adequate ventilation. Secure cylinder in use and storage. Close valve after each use and when empty. **USE IN ACCORDANCE WITH APPROPRIATE SDS.**

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FIRST AID: IF INHALED, remove person to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical help.

(b) (4)

RETURN WITH 25 PSIG.
TO BE REFILLED ONLY BY A LICENSED FACILITY
AUTHORIZED BY PRAXAIR DISTRIBUTION, INC.

DO NOT REMOVE THIS PRODUCT LABEL.
Store at 25°C (77°F) with excursions permitted between 15-30°C (59-86°F).
Volume: 2082 Liters

PRAXAIR DISTRIBUTION, INC.
145 Shimersville Road
Bethlehem, PA 18015

UN1956
COMPRESSED GAS, N.O.S.
(NITRIC OXIDE, NITROGEN)
2.2
Net Weight: 2.5 kg

59579-101-01

PRAXAIR
Medipure™
Medical Gases

MMG-100-AQ (09/2018)

NDC 59579-102-02

Noxivent™

nitric oxide for inhalation

800 PPM

Rx only

CAUTION: HIGH PRESSURE GAS. CAN CAUSE RAPID SUFFOCATION WITHOUT WARNING. Use equipment rated for cylinder pressure. Store and use with adequate ventilation. Secure cylinder in use and storage. Close valve after each use and when empty. **USE IN ACCORDANCE WITH APPROPRIATE SDS.**

WARNING: Administration of this gas mixture may be hazardous or contraindicated. For use only by or under the supervision of a licensed practitioner who is experienced in the use and administration of gas mixtures, and is familiar with the indications, effects, dosages, methods, and frequency and duration of administration, and with the hazards, contraindications, and side effects and precautions to be taken.

(b) (4)

FIRST AID: IF INHALED, remove person to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical help.

RETURN WITH 25 PSIG.
TO BE REFILLED ONLY BY A LICENSED FACILITY
AUTHORIZED BY PRAXAIR DISTRIBUTION, INC.

DO NOT REMOVE THIS PRODUCT LABEL.
Store at 25˚C (77˚F) with excursions permitted between 15-30˚C (59-86˚F).
Volume: 323 Liters

PRAXAIR DISTRIBUTION, INC.
145 Shimersville Road
Bethlehem, PA 18015

UN1956
COMPRESSED GAS, N.O.S.
(NITRIC OXIDE, NITROGEN)
2.2
Net Weight: 0.5 kg

59579-102-02

PRAXAIR

Medipure™
Medical Gases

MMG-800-AD (09/2018)

NDC 59579-102-01

Noxivent™

nitric oxide for inhalation

800 PPM

Rx only

CAUTION: HIGH PRESSURE GAS. CAN CAUSE RAPID SUFFOCATION WITHOUT WARNING. Use equipment rated for cylinder pressure. Store and use with adequate ventilation. Secure cylinder in use and storage. Close valve after each use and when empty. **USE IN ACCORDANCE WITH APPROPRIATE SDS.**

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(b) (4)

FIRST AID: IF INHALED, remove person to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical help.

RETURN WITH 25 PSIG.
TO BE REFILLED ONLY BY A LICENSED FACILITY
AUTHORIZED BY PRAXAIR DISTRIBUTION, INC.

DO NOT REMOVE THIS PRODUCT LABEL.
Store at 25˚C (77˚F) with excursions permitted between 15-30˚C (59-86˚F).
Volume: 2082 Liters

PRAXAIR DISTRIBUTION, INC.
145 Shimersville Road
Bethlehem, PA 18015

UN1956
COMPRESSED GAS, N.O.S.
(NITRIC OXIDE, NITROGEN)
2.2
Net Weight: 2.5 kg

59579-102-01

PRAXAIR

Medipure™
Medical Gases

MMG-800-AQ (09/2018)

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

NOXIVENT™ (nitric oxide) gas, for inhalation
Initial U.S. Approval: 1999

RECENT MAJOR CHANGES

Dosage and Administration (2.2) 10/2015

INDICATIONS AND USAGE

Noxivent™ is a vasodilator indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents.

DOSAGE AND ADMINISTRATION

The recommended dose is 20 ppm, maintained for up to 14 days or until the underlying oxygen desaturation has resolved (2.1).
Doses greater than 20 ppm are not recommended (2.1, 5.2)
Administration:

- Use only with a NOxBOXi® operated by trained personnel (2.2)
- Avoid abrupt discontinuation (2.2, 5.1).

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Rebound: Abrupt discontinuation of Noxivent™ 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 (5.3).
Heart Failure: In patients with pre-existing left ventricular dysfunction, Noxivent™ may increase pulmonary capillary wedge pressure leading to pulmonary edema (5.4).

ADVERSE REACTIONS

The most common adverse reaction is hypotension. (6).

To report SUSPECTED ADVERSE REACTIONS, contact Praxair, Inc. at 1-800-772-9247 and http://www.praxair.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Nitric oxide donor compounds may increase the risk of developing methemoglobinemia (7).

Revised: 9/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Noxivent™ is indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

Term and near-term neonates with hypoxic respiratory failure

The recommended dose of Noxivent™ is 20 ppm. Maintain treatment up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from Noxivent™ therapy.

Doses greater than 20 ppm are not recommended *[see Warnings and Precautions (5.2)]*.

2.2 Administration

Training in Administration

The user of Noxivent™ and Nitric Oxide Delivery Systems must satisfactorily complete a comprehensive periodic 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 Noxivent™ at 1-877-772-9247.

Nitric Oxide Delivery Systems

Noxivent™ must be administered using a calibrated NOxBOXi®. Only validated ventilator systems should be used in conjunction with Noxivent™. Consult the Nitric Oxide Delivery System label or call 877.722.9247/visit praxair.com for a current list of validated systems.

Keep available a backup battery power supply and an independent reserve nitric oxide delivery system to address power and system failures.

Monitoring

Measure methemoglobin within 4-8 hours after initiation of treatment with Noxivent™ and periodically throughout treatment *[see Warnings and Precautions (5.2)]*.

Monitor for PaO_2 and inspired NO_2 during Noxivent™ administration *[see Warnings and Precautions 5.3)]*.

Weaning and Discontinuation

Avoid abrupt discontinuation of Noxivent™ *[see Warnings and Precautions (5.1)]*. To wean Noxivent™, downtitrate in several steps, pausing several hours at each step to monitor for hypoxemia.

3 DOSAGE FORMS AND STRENGTHS

Noxivent™ (nitric oxide) gas is available in 100 ppm and 800 ppm concentrations.

4 CONTRAINDICATIONS

Noxivent™ is contraindicated in neonates dependent on right-to-left shunting of blood.

5 WARNINGS AND PRECAUTIONS

5.1 Rebound Pulmonary Hypertension Syndrome following Abrupt Discontinuation

Wean from Noxivent™ *[see Dosage and Administration (2.2)]*. Abrupt discontinuation of Noxivent™ 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 Noxivent™ 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 Noxivent™; it can take 8 hours or more before steady-state methemoglobin levels are attained. Monitor methemoglobin and adjust the dose of Noxivent™ to optimize oxygenation.

If methemoglobin levels do not resolve with decrease in dose or discontinuation of Noxivent™, 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 there is an unexpected change in NO_2 concentration, or if the NO_2 concentration reaches 3 ppm when measured in the breathing circuit, then the delivery system should be assessed in accordance with the NOxBOXi and NOxMixer Technical Guide troubleshooting section, and the NO_2 analyzer should be recalibrated. The dose of Noxivent™ and/or FiO_2 should be adjusted as appropriate.

5.4 Worsening Heart Failure

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

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the label;

Hypoxemia *[see Warnings and Precautions (5.2)]*
Worsening Heart Failure *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

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.

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

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

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received nitric oxide 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 nitric oxide than on placebo) was hypotension (14% vs. 11%).

6.2 Post-Marketing Experience

Post marketing reports of 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

7.1 Nitric Oxide Donor Agents

Nitric oxide donor agents such as prilocaine, sodium nitroprusside and nitroglycerine may increase the risk of developing methemoglobinemia.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

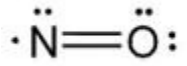
Overdosage with Noxivent™ is manifest by elevations in methemoglobin and pulmonary toxicities associated with inspired NO_2. Elevated NO_2 may cause acute lung injury. Elevations in methemoglobin reduce the oxygen delivery capacity of the circulation. In clinical studies, NO_2 levels >3 ppm or methemoglobin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

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

Noxivent™ (nitric oxide gas) is a drug administered by inhalation. Nitric oxide, the active substance in Noxivent™, is a pulmonary vasodilator. Noxivent™ 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). Noxivent™ 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 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.

Noxivent™ 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, Noxivent™ improves oxygenation (as indicated by significant increases in PaO_2).

12.3 Pharmacokinetics

The pharmacokinetics of nitric oxide has been studied in adults.

Absorption and Distribution

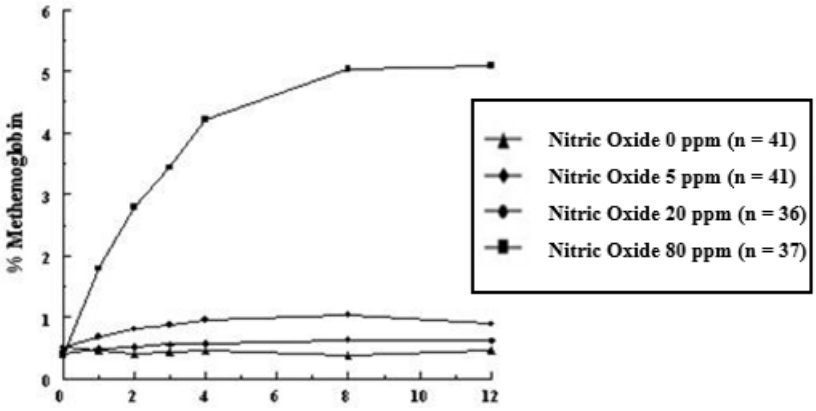
Nitric oxide is absorbed systemically after inhalation. Most of it traverses the pulmonary capillary bed where it combines with hemoglobin that is 60% to 100% oxygen-saturated. At this level of oxygen saturation, nitric oxide combines predominantly with oxyhemoglobin to produce methemoglobin and nitrate. 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 nitric oxide are shown in Figure 1.

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



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 nitric oxide groups, but reached approximately 5% in the 80 ppm nitric oxide 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 nitric oxide has been investigated in term and near-term newborns with hypoxic respiratory failure resulting from a variety of etiologies. Inhalation of nitric oxide 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 1.

Table 1: 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 nitric oxide 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 nitric oxide (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 nitric oxide or placebo. The primary results from the CINRGI study are presented in Table 2.

Table 2: Summary of Clinical Results from CINRGI Study

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

In addition, the nitric oxide 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 nitric oxide, 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 nitric oxide (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 nitric oxide 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). Noxivent™ is not indicated for use in ARDS.

14.3 Ineffective in Prevention of Bronchopulmonary Dysplasia (BPD)

The safety and efficacy of nitric oxide 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 overall 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 nitric oxide for prevention of BPD in preterm neonates ≤ 34 weeks gestational age is not recommended.

Additional information regarding another clinical study in which efficacy was not demonstrated is approved for Mallinckrodt Hospital Products IP Limited's INOmax® (nitric oxide) gas for Inhalation. However, due to Mallinckrodt Hospital Products IP Limited's marketing exclusivity rights, this drug product is not labeled with that pediatric information.

16 HOW SUPPLIED/STORAGE AND HANDLING

Noxivent™ (nitric oxide) is available in the following sizes:

Size AD	Portable aluminum cylinders containing 362 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 323 liters) (NDC 59579-102-02)
Size AQ	Aluminum cylinders containing 2154 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 2082 liters) (NDC 59579-102-01)
Size AD	Portable aluminum cylinders containing 362 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 323 liters) (NDC 59579-101-02)
Size AQ	Aluminum cylinders containing 2154 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 2082 liters) (NDC 59579-101-01)

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.

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.

Distributed by
Praxair Distribution, Inc.
10 Riverview Drive
Danbury, CT 06810

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA207141Orig1s000

LABELING REVIEW(s)

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	September 12, 2018
ANDA Number(s)	207141
Review Number	5
Applicant Name	Praxair Distribution, Inc.
Established Name & Strength(s)	Nitric Oxide Gas for Inhalation, 100 ppm and 800 ppm
Proposed Proprietary Name	Noxivent (conditionally approved on January 30, 2018)
Submission Received Date	September 11, 2018
Primary Labeling Reviewer	A Jung
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

☒ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.

☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No (If yes, indicate ANDA number)

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on (add date) based on your submission(s) received (add date):

NA

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission received September 11, 2018.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).
None

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s).

Reviewer Comments:

Labeling Deficiencies determined on September 6, 2018 based on submission received August 21, 2018:

1. CONTAINER LABEL
    a. When addressing the Labeling deficiencies communicated to you through the discipline review letter dated August 13, 2018, it appears that you used the original version of the container labels rather than the most recent container labels. Therefore, some of the previous corrections you made based on previous agency comments have been lost in your container labels submitted on August 21, 2018. Therefore, we ask that you readdress the following deficiencies which were communicated to you on March 2, 2017:
        i. Increase the prominence of "for inhalation" from "nitric oxide for inhalation" to be in line with the reference listed drug label. (b) (4)
        ii. Increase the prominence of the middle portion of the NDC number to help differentiate each product within this product line (i.e 59579-101-02) and relocate it to the top of the label.
        iii. Add the barcode according to the 21 CFR 201.25.
    b. (b) (4)

Response/Evaluation: Applicant made the changes as requested. Satisfactory.

2. PRESCRIBING INFORMATION

(b) (4)

Response/Evaluation: Applicant made the changes as requested. Satisfactory.

2.1 CONTAINER AND CARTON LABELS

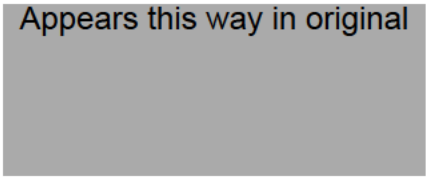
Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:
Container labels are satisfactory.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].



Reviewer Comments:

Drug Facts Information:

Entry dated 9/18/15 for Email notifying of Controlled Correspondence (CC) #48965. CC review and response can be found in the following:
http://panorama.fda.gov/task/view?ID=54dbb45a000923da4badc5b569224f48

Entry dated 9/14/16 for Internal meeting minutes with Policy.

Entry dated 6/17/17 for consult response from DMEPA regarding (b) (4) See discussion regarding potential risk for delay of therapy due to substitution of NOXIVENT for INOmax in OGDP memo (at 20-21). DMEPA also stated that "if the Review Team deems appropriate, a Dear Healthcare Provider letter may be issued by the generic company to respiratory therapy professionals [associated with NICUs] to communicate that generic Nitric Oxide products are incompatible with the DSIR Plus delivery system and need to be used with their compatible delivery systems."

On March 21, 2017, DLR asked DMEPA for clarification as to whether a Dear Healthcare Provider Letter would be required for safe use of the generic nitric oxide drug product and on March 22, 2017, DMEPA concluded that it was not necessary for safe use. DLR, in consultation with DCR, agrees that a Dear Healthcare Provider Letter is not necessary for safe use of the generic drug product as both drug products will bear product labeling that will inform healthcare providers of information regarding the clinical effect and safety profile of the drug product when used with their respective NODS. Further, DLR concludes that there is a low probability of the error occurring, since hospitals follow a predetermined formulary (designated by physicians and pharmacists on staff) and would be very unlikely to simultaneously use multiple NO/NODS systems; particularly for high-cost items used in high intensity environments (NICUs). In addition, labeling, including proprietary names (NOXIVENT versus INOmax), etc. is prominent, clear, and readily distinguishable. NICU staff are among the most highly trained hospital staff known. It is very unlikely that NICU staff would be unaware of the fact that the generic NO drug product (NOXIVENT) should be used with its corresponding NODS and very unlikely that this event would occur. In addition, DLR also concludes that the error is readily detectable because, labeling, including proprietary names (NOXIVENT versus INOmax), etc. is prominent, clear and readily distinguishable. Further, NICU staff will be trained and made aware of the differences (if necessary in those rare instances where both systems may coexist in a given NICU). Thus, for these reasons, a Dear Healthcare Provider Letter is not necessary for safe use of the generic NO drug product.

Entry dated 11/20/17 is for the BPCA template.

Entry dated 8/16/18 memo regarding patent certification and use codes pertaining to Nitric Oxide for Inhalation (NDA 20845)

Entry dated 9/24/18 OGDP memo regarding therapeutic equivalence consideration for ANDA 207141.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? YES

If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? YES

If Yes, please explain.

(b) (5)

Is the drug product listed on the Susceptibility Test Interpretive Criteria web page**?** NO

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(*If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so enter the most recently approved ANDA labeling information as applicable.)*

NDA# /Supplement# (S-000 if original): NDA20845/S-017

Supplement Approval Date: 10/9/15

Proprietary Name: Inomax

Established Name: Nitric Oxide Gas

Description of Supplement: PAS for the following changes: S-016: The removal of the 100 ppm nitric oxide concentration from the labeling and revisions to the DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS sections of the INOmax package inserts. **S-017:** Revisions to the labeling based on the clinical study entitled "Bronchopulmonary Dysplasia (BPD) in Preterm Infants Requiring Mechanical Ventilation or Positive Pressure Support on Days 5 to 14 After birth (IK-3001-BPD-301)".

S-018 CBE for CMC approved on 4/5/16: This "Changes Being Effected" supplemental new drug application proposes to include a MR conditional triangle and an appropriate warning "Keep cylinder at 100 gauss or less" label. (b) (4)

S-019 was approved for the following changes on 11/2/17: This "Changes Being Effected in 30 days" supplemental new drug application provides for a new (b) (4)

Note that **NDA filed S-020** on 7/14/17 for the following changes but withdrew the supplement on 1/8/18:

- To include information in the INOmax package insert regarding the use of INOmax therapy in the MRI suite.

(b) (4)

http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af8047a1f3

On 8/15/18, the applicant **resubmitted S-020** to include information regarding the use of INOmax therapy in the MRI suite and it is now pending review.

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

ANDA#/Supplement# (S-000 if original): Click here to enter text.

Supplement Approval Date: Click here to enter text.

Proprietary Name: Click here to enter text.

Established Name: Click here to enter text.

Description of Supplement:

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** BPCA template: http://sharepoint.fda.gov/orgs/CDER-OGD-DLPS/DivisionofLabeling/DrugFileFolders/Lists/Drug%20File%20Folders/Attachments/654/INOmax%20Model%20Labeling_Final.pdf
☐ **OTHER (Describe):** Click here to enter text.

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

(b) (4)

[redacted]

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: DARRTS, Annual Report Submitted 2/23/17]

Rx only

INOmax®

nitric oxide FOR INHALATION

800 PPM

CAUTION: HIGH PRESSURE GAS. CAN CAUSE RAPID SUFFOCATION WITHOUT WARNING. Use equipment rated for cylinder pressure. Store and use with adequate ventilation. Secure cylinder in use and storage. Close valve after each use and when empty. USE IN ACCORDANCE WITH APPROPRIATE SDS.

WARNING: Administration of this gas mixture may be hazardous or contraindicated. For use only by or under the supervision of a licensed practitioner who is experienced in the use and administration of gas mixtures, and is familiar with the indications, effects, dosages, methods, and frequency and duration of administration, and with the hazards, contraindications and side effects and the precautions to be taken.

FIRST AID: IF INHALED, remove person to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical help.

RETURN WITH 25 PSIG.
TO BE REFILLED ONLY BY A PHARMACEUTICAL FACILITY AUTHORIZED BY INO Therapeutics LLC
Manufactured Under Pharmaceutical Current Good Manufacturing Practices (cGMPs).
DO NOT REMOVE THIS PRODUCT LABEL.

Store at 25°C (77°F)
[see USP Controlled Room Temperature].

Mallinckrodt™ Pharmaceuticals

Volume 353 Liters

Manufactured by:
Mallinckrodt Manufacturing LLC
1060 Allendale Dr.
Port Allen, LA 70767 USA
For Product Inquiry 1-877-KNOW INO
(566-9466)

UN 1956
Compressed Gas, N.O.S.
(Nitric Oxide, Nitrogen)
2.2
Net Weight: 0.5 Kg

NDC 64693-002-01

N 3 64693 00201 8

MADE IN USA

Label No. SPC-LBL-0058 R8

Inomax was originally approved on 12/23/1999. The above labeling is in-line with the below representatives from the originally approved labels. The only notable difference s are company logos and the boxed CAUTION statement is replaced by Rx Only statement in the current labeling:

2 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 9/12/2018.

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	NO		NA	NA
Not Yet Official	NO	-	NA	NA

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **NA**

Reviewer Comments:

None

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 9/12/2018.

Table 3 provides Orange Book patents for the Model Labeling NDA 20845 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling

Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter "Carve-out" or "None")
8282966*PED	Dec 30, 2029	U-1286	A method of reducing the risk of pulmonary edema in patients in need of treatment with inhaled NO	IV	11/12/2014	None
8291904*PED	Jul 6, 2031	U-1226	A method of providing a predetermined concentration of NO to a patient	PIV/viii	5/20/2014	None-see patent memo
8293284*PED	Dec 30, 2029	U-1286	A method of reducing the risk of pulmonary edema in patients in need of treatment with inhaled NO	IV	5/20/2014	None
8431163*PED	Dec 30, 2029	U-1286	A method of reducing the risk of pulmonary edema in patients in need of treatment with inhaled NO	IV	5/20/2014	None
8573209*PED	Jul 6, 2031	-	-	IV	5/20/2014	None
8573210*PED	Jul 6, 2031	U-1453	A method of treating hypoxic respiratory failure by verifying gas information of NO prior to delivery to a patient	PIV/viii	5/20/2014	None- see patent memo
8776794*PED	Jul 6, 2031	U-1226	A method of providing a predetermined concentration of NO to a patient	PIV/viii	11/12/2014	None- see patent memo
8776795*PED	Jul 6, 2031	U-1226	A method of providing a predetermined concentration of NO to a patient	PIV/viii	11/12/2014	None- see patent memo
8795741*PED	Dec 30, 2029	U-1286	A method of reducing the risk of pulmonary edema in patients in need of treatment with inhaled NO	IV	11/12/2014	None
8846112*PED	Dec 30, 2029	U-1286	A method of reducing the risk of pulmonary edema in patients in need of treatment with inhaled NO	IV	11/12/2014	None
9265911*PED#	Jul 6, 2031	U-1824	A method of providing NO therapy to a patient by verifying gas information of NO prior to delivery to a patient	PIV/viii	5/5/2016	None- see patent memo
9279794*PED#	Aug 19, 2034	U-1823	A method of providing NO therapy to a patient by compensating long-term sensitivity drift of electrochemical gas sensors used in systems for delivering therapeutic NO to a patient	PIV/viii	5/5/206 (PIV) 8/20/18 (viii)	None-see patent memo
9295802*PED#	Jul 6, 2031	U-1226	A method of providing a predetermined concentration of NO to a patient	PIV/viii	5/5/2016	None-see patent memo
9408993*PED#	Jul 6, 2031	U-1824	A method of providing NO therapy to a patient by verifying gas information of NO prior to delivery to a patient	PIV/viii	8/26/2016	None-see patent memo

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
9770570*PED#	Nov 3, 2036	U-2148	A method of providing nitric oxide therapy to a patient by measuring and displaying an indication of the calculated delivery concentration of nitric oxide as compared to the desired delivery concentration of nitric oxide	viii	8/20/18	None-see patent memo

Applies only for the 800 ppm strength and not the 100 ppm strength.

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

No change from review C4.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact (enter Carve-out or None)**
M-167#	Oct 9, 2018	Approved for revisions to the labeling based on the clinical study entitled 'bronchopulmonary dysplasia (bpd) in preterm infants requiring mechanical ventilation or positive pressure support on days 5 to 14 after birth'.	With respect to differences in the labeling at section 14.3, the differences are to address three-year marketing exclusivity (M-167) granted for minor, insignificant changes to the RLD's labeling. Applicant verifies that the information associated with marketing exclusivity M-167 is not included in the proposed ANDA 207141 labeling attached hereto. (b) (4)	10/2/17	Carve-out

Applies only for the 800 ppm strength and not the 100 ppm strength.

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **YES**

Reviewer Comments:

On 12/11/17, the applicant updated their labeling to be in-line with the BPCA template. No change from Review C4.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)

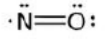
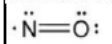
Previous Labeling Review	Currently Proposed	Assessment
11 DESCRIPTION Noxivent™ (nitric oxide gas) is a drug administered by inhalation. Nitric oxide, the active substance in Noxivent™, is a pulmonary vasodilator. Noxivent™ is a gaseous blend of nitric oxide and nitrogen (0.08% and 99.92%, respectively for 800 ppm; 0.01% and 99.99%, respectively for 100 ppm). Noxivent™ 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: 	**11 DESCRIPTION** Noxivent™ (nitric oxide gas) is a drug administered by inhalation. Nitric oxide, the active substance in Noxivent™, is a pulmonary vasodilator. Noxivent™ 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). Noxivent™ 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: 	No change

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products

Previous Labeling Review	Currently Proposed	Assessment
16 HOW SUPPLIED/STORAGE AND HANDLING Noxivent™ (nitric oxide) is available in the following sizes: Size AD — Portable aluminum cylinders containing 362 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 323 liters) (NDC 59579-102-02) Size AQ — Aluminum cylinders containing 2154 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 2082 liters) (NDC 59579-102-01) Size AD — Portable aluminum cylinders containing 362 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 323 liters) (NDC 59579-101-02) Size AQ — Aluminum cylinders containing 2154 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 2082 liters) (NDC 59579-101-01) 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. 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.	**16 HOW SUPPLIED/STORAGE AND HANDLING** Noxivent™ (nitric oxide) is available in the following sizes: Size AD — Portable aluminum cylinders containing 362 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 323 liters) (NDC 59579-102-02) Size AQ — Aluminum cylinders containing 2154 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 2082 liters) (NDC 59579-102-01) Size AD — Portable aluminum cylinders containing 362 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 323 liters) (NDC 59579-101-02) Size AQ — Aluminum cylinders containing 2154 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 2082 liters) (NDC 59579-101-01) 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. 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.	No change

Table 7: Manufacturer/Distributor/Packer Statements

Previous Labeling Review	Currently Proposed	Assessment

Table 7: Manufacturer/Distributor/Packer Statements		
Distributed by Praxair Distribution, Inc. 10 Riverview Drive Danbury, CT 06810	Distributed by Praxair Distribution, Inc. 10 Riverview Drive Danbury, CT 06810	No change

5. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline (e.g., OPQ, OB, DCR) reviewer(s):

Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments:
No change from Review C4.

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	100 PPM: 323 L and 2082 L delivered volume 800 PPM: 323 L and 2082 L delivered volume	9/11/18	Satisfactory
Blister	NA	-	-	-
Carton	NA	-	-	-
(Other – specify)	NA	-	-	-
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	9/2018	9/11/18	Satisfactory
Medication Guide	NA	-	-	-
Patient Information	NA	-	-	-
SPL Data Elements		5/2014	3/15/17	Satisfactory

Huijeong Jung

Digitally signed by Huijeong Jung
Date: 9/27/2018 05:02:27PM
GUID: 508da702000287c1e12e719fda6a6d14

Malik Imam

Digitally signed by Malik Imam
Date: 9/28/2018 09:00:20AM
GUID: 508da70800028c685bf6578d234e223f

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	September 4, 2018
ANDA Number(s)	207141
Review Number	4
Applicant Name	Praxair Distribution, Inc.
Established Name & Strength(s)	Nitric Oxide Gas for Inhalation, 100 ppm and 800 ppm
Proposed Proprietary Name	Noxivent (conditionally approved on January 30, 2018)
Submission Received Date	August 21, 2018
Primary Labeling Reviewer	A Jung
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

☐ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.

☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No (If yes, indicate ANDA number)

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on September 6, 2018 based on your submission(s) received August 21, 2018:

1. CONTAINER LABEL
    a. When addressing the Labeling deficiencies communicated to you through the discipline review letter dated August 13, 2018, it appears that you used the original version of the container labels rather than the most recent container labels. Therefore, some of the previous corrections you made based on previous agency comments have been lost in your container labels submitted on August 21, 2018. Therefore, we ask that you readdress the following deficiencies which were communicated to you on March 2, 2017:
        i. Increase the prominence of "for inhalation" from "nitric oxide for inhalation" to be in line with the reference listed drug label. (b) (4)
        ii. Increase the prominence of the middle portion of the NDC number to help differentiate each product within this product line (i.e 59579-101-02) and relocate it to the top of the label.
        iii. Add the barcode according to the 21 CFR 201.25.
    b. (b) (4)

2. PRESCRIBING INFORMATION
(b) (4)

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are

addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

NA

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).
NA

Appears this way in original

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s).

Appears this way in original

Reviewer Comments: The below comments are from the labeling review C3 based on the submission dated August 4, 2017, September 11, 2017, October 2, 2017, December 11, 2017, December 11, 2017, and February 28, 2018.

1. CONTAINER LABELS

a. (b) (4) Please change the statement to "USE IN ACCORDANCE WITH APPROPRIATE SDS" or provide justification on using a different statement from the RLD.

Response/Evaluation: Applicant chose to be the same as RLD by using the statement, "USE IN ACCORDANCE WITH APPROPRIATE SDS". Satisfactory.

b. (b) (4) to "CAUTION: HIGH PRESSURE…".

Response/Evaluation: Applicant changed as requested. Satisfactory.

(b) (4)

Response/Evaluation: Applicant changed the volumes for the 800 ppm containers in accordance with the current information in the HOW SUPPLIED 323 liters and 2082 Liters. Applicant also changed the volumes for the 100 ppm containers in accordance with the updated information in the HOW SUPPLIED (323 liters and 2082 Liters).

(b) (4)

2. PRESCRIBING INFORMATION

a. HIGHLIGHTS OF PRESCRIBING INFORMATION, Limitation statement and Title: We recommend that you use all upper case letters for the proposed proprietary name, NOXIVENT, for this section, only. For example, please see the RLD labeling. (b) (4)

Response/Evaluation: Applicant made the requested changes. Satisfactory

(b) (4)

(b) (4)

[redacted]

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review? **NO**

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:
OND/DCRP consult referred to in Review C3 is cancelled. Please refer to memo to file from OGDP.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? YES
If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Entry dated 9/18/15 for Email notifying of Controlled Correspondence (CC) #48965. CC review and response can be found in the following:
http://panorama.fda.gov/task/view?ID=54dbb45a000923da4badc5b569224f48

Entry dated 9/14/16 for Internal meeting minutes with Policy.

Entry dated 6/17/17 for consult to DMEPA regarding (b) (4) [redacted]

Entry dated 11/20/17 is for the BPCA template.

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3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so enter the most recently approved ANDA labeling information as applicable.)

NDA# /Supplement# (S-000 if original): NDA20845/S-017

Supplement Approval Date: 10/9/15

Proprietary Name: Inomax

Established Name: Nitric Oxide Gas

Description of Supplement: PAS for the following changes: S-016: **The removal of the 100 ppm nitric oxide concentration from the labeling and revisions to the DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS sections of the INOmax package inserts.** S-017: **Revisions to the labeling based on the clinical study entitled "Bronchopulmonary Dysplasia (BPD) in Preterm Infants Requiring Mechanical Ventilation or Positive Pressure Support on Days 5 to 14 After birth (IK-3001-BPD-301)".**

S-018 CBE for CMC approved on 4/5/16: This "Changes Being Effected" supplemental new drug application proposes to include a MR conditional triangle and an appropriate warning "Keep cylinder at 100 gauss or less" label. (b) (4)

[redacted]

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Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
On 8/15/18, the applicant [redacted] (b) (4) S-020 to include information regarding the use of INOmax therapy in the MRI suite and it is now pending review.
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:**
☒ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** BPCA template: http://sharepoint.fda.gov/orgs/CDER-OGD-DLPS/DivisionofLabeling/DrugFileFolders/Lists/Drug%20File%20Folders/Attachments/654/INOmax%20Model%20Labeling_Final.pdf
☐ **OTHER (Describe):** Click here to enter text.

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

In their amendment dated 12/11/17, the applicant updated the PI in accordance to the BPCA template which provided carve-out for M-167 using the current RLD labeling, NDA 20845/S-017. On 2/28/18 the applicant further updated the labeling [redacted] (b) (4) See section 1.1 for comment to applicant.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: DARRTS, Annual Report Submitted 2/23/17]

Rx only

INOmax®

nitric oxide FOR INHALATION

800 PPM

CAUTION: HIGH PRESSURE GAS. CAN CAUSE RAPID SUFFOCATION WITHOUT WARNING. Use equipment rated for cylinder pressure. Store and use with adequate ventilation. Secure cylinder in use and storage. Close valve after each use and when empty. USE IN ACCORDANCE WITH APPROPRIATE SDS.

WARNING: Administration of this gas mixture may be hazardous or contraindicated. For use only by or under the supervision of a licensed practitioner who is experienced in the use and administration of gas mixtures, and is familiar with the indications, effects, dosages, methods, and frequency and duration of administration, and with the hazards, contraindications and side effects and the precautions to be taken.

FIRST AID: IF INHALED, remove person to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical help.

RETURN WITH 25 PSIG.
TO BE REFILLED ONLY BY A PHARMACEUTICAL FACILITY AUTHORIZED BY INO Therapeutics LLC
Manufactured Under Pharmaceutical Current Good Manufacturing Practices (cGMPs).
DO NOT REMOVE THIS PRODUCT LABEL.

Store at 25°C (77°F)
[see USP Controlled Room Temperature].

Mallinckrodt™ Pharmaceuticals

Volume 353 Liters

Manufactured by:
Mallinckrodt Manufacturing LLC
1060 Allendale Dr.
Port Allen, LA 70767 USA
For Product Inquiry 1-877-KNOW INO
(566-9466)

UN 1956
Compressed Gas, N.O.S.
(Nitric Oxide, Nitrogen)
2.2
Net Weight: 0.5 Kg

NDC 64693-002-01

N 3 64693 00201 8

MADE IN USA

Label No. SPC-LBL-0058 R8

Inomax was originally approved on 12/23/1999. The above labeling is in-line with the below representatives from the originally approved labels. The only notable difference s are company logos and the boxed CAUTION statement is replaced by Rx Only statement in the current labeling:

2 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 9/6/2018.

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	No		NA	NA
Not Yet Official	No	-	NA	NA

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **NA**

Reviewer Comments:

None

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 9/6/2018.

Table 3 provides Orange Book patents for the Model Labeling NDA 20845 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling

Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter "Carve-out" or "None")
5732693*PED	Jun 13, 2017	U-1230	A method of providing NO therapy to a patient	III	3/15/2017	None
5752504*PED	Jun 13, 2017	U-1230	A method of providing NO therapy to a patient	III	3/15/2017	None
6125846*PED	Nov 16, 2017	U-1457	A method of purging a NO delivery system	III	3/15/2017	None
8282966*PED	Dec 30, 2029	U-1286	A method of reducing the risk of pulmonary edema in patients in need of treatment with inhaled NO	IV	3/15/2017	None
8291904*PED	Jul 6, 2031	U-1226	A method of providing a predetermined concentration of NO to a patient	~~IV~~ viii	~~8/4/17 (w/dviii)~~ 8/20/18	None
8293284*PED	Dec 30, 2029	U-1286	A method of reducing the risk of pulmonary edema in patients in need of treatment with inhaled NO	IV	3/15/2017	None
8431163*PED	Dec 30, 2029	U-1286	A method of reducing the risk of pulmonary edema in patients in need of treatment with inhaled NO	IV	3/15/2017	None
8573209*PED	Jul 6, 2031	-	-	IV	3/15/2017	None
8573210*PED	Jul 6, 2031	U-1453	A method of treating hypoxic respiratory failure by verifying gas information of NO prior to delivery to a patient	~~IV~~ vii	~~8/4/17 (w/dviii)~~ 8/20/18	None
8776794*PED	Jul 6, 2031	U-1226	A method of providing a predetermined concentration of NO to a patient	~~IV~~ viii	~~8/4/17 (w/dviii)~~ 8/20/18	None
8776795*PED	Jul 6, 2031	U-1226	A method of providing a predetermined concentration of NO to a patient	~~IV~~ vii	~~8/4/17 (w/dviii)~~ 8/20/18	None
8795741*PED	Dec 30, 2029	U-1286	A method of reducing the risk of pulmonary edema in patients in need of treatment with inhaled NO	IV	3/15/2017	None
8846112*PED	Dec 30, 2029	U-1286	A method of reducing the risk of pulmonary edema in patients in need of treatment with inhaled NO	IV	3/15/2017	None
9265911*PED#	Jul 6, 2031	U-1824	A method of providing NO therapy to a patient by verifying gas information of NO prior to delivery to a patient	~~IV~~ viii	~~8/4/17 (w/dviii)~~ 8/20/18	None
9279794*PED#	Aug 19, 2034	U-1823	A method of providing NO therapy to a patient by compensating long-term sensitivity drift of electrochemical gas sensors used in systems for delivering therapeutic NO to a patient	~~IV~~ viii	~~3/15/2017~~ 8/20/18	None
9295802*PED#	Jul 6, 2031	U-1226	A method of providing a predetermined concentration of NO to a patient	~~IV~~ vii	~~8/4/17 (w/dviii)~~ 8/20/18	None
9408993*PED#	Jul 6, 2031	U-1824	A method of providing NO therapy to a patient by verifying gas information of NO prior to delivery to a patient	~~IV~~ viii	~~8/4/17 (w/dviii)~~ 8/20/18	None
9770570*PED#	Nov 3, 2036	U-2148	A method of providing nitric oxide therapy to a patient by measuring and displaying an indication of the calculated delivery concentration of nitric oxide as compared to the desired delivery concentration of nitric oxide	~~IV~~ viii	~~2/28/18~~ 8/20/18	None

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Refer to Memo to File in the platform dated August 16, 2018 regarding viii statements.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
M-167#	Oct 9, 2018	Approved for revisions to the labeling based on the clinical study entitled 'bronchopulmonary dysplasia (bpd) in preterm infants requiring mechanical ventilation or positive pressure support on days 5 to 14 after birth'	With respect to differences in the labeling at section 14.3, the differences are to address three-year marketing exclusivity (M-167) granted for minor, insignificant changes to the RLD's labeling. Applicant verifies that the information associated with marketing exclusivity M-167 is not included in the proposed ANDA 207141 labeling attached hereto. (b) (4) [redacted]	10/2/17	Carve-out

Applies only for the 800 ppm strength and not the 100 ppm strength.

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **YES**

Reviewer Comments:

On 11/27/17, the BPCA template was sent to the applicant. On 12/11/17, the applicant updated their labeling to be in-line with the BPCA template. No change from Review #3.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **YES**
Are there changes to the manufacturer/distributor/packer statements? **NO**

If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Noxivent™ (nitric oxide gas) is a drug administered by inhalation. Nitric oxide, the active substance in Noxivent™, is a pulmonary vasodilator. Noxivent™ 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). Noxivent™ is supplied n aluminum cylinders as a compressed gas under high pressure (2000 pounds per square nch gauge [psig]).	Noxivent™ (nitric oxide gas) is a drug administered by inhalation. Nitric oxide, the active substance in Noxivent™, is a pulmonary vasodilator. Noxivent™ 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). Noxivent™ is supplied in aluminum cylinders as a compressed gas under high pressure (2000 pounds per square inch gauge [psig]).	No change

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**
(b) (4)	Noxivent™ (nitric oxide) is available in the following sizes: Size AD — Portable aluminum cylinders containing 362 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 323 liters) (NDC 59579-102-02) Size AQ — Aluminum cylinders containing 2154 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 2082 liters) (NDC 59579-102-01) Size AD — Portable aluminum cylinders containing 362 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 323 liters) (NDC 59579-101-02) Size AQ — Aluminum cylinders containing 2154 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 2082 liters) (NDC 59579-101-01) 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. 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.	Volume information has been changed slightly. See Section 5 for communication to the DP Quality review team.

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Distributed by Praxair Distribution, Inc. 10 Riverview Drive Danbury, CT 06810	Distributed by Praxair Distribution, Inc. 10 Riverview Drive Danbury, CT 06810	No change

5. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline (e.g., OPQ, OB, DCR) reviewer(s):

Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments:

The following Issue was sent to the DP Quality review team on 9/6/18 (ref # 25705187)

Dear DP Quality team:

Labeling team is currently reviewing the Praxair's updated labeling received on August 21, 2018. The HOW SUPPLIED section has been revised again with new volume information. The new volume information appears similar to but not the same as the volume information noted in your review checked into the Platform on 5/24/18. Please review to ensure that the information is acceptable from quality perspective and inform us if you have any concern. Our team has found other minor labeling deficiencies. RPM has informed us that we need to get the DRL to the applicant ASAP. We are targeting tomorrow to wrap up our review.

Thank you for your kind attention.

-Labeling Review Team

On 9/7/18 the DP Quality review team provided the following assessment via email to the Labeling team:

The Currently Proposed label is acceptable. The information is acceptable from quality perspective.

They also followed up with the following platform update on 9/7/2018:

The Currently Proposed label is acceptable from quality perspective. They are proposing to supply same quantity of drug product for both the strengths unlike earlier label with different quantities. We will make a note in our review about the changes. I will be closing the issue in the Panorama. thanks.

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	100 PPM: 323 L and 2082 L delivered volume 800 PPM: 323 L and 2082 L delivered volume	8/21/18	Revise
Blister	NA	-	-	-
Carton	NA	-	-	-
(Other – specify)	NA	-	-	-
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	8/2018	8/21/18	Revise
Medication Guide	NA	-	-	-

Patient Information	NA	-	-	-
SPL Data Elements		5/2014	3/15/17	Satisfactory

Appears this way in original

Huijeong Jung

Digitally signed by Huijeong Jung
Date: 9/07/2018 01:44:20PM
GUID: 508da702000287c1e12e719fda6a6d14

Lisa Kwok

Digitally signed by Lisa Kwok
Date: 9/07/2018 01:49:00PM
GUID: 508da70800028c5cddf24c815a550d26

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	October 23, 2017; November 3, 2017; November 14, 2017; January 19, 2018; February 1, 2018; March 5, 2018; August 8, 2018
ANDA Number(s)	207141
Review Number	3
Applicant Name	Praxair Distribution, Inc.
Established Name & Strength(s)	Nitric Oxide Gas for Inhalation, 100 ppm and 800 ppm
Proposed Proprietary Name	Noxivent (conditionally approved on January 30, 2018)
Submission Received Date	August 4, 2017, September 11, 2017, October 2, 2017, December 11, 2017, December 12, 2017 (request for re-evaluation of proprietary), and February 28, 2018
Primary Labeling Reviewer	A Jung
Secondary Labeling Reviewer	L Kwok

Review Conclusion

☐ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.

☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List ☒YES ☐NO

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on August 8, 2018 based on your submission(s) dated August 4, 2017, September 11, 2017, October 2, 2017, December 11, 2017, and February 28, 2018:

1. CONTAINER LABELS
   a. [redacted] (b) (4) Please change the statement to "USE IN ACCORDANCE WITH APPROPRIATE SDS" or provide justification on using a different statement from the RLD.
   b. [redacted] (b) (4) to "CAUTION: HIGH PRESSURE…".
   c. [redacted] (b) (4)

2. PRESCRIBING INFORMATION
   a. HIGHLIGHTS OF PRESCRIBING INFORMATION, Limitation statement and Title: We recommend that you use all upper case letters for the proposed proprietary name, NOXIVENT, for this section, only. For example, please see the RLD labeling. [redacted] (b) (4)

[redacted] (b) (4)

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia

– National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) dated (add date) **NA**

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling. **NA**

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements. **NA**

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).
NA

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

Appears this way in original

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(b) (4)

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:

Labels were previously found adequate but the following information will be requested:

Comment:

- [redacted] (b) (4) [redacted] ” to “CAUTION: HIGH PRESSURE…”.

[redacted] (b) (4) [redacted] Please change the statement to “USE IN ACCORDANCE WITH APPROPRIATE SDS” or provide justification on using a different statement from the RLD.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

Per policy’s recommendation Labeling sent consult to OND/ODEI/DCRP regarding NDA labeling history on 8/16/17.

http://panorama.fda.gov/task/view?ID=5994c21f0093100e232670b2e30c1faf

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? YES

If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Entry dated 9/18/15 for Email notifying of Controlled Correspondence (CC) #48965. CC review and response can be found in the following:

http://panorama.fda.gov/task/view?ID=54dbb45a000923da4badc5b569224f48

Entry dated 9/14/16 for Internal meeting minutes with Policy.

Entry dated 6/17/17 for consult to DMEPA regarding [redacted] (b) (4) [redacted]

[redacted] (b) (5) [redacted]

MODEL PRESCRIBING INFORMATION	Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)

Appears this way in original

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and enter the most recently approved ANDA labeling information as applicable.)

NDA# /Supplement# (S-000 if original): NDA20845/S-017

Supplement Approval Date: 10/9/15

Proprietary Name: Inomax

Established Name: Nitric Oxide Gas

Description of Supplement: PAS for the following changes: **S-016**: The removal of the 100 ppm nitric oxide concentration from the labeling and revisions to the DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS sections of the INOmax package inserts. **S-017**: Revisions to the labeling based on the clinical study entitled "Bronchopulmonary Dysplasia (BPD) in Preterm Infants Requiring Mechanical Ventilation or Positive Pressure Support on Days 5 to 14 After birth (IK-3001-BPD-301)".

S-018 CBE for CMC approved on 4/5/16: This "Changes Being Effected" supplemental new drug application proposes to include a MR conditional triangle and an appropriate warning "Keep cylinder at 100 gauss or less" label. (b) (4)

(b) (4)

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Rx only

INOmax®

nitric oxide FOR INHALATION

800 PPM

CAUTION: HIGH PRESSURE GAS. CAN CAUSE RAPID SUFFOCATION WITHOUT WARNING. Use equipment rated for cylinder pressure. Store and use with adequate ventilation. Secure cylinder in use and storage. Close valve after each use and when empty. USE IN ACCORDANCE WITH APPROPRIATE SDS.

WARNING: Administration of this gas mixture may be hazardous or contraindicated. For use only by or under the supervision of a licensed practitioner who is experienced in the use and administration of gas mixtures, and is familiar with the indications, effects, dosages, methods, and frequency and duration of administration, and with the hazards, contraindications and side effects and the precautions to be taken.

FIRST AID: IF INHALED, remove person to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical help.

RETURN WITH 25 PSIG.
TO BE REFILLED ONLY BY A PHARMACEUTICAL FACILITY AUTHORIZED BY INO Therapeutics LLC
Manufactured Under Pharmaceutical Current Good Manufacturing Practices (cGMPs).
DO NOT REMOVE THIS PRODUCT LABEL.

Store at 25°C (77°F)
[see USP Controlled Room Temperature].

Mallinckrodt™ Pharmaceuticals

Volume 353 Liters

Manufactured by:
Mallinckrodt Manufacturing LLC
1060 Allendale Dr.
Port Allen, LA 70767 USA
For Product Inquiry 1-877-KNOW INO
(566-9466)

UN 1956
Compressed Gas, N.O.S.
(Nitric Oxide, Nitrogen)
2.2
Net Weight: 0.5 Kg

NDC 64693-002-01

N 3 64693 00201 8

MADE IN USA

Label No. SPC-LBL-0058 R8

Inomax was originally approved on 12/23/1999. The above labeling is in-line with the below representatives from the originally approved labels. The only notable differences are company logos and the boxed CAUTION statement is replaced by Rx Only statement in the current labeling:

2 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

3.3 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

The USP was searched on 8/8/2018.

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Official Monograph	No		NA	NA
Pending Monograph Proposed	No	NA	NA	NA

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **NA**

Reviewer Comments:

None

3.4 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 3/5/2018.

Table 3 provides Orange Book patents for the Model Labeling NDA 20845 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling

Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter "Carve-out" or "None")
5732693*PED	Jun 13, 2017	U-1230	A method of providing NO therapy to a patient	III	3/15/2017	None
5752504*PED	Jun 13, 2017	U-1230	A method of providing NO therapy to a patient	III	3/15/2017	None
6125846*PED	Nov 16, 2017	U-1457	A method of purging a NO delivery system	III	3/15/2017	None
8282966*PED	Dec 30, 2029	U-1286	A method of reducing the risk of pulmonary edema in patients in need of treatment with inhaled NO	IV	3/15/2017	None
8291904*PED	Jul 6, 2031	U-1226	A method of providing a predetermined concentration of NO to a patient	IV	8/4/17 (w/d viii)	None
8293284*PED	Dec 30, 2029	U-1286	A method of reducing the risk of pulmonary edema in patients in need of treatment with inhaled NO	IV	3/15/2017	None
8431163*PED	Dec 30, 2029	U-1286	A method of reducing the risk of pulmonary edema in patients in need of treatment with inhaled NO	IV	3/15/2017	None
8573209*PED	Jul 6, 2031	-	-	IV	3/15/2017	None
8573210*PED	Jul 6, 2031	U-1453	A method of treating hypoxic respiratory failure by verifying gas information of NO prior to delivery to a patient	IV	8/4/17 (w/d viii)	None
8776794*PED	Jul 6, 2031	U-1226	A method of providing a predetermined concentration of NO to a patient	IV	8/4/17 (w/d viii)	None
8776795*PED	Jul 6, 2031	U-1226	A method of providing a predetermined concentration of NO to a patient	IV	8/4/17 (w/d viii)	None
8795741*PED	Dec 30, 2029	U-1286	A method of reducing the risk of pulmonary edema in patients in need of treatment with inhaled NO	IV	3/15/2017	None
8846112*PED	Dec 30, 2029	U-1286	A method of reducing the risk of pulmonary edema in patients in need of treatment with inhaled NO	IV	3/15/2017	None
9265911*PED#	Jul 6, 2031	U-1824	A method of providing NO therapy to a patient by verifying gas information of NO prior to delivery to a patient	IV	8/4/17 (w/d viii)	None
9279794*PED#	Aug 19, 2034	U-1823	A method of providing NO therapy to a patient by compensating long-term sensitivity drift of electrochemical gas sensors used in systems for delivering therapeutic NO to a patient	IV	3/15/2017	None
9295802*PED#	Jul 6, 2031	U-1226	A method of providing a predetermined concentration of NO to a patient	IV	8/4/17 (w/d viii)	None

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
9408993*PED#	Jul 6, 2031	U-1824	A method of providing NO therapy to a patient by verifying gas information of NO prior to delivery to a patient	IV	8/4/17 (w/d viii)	None
9770570*PED#	Nov 3, 2036	U-2148	A method of providing nitric oxide therapy to a patient by measuring and displaying an indication of the calculated delivery concentration of nitric oxide as compared to the desired delivery concentration of nitric oxide	IV	2/28/18	None

Applies only for the 800 ppm strength and not the 100 ppm strength.

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

Labeling is in-line with the RLD.

Mallinckrodt recently listed patent number 9770570 and 9770570*PED which will expire on November 3, 2036. (b) (4)

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter "Carve-out" or "None")

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4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **YES**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)

Previous Labeling Review	Currently Proposed	Assessment
Noxivent™ (nitric oxide gas) is a drug administered by inhalation. Nitric oxide, the active substance in Noxivent™, is a pulmonary vasodilator. Noxivent™ 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). Noxivent™ is supplied in aluminum cylinders as a compressed gas under high pressure (2000 pounds per square inch gauge [psig]).	Noxivent™ (nitric oxide gas) is a drug administered by inhalation. Nitric oxide, the active substance in Noxivent™, is a pulmonary vasodilator. Noxivent™ 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). Noxivent™ is supplied in aluminum cylinders as a compressed gas under high pressure (2000 pounds per square inch gauge [psig]).	No change

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products

Previous Labeling Review	Currently Proposed	Assessment
		(b) (4)

Table 7: Manufacturer/Distributor/Packer Statements

Previous Labeling Review	Currently Proposed	Assessment

Table 7: Manufacturer/Distributor/Packer Statements		
Distributed by Praxair Distribution, Inc. 39 Old Ridgebury Road Danbury, CT 06810 USA	Distributed by Praxair Distribution, Inc. 10 Riverview Drive Danbury, CT 06810	Acceptable

5. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline (e.g., OPQ, OB) reviewer(s):

Reviewer Comments:

The last quality review in the platform was dated 2/26/18.

Appendix D: Chemistry Review Template – Labeling section

A. Labeling & Package Insert

a) DESCRIPTION section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer. *None*

b) HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No
If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No
If "No," explain.

c) DOSAGE AND ADMINISTRATION section, for injectable, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☒ N/A
If "No," explain.

d) For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No
If "No," explain.
N/A

e) Inhalation Gas

(b) (4)

f) Describe issue(s) sent to and/or received from the OGD Labeling Reviewer:

(b) (4)

. *Delivery system to introduce the medication to the patient.*

Issues as described in "f" were not found in the platform. However, there were interdisciplinary discussions regarding the (b) (4) *which resulted in DMEPA consult. Quality initiated CDRH consults for the evaluation of the delivery system. In light of the pending CP, Policy would need to clear before Labeling can be approved.*

The following issue (ref #18956950) was sent to the Quality review team on 11/14/17:

We are currently wrapping up the labeling review of 207141 and wanted to inform you of an important labeling change proposed by the applicant.
In their amendment dated November 3, 2017 [Reviewer note: this date was corrected to Oct 2, 2017], among other labeling changes the applicant is now specifying the NO delivery system to be "NOxBOXi® (b) (4) Also, the HOW SUPPLIED section has been revised. (b) (4) and will make a comment to the applicant, (b) (4)

(b) (4)

I wanted to inform you in case the information impacts your quality review or CDRH consult. Please inform us if you have any labeling related issue.

Please feel free to mark it as resolved after you have a chance to read it. However, please follow up with us if you have any labeling related issue.

Thank you.

****

Following are email communications with the Quality reviewer (in reverse chronological order):

From:
Sent: Wednesday, November 15, 2017 4:22 PM
To:
Cc:
Subject: RE: ANDA 207141 Nitric Oxide Gas for Inhalation, 100 ppm and 800 ppm - FYI on Device change per updated Labeling

The updated information is accurate from Quality perspective.

Thanks,

From:
Sent: Wednesday, November 15, 2017 4:17 PM
To:
Cc: Subject: RE: ANDA 207141 Nitric Oxide Gas for Inhalation, 100 ppm and 800 ppm - FYI on Device change per updated Labeling

Please inform us if the updated information is accurate from Quality perspective or needs revision. We need your assessment on the difference. If it is not okay and it needs to be reverted to the previously submitted information kindly inform us what to communicate to the applicant. We understand that you do not have any outstanding deficiency. Since we do, we can communicate any quality related labeling deficiency to the applicant.

Thank you.

From:
Sent: Wednesday, November 15, 2017 4:10 PM
To:
Cc:

Subject: RE: ANDA 207141 Nitric Oxide Gas for Inhalation, 100 ppm and 800 ppm - FYI on Device change per updated Labeling

As I mentioned, The CMC review is acceptable, with the pending status of labeling and the outcome of the CDRH counsel.

I went through the labeling (what you sent us as attachment), and found that the table for the packaging table of Nitric oxide cylinders are close to what we have with the CMC review, but not the same.

Please see the attachment for the comparisons.

Thanks,

On 1/22/18, the Quality review team completed their review with an IR to the applicant requesting elemental impurities information as per ICH Q3D. The review did not update the Labeling section of their information. Therefore, the above communication was not reflected in their review. However, the Quality team verified on 1/24/18 (following meeting with Policy re: path forward) that the difference in volume (currently proposed vs. previously proposed for the 800 ppm) is so small that it is not a concern.

The following is communication with CDRH (in reverse chronological order):

From: (CDRH)
Sent: Wednesday, January 31, 2018 3:36 PM
To:
Subject: RE: ANDA 207141 NO

Hello,

The user manual for the NOxBOXi and NOxMixer is the "NOxBOXi and NOxMixer Technical Guide". The "Operating Instuctions" found on the website would be the quick reference guide. In our review documents, we only have the versions with the NOxMixer. The NOxMixer has been described as integrated into the NOxBOXi in the 510(k).

From:
Sent: Wednesday, January 31, 2018 2:11 PM
To: (CDRH) **Subject:** FW: ANDA 207141 NO

From:
Sent: Wednesday, January 24, 2018 2:19 PM
To:
Cc:
Subject: ANDA 207141 NO

Hello,

I wanted to follow up on the conversation we had at the tail end of today's discussion on 207141.

The RLD provides the following info regarding the manual in section 5.3 and the currently proposed ANDA's portion is next to it:

NDA 20845, S-017	ANDA 207141 (10/2/17 and 12/17 submissions)
5.3 Airway Injury from Nitrogen Dioxide	**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 there is an unexpected change in NO_2 concentration, or if the NO_2 concentration reaches 3 ppm 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.	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 there is an unexpected change in NO_2 concentration, or if the NO_2 concentration reaches 3 ppm when measured in the breathing circuit, then the delivery system should be assessed in accordance with the NOxBOXi and NOxMixer Technical Guide troubleshooting section or the Nitric Oxide Delivery System O&M Manual troubleshooting section, and the NO_2 analyzer should be recalibrated. The dose of Noxivent™ and/or FiO_2 should be adjusted as appropriate.

We understand that CDRH is reviewing the NODS labeling to determine whether the instructions for operating the NODS in the User Manual meet the standards for clearance, so I wanted to share the above information. I checked out the Noxboxi website and there are downloads for operating instructions for Noxboxi with and without Noxmixer.

http://noxboxltd.com/noxbox-i

[redacted] (b) (4) RLD labeling in section [redacted] (b) (4) t states "Nitric Oxide Deliver System O&M Manual".

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	[redacted] (b) (4)	3/15/17	Revise
Blister	NA	-	-	-
Carton	NA	-	-	-
(Other – specify)	NA	-	-	-
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	2/2018	2/28/18	Revise
Medication Guide	NA	-	-	-
Patient Information	NA	-	-	-

SPL Data Elements		5/2014	3/15/17	Satisfactory

Appears this way in original

Huijeong Jung

Digitally signed by Huijeong Jung
Date: 8/09/2018 12:22:16PM
GUID: 508da702000287c1e12e719fda6a6d14

Lisa Kwok

Digitally signed by Lisa Kwok
Date: 8/13/2018 12:42:07PM
GUID: 508da70800028c5cddf24c815a550d26

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	March 31, 2017 & June 18, 2017 & July 23, 2017
ANDA Number(s)	207141
Review Number	2
Applicant Name	Praxair Distribution, Inc.
Established Name & Strength(s)	Nitric Oxide Gas For Inhalation, 100 ppm and 800 ppm
Proposed Proprietary Name	Noxivent (approved July 14, 2016)
Submission Received Date	3/15/2017
Labeling Reviewer	Melaine Shin
Labeling Team Leader	Ashley Jung

Review Conclusion

☐ ACCEPTABLE – No Comments

☐ ACCEPTABLE – Include Post Approval Comments

☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

☒ On Policy Alert List:

1 Page has been withheld in full as b4 (CCI/TS) immediately following this page

(b) (4)

3. Please provide a photo of the proposed cylinder.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission dated .

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.
These comments will be addressed post approval (in the first labeling supplement review).
Click here to enter text.

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

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(b) (4)

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments: Revised labels are acceptable.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

(b) (4)

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? YES If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? If Yes, please explain.

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3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)

Appears this way in original

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)

☒**MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)

NDA#/Supplement# (S-000 if original): 020845/S-017

Supplement Approval Date: 10/9/2015

Proprietary Name: Inomax

Established Name: Nitric Oxide

Description of Supplement: These "Prior Approval" supplemental new drug applications propose the following:

S-016: The removal of the 100 ppm nitric oxide concentration from the labeling and revisions to the DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS sections of the INOmax package inserts.

S-017: Revisions to the labeling based on the clinical study entitled "Bronchopulmonary Dysplasia (BPD) in Preterm Infants Requiring Mechanical Ventilation or Positive Pressure Support on Days 5 to 14 After birth (IK-3001-BPD-301)".

FYI: S-018 CBE for CMC: This "Changes Being Effected" supplemental new drug application proposes to include a MR conditional triangle and an appropriate warning "Keep cylinder at 100 gauss or less" label. (b) (4)

(b) (4)

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:**
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.
☐ **OTHER (Describe):** Click here to enter text.

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **NO**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments: Not Acceptable. (b) (4) [redacted]

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: DailyMed]

1 Page has been withheld in full as b4 (CCI/TS) immediately following this page

3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results				
	Date Searched	**Monograph ? YES or NO**	**Monograph Title (NA if no monograph)**	**Packaging and Storage/Labeling Statements (NA if no monograph)**
USP	6/18/2017	No	NA	NA
PENDING USP	6/18/2017	No	NA	NA

Reviewer Comments:

Click here to enter text.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 6/18/2017.

Table 3 provides Orange Book patents for the Model Labeling (NDA 020845) and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling

Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
5732693*PED	Jun 13, 2017	U-1230	A METHOD OF PROVIDING NITRIC OXIDE THERAPY TO A PATIENT	III	3/15/2017	None
5752504*PED	Jun 13, 2017	U-1230	A METHOD OF PROVIDING NITRIC OXIDE THERAPY TO A PATIENT	III	3/15/2017	None
6125846*PED	Nov 16, 2017	U-1457	A METHOD OF PURGING A NITRIC OXIDE DELIVERY SYSTEM	III	3/15/2017	None
8282966*PED	Dec 30, 2029	U-1286	A METHOD OF REDUCING THE RISK OF PULMONARY EDEMA IN PATIENTS IN NEED OF TREATMENT WITH INHALED NITRIC OXIDE	IV	3/15/2017	None
8291904*PED	Jul 6, 2031	U-1226	A METHOD OF PROVIDING A PREDETERMINED CONCENTRATION OF NITRIC OXIDE TO A PATIENT	IV for drug product Viii for U-1226	3/15/2017	None
8293284*PED	Dec 30, 2029	U-1286	A METHOD OF REDUCING THE RISK OF PULMONARY EDEMA IN PATIENTS IN NEED OF TREATMENT WITH INHALED NITRIC OXIDE	IV	3/15/2017	None
8431163*PED	Dec 30, 2029	U-1286	A METHOD OF REDUCING THE RISK OF PULMONARY EDEMA IN PATIENTS IN NEED OF TREATMENT WITH INHALED NITRIC OXIDE	IV	3/15/2017	None
8573209*PED	Jul 6, 2031			IV	3/15/2017	
8573210*PED	Jul 6, 2031	U-1453	A METHOD OF TREATING HYPOXIC RESPIRATORY FAILURE BY VERIFYING GAS INFORMATION OF NITRIC OXIDE PRIOR TO DELIVERY TO PATIENT	IV for Drug product Viii for U-1453	3/15/2017	None
8776794*PED	Jul 6, 2031	U-1226	A METHOD OF PROVIDING A PREDETERMINED CONCENTRATION OF NITRIC OXIDE TO A PATIENT	IV for Drug product Viii for U-1226	3/15/2017	None
8776795*PED	Jul 6, 2031	U-1226	A METHOD OF PROVIDING A PREDETERMINED CONCENTRATION OF NITRIC OXIDE TO A PATIENT	IV for Drug product Viii for U-1226	3/15/2017	None
8795741*PED	Dec 30, 2029	U-1286	A METHOD OF REDUCING THE RISK OF PULMONARY EDEMA IN PATIENTS IN NEED OF TREATMENT WITH INHALED NITRIC OXIDE	IV	3/15/2017	None
8846112*PED	Dec 30, 2029	U-1286	A METHOD OF REDUCING THE RISK OF PULMONARY EDEMA IN PATIENTS IN NEED OF TREATMENT WITH INHALED NITRIC OXIDE	IV	3/15/2017	None

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
9265911*PED	Jul 6, 2031	U-1824	A METHOD OF PROVIDING NITRIC OXIDE THERAPY TO A PATIENT BY VERIFYING GAS INFORMATION OF NITRIC OXIDE PRIOR TO DELIVERY TO PATIENT	IV for drug product Viii for U-1824	3/15/2017	None
9279794*PED	Aug 19, 2034	U-1823	A METHOD OF PROVIDING NITRIC OXIDE THERAPY TO A PATIENT BY COMPENSATING LONG-TERM SENSITIVITY DRIFT OF ELECTROCHEMICAL GAS SENSORS USED IN SYSTEMS FOR DELIVERING THERAPEUTIC NITRIC OXIDE TO A PATIENT	IV	3/15/2017	None
9295802*PED	Jul 6, 2031	U-1226	A METHOD OF PROVIDING A PREDETERMINED CONCENTRATION OF NITRIC OXIDE TO A PATIENT	IV for drug product Viii for U-1226	3/15/2017	None
9408993*PED	Jul 6, 2031	U-1824	A METHOD OF PROVIDING NITRIC OXIDE THERAPY TO A PATIENT BY VERIFYING GAS INFORMATION OF NITRIC OXIDE PRIOR TO DELIVERY TO PATIENT	IV for Drug product Viii for U-1824	3/15/2017	None

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NO**

Reviewer Comments:

(b) (4)

[redacted]

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact**

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
M-167	October 9, 2018	APPROVED FOR REVISIONS TO TH LABELING BASED ON THE CLINICA STUDY ENTITLED 'BRONCHOPULMONARY DYSPLASI (BPD) IN PRETERM INFANTS REQUIRING MECHANICAL VENTILATION OR POSITIVE PRESSU SUPPORT ON DAYS 5 TO 14 AFTER BIRTH'.	(b) (4)	/15/2017	None

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NO**

Reviewer Comments: (b) (4) we will inform the applicant to revise the insert labeling.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **YES**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Noxivent™ (nitric oxide gas) is a drug administered by inhalation. Nitric oxide, the active substance in Noxivent™, is a pulmonary vasodilator. Noxivent™ 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).	Noxivent™ (nitric oxide gas) is a drug administered by inhalation. Nitric oxide, the active substance in Noxivent™, is a pulmonary vasodilator. Noxivent™ 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).	**No Change**

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products
(b) (4) [redacted]

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Distributed by Praxair Distribution, Inc. 39 Old Ridgebury Road Danbury, CT 06810 USA	Distributed by Praxair Distribution, Inc. 39 Old Ridgebury Road Danbury, CT 06810 USA	No change

5. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments: NA

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

Reviewer Comments: NA

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	(b) (4) [redacted]	3/15/2017	Satisfactory
Blister	NA			
Carton	NA			
(Other – specify)	NA			
Table 9 Review Summary of Prescribing Information and Patient Labeling				

	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	3/2017	3/15/2017	Revise
Medication Guide	NA			
Patient Information	NA			
SPL Data Elements only		5/2014	3/15/2017	Satisfactory

Appears this way in original

Melaine Shin

Digitally signed by Melaine Shin
Date: 3/31/2017 03:31:04PM
GUID: 508da70900028c98567d39baedf7b37b

Huijeong Jung

Digitally signed by Huijeong Jung
Date: 7/10/2017 06:00:37PM
GUID: 508da702000287c1e12e719fda6a6d14

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	8/24/2016 & 9/14/2016 & 1/19/2017
ANDA Number(s)	207141
Review Number	1
Applicant Name	Praxair Distribution, Inc.
Established Name & Strength(s)	Nitric Oxide Gas For Inhalation, 100 ppm and 800 ppm
Proposed Proprietary Name	Noxivent (approved 7/14/16)
Submission Received Date	5/20/2014 (original) & 7/5/2016 (amendment)
Labeling Reviewer	Melaine Shin
Labeling Team Leader	Ashley Jung

Review Conclusion

☐ ACCEPTABLE – No Comments

☐ ACCEPTABLE – Include Post Approval Comments

☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

☒ On Policy Alert List

TABLE OF CONTENTS

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on 1/19/2017 based on your submissions dated 5/20/2014 & 7/5/2016:

1. GENERAL COMMENTS

   a. Please provide most current patent certifications to all patents listed in the orange book. If you are doing a split certification to a single patent, we ask that you indicate your intention clearly in the same document.

   b. We ask that you address the marketing exclusivity associated with M-167 (APPROVED FOR REVISIONS TO THE LABELING BASED ON THE CLINICAL STUDY ENTITLED 'BRONCHOPULMONARY DYSPLASIA (BPD) IN PRETERM INFANTS REQUIRING MECHANICAL VENTILATION OR POSITIVE PRESSURE SUPPORT ON DAYS 5 TO 14 AFTER BIRTH') expiring October 9, 2018.

   c. On December 27, 2016, Mallinckrodt Pharmaceuticals submitted a citizen petition to FDA (Docket No. FDA-2016-P-4587), regarding applications that reference Inomax (Nitric Oxide) for Inhalation. The issues raised by this petition are currently under review by the Agency, and FDA has not made a final decision on the issues the petition raises. These deficiency comments included in this communication reflect only our current thinking and this communication does not represent a final decision by the Agency on the issues raised in the pending citizen petition. As such, your labeling may be subject to further revision as we complete our review of the issues the petition raises.

2. CONTAINER LABEL

   a. Increase the prominence of "for inhalation" from "nitric oxide for inhalation" to be in line with the reference listed drug label.

   b. (b) (4)

   c. Increase the prominence of the middle portion of the NDC number to help differentiate each product within this product line (i.e xxxx-XXX-xxx) and relocate it to the top of the label.

   d. Add the barcode according to the 21 CFR 201.25.

3. PRESCRIBING INFORMATION

(b) (4)

4. STRUCTURED PRODUCT LABELING

(b) (4)

Please revise and/or clarify.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission(s) dated (add date).

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.
These comments will be addressed post approval (in the first labeling supplement review).
Click here to enter text.

2. LABELING REVIEW INFORMATION

2.1 REGULATORY INFORMATION

Has the ANDA been accepted for filing? YES
Are there any pending issues in DLR's SharePoint Drug Facts? YES If Yes, please explain. (b) (4)
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? YES If Yes, please explain.

CP	FDA-2016-P-4587	Inomax	inhaled nitric oxide	Requests that the FDA require inhaled nitric oxide drug products and nitric oxide delivery systems be reviewed by CDER and CDRH in a coordinated fashion.	20845	No Actions (AP/TA/CR) can be taken prior to contacting Policy Lead	Disciplines can send IR/ECD; No CC without contacting Policy Lead		12/29/2016	Mary Alice Hiatt

There is a CP pending for the RLD Inomax.

CP: FDA-2016-P-4587:

Mallinckrodt submitted this Petition to assure that follow-on drug products citing INOMAX as the reference listed drug incorporate the features necessary for the safe and effective administration of inhaled nitric oxide. This necessitates not only the customary Agency review of the quality of the proposed drug product, but also careful evaluation of the design and operation of the associated delivery system to assure it is equivalent to the INOmax DSIR Plus delivery system used for INOMAX, and includes the same critical safety features.

2.2 MODEL LABELING

2.2.1 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)

Appears this way in original

(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA RLD information.)

NDA#/Supplement# (S-000 if original): 020845/S-017

Supplement Approval Date: 10/9/2015

Proprietary Name: Inomax

Established Name: Nitric Oxide

Description of Supplement: These "Prior Approval" supplemental new drug applications propose the following:

S-016: The removal of the 100 ppm nitric oxide concentration from the labeling and revisions to the DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS sections of the INOmax package inserts.

S-017: Revisions to the labeling based on the clinical study entitled "Bronchopulmonary Dysplasia (BPD) in Preterm Infants Requiring Mechanical Ventilation or Positive Pressure Support on Days 5 to 14 After birth (IK-3001-BPD-301)".

FYI: S-018 CBE for CMC: This "Changes Being Effected" supplemental new drug application proposes to include a MR conditional triangle and an appropriate warning "Keep cylinder at 100 gauss or less" label. (b) (4)

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(b) (4)

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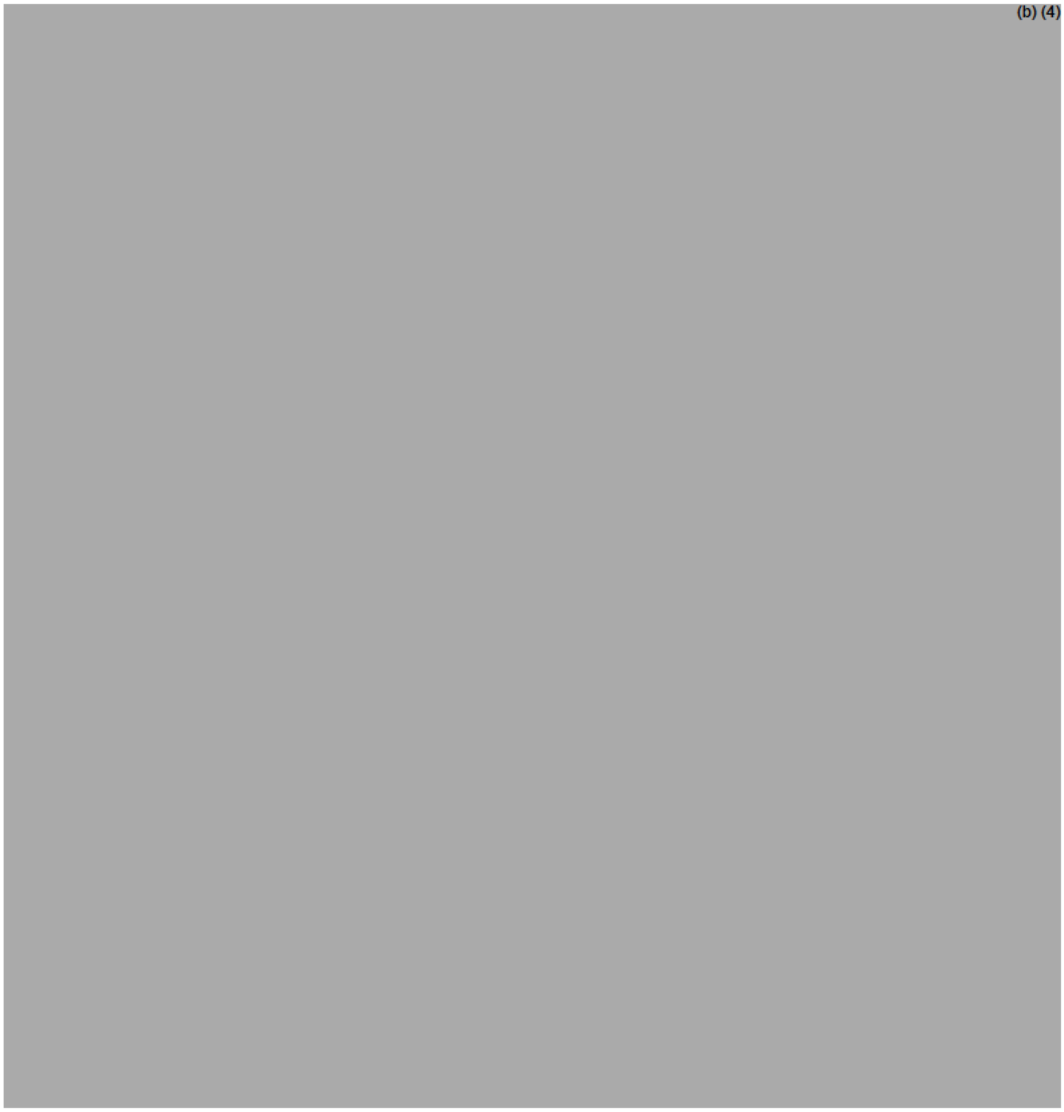

2.3 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results

	Date Searched	Monograph ? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	8/30/2016	NO	NA	NA
PENDING USP	8/30/2016	NO	NA	NA

2.4 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 1/19/2017.

Table 3 provides Orange Book patents for the Model Labeling and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact**
5732693*PED	Jun 13, 2017	U-1230	A METHOD OF PROVIDING NITRIC OXIDE THERAPY TO A PATIENT	III	5/20/2014	none
5752504*PED	Jun 13, 2017	U-1230	A METHOD OF PROVIDING NITRIC OXIDE THERAPY TO A PATIENT	III	5/20/2014	none
6125846*PED	Nov 16, 2017	U-1457	A METHOD OF PURGING A NITRIC OXIDE DELIVERY SYSTEM	III	5/20/2014	none
8282966*PED	Dec 30, 2029	U-1286	A METHOD OF REDUCING THE RISK OF PULMONARY EDEMA IN PATIENTS IN NEED OF TREATMENT WITH INHALED NITRIC OXIDE	viii	5/20/2014	None, it was determined from the 8/1/2016 policy meeting that this certification is acceptable and there is nothing to carve out.
				IV	11/12/2014	
8291904*PED	Jul 6, 2031	U-1226	A METHOD OF PROVIDING A PREDETERMINED CONCENTRATION OF NITRIC OXIDE TO A PATIENT	IV & viii	5/20/2014	The section viii certification is not consistent with the labeling submitted.
8293284*PED	Dec 30, 2029	U-1286	A METHOD OF REDUCING THE RISK OF PULMONARY EDEMA IN PATIENTS IN NEED OF TREATMENT WITH INHALED NITRIC OXIDE	IV	5/20/2014	None, it was determined from the 8/1/2016 policy meeting that this certification is acceptable and there is nothing to carve out.
8431163*PED	Dec 30, 2029	U-1286	A METHOD OF REDUCING THE RISK OF PULMONARY EDEMA IN PATIENTS IN NEED OF TREATMENT WITH INHALED NITRIC OXIDE	IV	5/20/2014	None, it was determined from the 8/1/2016 policy meeting that this certification is acceptable and there is nothing to carve out.
8573209*PED	Jul 6, 2031					none
8573210*PED	Jul 6, 2031	U-1453	A METHOD OF TREATING HYPOXIC RESPIRATORY FAILURE BY VERIFYING GAS INFORMATION OF NITRIC OXIDE PRIOR TO DELIVERY TO PATIENT	IV & viii	5/20/2014	None, carved out
				viii	7/5/2016	
8776794*PED	Jul 6, 2031	U-1226	A METHOD OF PROVIDING A PREDETERMINED CONCENTRATION OF NITRIC OXIDE TO A PATIENT	viii	7/5/2016	The section viii certification is not consistent with the labeling submitted.
				IV & viii	11/12/2014	
8776795*PED	Jul 6, 2031	U-1226	A METHOD OF PROVIDING A PREDETERMINED CONCENTRATION OF NITRIC OXIDE TO A PATIENT	IV & viii	11/12/2014	The section viii certification is not consistent with the labeling submitted. See section 1.1 for more details.
8795741*PED	Dec 30, 2029	U-1286	A METHOD OF REDUCING THE RISK OF PULMONARY EDEMA IN PATIENTS IN NEED OF TREATMENT WITH INHALED NITRIC OXIDE	IV	11/12/2014	None, it was determined from the 8/1/2016 policy meeting that this certification is acceptable and there is nothing to carve out.
8846112*PED	Dec 30, 2029	U-1286	A METHOD OF REDUCING THE RISK OF PULMONARY EDEMA IN PATIENTS IN NEED OF TREATMENT WITH INHALED NITRIC OXIDE	IV	11/12/2014	None
9265911*PED	Jul 6, 2031	U-1824	A METHOD OF PROVIDING NITRIC OXIDE THERAPY TO A PATIENT BY VERIFYING GAS INFORMATION OF NITRIC OXIDE PRIOR TO DELIVERY TO PATIENT	IV & viii	5/5/2016	None, carved out
9279794*PED	Aug 19, 2034	U-1823	A METHOD OF PROVIDING NITRIC OXIDE THERAPY TO A PATIENT BY COMPENSATING LONG-TERM SENSITIVITY DRIFT OF ELECTROCHEMICAL GAS SENSORS USED IN SYSTEMS FOR DELIVERING THERAPEUTIC NITRIC OXIDE TO A PATIENT	IV	5/5/2016	None

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact**
M-167	October 9, 2018	APPROVED FOR REVISIONS TO THE LABELING BASED ON THE CLINICAL STUDY ENTITLED 'BRONCHOPULMONARY DYSPLASIA (BPD) IN PRETERM INFANTS REQUIRING MECHANICAL VENTILATION OR POSITIVE PRESSURE SUPPORT ON DAYS 5 TO 14 AFTER BIRTH'.	Not yet certified		

2.5 MANUFACTURING FACILITY

Table 5 provides a description of the drug product manufacturing facility.

Table 5: Comparison of Manufacturer/Distributor/Packer Labeling Statements		
Name and Address of Facility ANDA Manufactured (Cite Source)	**Name and Address on ANDA Container/Carton**	**Name and Address on ANDA Prescribing Information**
3.2.P.3.1 Manufacturer (Nitric Oxide 100 ppm and 800 ppm, Inhalation Gas) The drug products are manufactured, packaged, labeled, tested and released by: Praxair Distribution, Inc. (b) (4)	PRAXAIR DISTRIBUTION, INC. (b) (4)	Distributed by Praxair Distribution, Inc. 39 Old Ridgebury Road Danbury, CT 06810 USA

3. ASSESSMENT OF ANDA LABELING AND LABELS

The results for each material reviewed in this section provide the basis for the labeling comments to the applicant.

Is this product Rx or OTC? Please check one.

☒ Rx Product (If Rx, skip 3.2 OTC DRUG PRODUCT and go to 3.3 CONTAINER/CLOSURE.)
☐ OTC Product (If OTC, skip 3.1 RX DRUG PRODUCT and go to 3.3 CONTAINER/CLOSURE)

3.1 RX (PRESCRIPTION) DRUG PRODUCT

3.1.1 RX: PRESCRIBING INFORMATION

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **NO**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**
Is the established name for this ANDA acceptable? **YES**
Does the Model Labeling have combined insert labeling for multiple NDAs or dosage forms? **NO**
Are the required USP recommendations reflected in the labeling? **NA**
Is the applicant's "patent carve out" acceptable? **NO**
Is the applicant's "exclusivity carve out" acceptable? **NA**
Is the Manufacturer statement acceptable? **YES**

Reviewer Comments:

Not acceptable. See the meeting minutes from 8/1/16 internal meeting with Policy and comments in sections 1 and 2.4.

3.1.1.1 RX: DESCRIPTION

We reviewed the DESCRIPTION section for accuracy (with input from the chemistry review, if appropriate) and acceptability from Labeling perspective. We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling.

Table 6: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

Model Labeling Inactive Ingredients	ANDA Labeling Inactive Ingredients
Nitric oxide and nitrogen	Nitric oxide and nitrogen

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling Memorandum of Understanding (MOU)?
YES, chemistry review complete
(Note: The MOU became effective on November 1, 2014. MOU does not apply to amendment reviews for ANDAs originally reviewed before November 1, 2014.)

If the chemistry review follows the MOU, labeling reviewer is not responsible for reviewing for accuracy of the DESCRIPTION section for chemical properties, system components of the drug product, etc. Please refer to the MOU, Appendix A, DESCRIPTION section for delineation of responsibilities. If chemistry review does NOT follow the MOU, labeling reviewer will follow the traditional review approach of reviewing the entire DESCRIPTION section.)

Are the inactive ingredients information consistent with "Components and Composition" information as provided in Module 3.2.P.1? (If Chemistry follows the MOU, refer to the Labeling section of Chemistry review.) **YES**

For products required to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **NA**

Does any inactive ingredient require special warnings, precautions, or labeling statements? **NO**

If the labeling includes a "Does not contain…" statement, is it acceptable/allowed? **NA** Has the statement been verified by chemistry? **NA**

Reviewer Comments:
Acceptable.

3.1.1.2 RX: HOW SUPPLIED/STORAGE AND HANDLING

We compared the descriptions of the model product to the ANDA finished product. Product differences, such as scoring configuration and storage conditions, are highlighted in Table 7 and will be referred to the appropriate review discipline for evaluation.

Table 7: Comparison of Model Labeling to ANDA Labeling

Model Labeling

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 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)

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.

ANDA Labeling

16 HOW SUPPLIED/STORAGE AND HANDLING

Noxivent™ (nitric oxide) is available in the following sizes:

(b) (4)

[redacted]

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.

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling MOU? **YES, chemistry review complete**
If the chemistry review does NOT follow the MOU, is the description (scoring, color and imprint) of the finished product in the HOW SUPPLIED section consistent with the information in Module 3.2.P.5.1 for Drug Product Specification? **NA**
Does the ANDA require the same color coding as the Model Labeling? **NA**
Is there any difference in scoring configuration between the ANDA and the Model Labeling? **NA**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **YES**
If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **NA**
Is the storage or dispensing statement acceptable as compared to the Model Labeling? **YES**
Is the storage or dispensing statement acceptable as compared to the USP? **NA**

Reviewer Comments:
Acceptable.

3.1.2 RX: MEDICATION GUIDE

Is Medication Guide required? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.3.

Reviewer Assessment:

Was Medication Guide submitted? **CLICK HERE**
Is the Medication Guide same as the model labeling, except for allowable differences? **CLICK HERE**
Does the Medication Guide meet the requirements of 21 CFR 208.20? **CLICK HERE**
Has the Applicant committed to provide a sufficient number of medication guides? **CLICK HERE**
Is the phonetic spelling of the proprietary or established name present? **CLICK HERE**
Is FDA 1-800-FDA-1088 phone number included? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.3 RX: OTHER PATIENT LABELING

Are other patient labeling required? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.

Reviewer Assessment:

Was other patient labeling submitted? **CLICK HERE**
Is the patient labeling the same as the model labeling, except for allowable differences? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.4 RX: CONTAINER LABEL

Was container label (other than Blisters) submitted? **YES**
(For BLISTER labels go to section 3.1.5.)

We evaluated the container labels for the inclusion of all required statements and safety considerations.

Reviewer Assessment:

Is the established name acceptable? **YES**
Is title case used in expressing the established name? **YES**
Does labeling comply with Tall Man lettering recommendations found on FDA webpage? **NA**
Is container label too small to contain all required information? **NO** If yes, does the container meet the "too small" exemption found in 21 CFR 201.10(i)? **NA**

Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **YES**

Is the following information properly displayed?

- Net quantity statement: **NO**
- Route(s) of administration (other than oral): **YES**
- Warnings (if any) or cautionary statements (if any): **NO**
- Medication Guide Pharmacist instructions per 21 CFR 208.24(d)**:** **NA**
- Controlled substance symbol: **NA**
- Usual Dosage statement: **NA**
- Product strength equivalency statement: **NA**
- NDC: **NO**
- Bar code per 21 CFR 201.25(c)(2): **NO**

Is the Manufacturer/Distributor/Packager statement acceptable? **NO**
For foreign manufacturers, does the labeling have the country of origin? **NA**
Are the required USP recommendations reflected on the label(s)? **NA**
Is the storage or dispensing statement consistent with the How Supplied section of the insert? **YES**

Does any inactive ingredient require special warnings, precautions, or labeling statements? **NO**

Are multiple strengths differentiated by use of different color or other acceptable means? **YES**
Are the labels of related products differentiated to avoid selection errors? **NA**

Does the ANDA require the same color coding as the Model Labeling? **NO**

Are the requirements of 21 CFR 201.15 met for all required label statements? **YES**
Are the requirements of 21 CFR 201.100 met for all required label statements? **YES**

Reviewer Comments:
Not Acceptable. See section 1. There is no ANDA with same active ingredient submitted by the applicant.

3.1.4.1 RX: CONTAINER LABEL FOR PARENTERAL SOLUTIONS

Is container for parenteral solution? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.2.

Reviewer Assessment:

Is the product strength expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP, General Chapter <1> Injection? **CLICK HERE**
If volume is less than 1 mL, is strength per fraction of a milliliter the only expression of strength? **CLICK HERE**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.4.2 RX: CONTAINER LABEL FOR SOLID INJECTABLE

Is container for solid injectable? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.3.

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **CLICK HERE**
Are instructions for reconstitution and resultant concentration provided, if space permits? **CLICK HERE**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.4.3 RX: CONTAINER LABEL FOR PHARMACY BULK PACKAGE

Is container a Pharmacy Bulk Package (parenteral preparations for admixtures)? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.5.

Reviewer Assessment:

Is there a prominent, boxed declaration reading "Pharmacy Bulk Package – Not for Direct Infusion" on the principal display panel following the expression of strength? **CLICK HERE**
Does the container label include graduation marks? **CLICK HERE**
Does label contain the required information on proper aseptic technique including time frame in which the container may be used once it has been entered? **CLICK HERE**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **CLICK HERE**

Reviewer Comments:

3.1.5 RX: UNIT DOSE BLISTER LABEL

Is container a Unit Dose Blister Pack? **NO**

If YES go to Reviewer Assessment below, if NO go to section 3.1.6.

Reviewer Assessment:

Does each blister include only one dosage unit (e.g., one tablet, one capsule)? **CLICK HERE**
Do proprietary name, established name, strength, bar code, and manufacturer appear accurately on each blister cell? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.6 RX: CARTON (OUTER OR SECONDARY PACKAGING) LABELING

Was carton labeling submitted? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Are the answers to the Container Label questions the same for the Carton Labeling? **CLICK HERE** If no, please explain the differences in the Reviewer Comments section.
If container is too small or otherwise unable to accommodate a label with enough space to include all required information, is all required information present on the carton labeling? **CLICK HERE**
If country of origin is not on Container, does it appear on outer packaging labeling? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

Table 8: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling Inactive Ingredients	**ANDA Inactive Ingredients**
Click here to enter text.	Click here to enter text.

Reviewer Assessment:

Are the inactive ingredients information consistent with "Components and Composition" information as provided in Module 3.2.P.1? **CLICK HERE**
Are the inactive ingredients listed in alphabetical order? **CLICK HERE**
For products required/recommended to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **CLICK HERE**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **CLICK HERE**
If the labeling includes a "Does not contain…" statement, is it acceptable/allowed? **CLICK HERE** Has the statement been verified by chemistry? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

Is the description (scoring, color and imprint) of the finished product consistent with the Drug Product Quality submission? **CLICK HERE**
Is there any difference in scoring configuration between the ANDA and the Model Labeling? **CLICK HERE**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **CLICK HERE**
If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **CLICK HERE**
Is the storage or dispensing statement acceptable as compared to the Model Labeling? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.2 CONTAINER/CLOSURE

We evaluated the container/closure system of this product to determine if special child-resistant packaging is

required based on packaging configuration. Additionally, we evaluated other aspects of the container closure that relate to the dosage form, product formulation, and product class. Below is a description of the container/closure for the ANDA product.

Reviewer Assessment:

Describe container closure (e.g., 30s CRC, 100s non-CRC) and cite source of information in **Reviewer Comments** text box.
Does the container require a child-resistant closure (CRC) as described in the Poison Prevention Act and regulations? **NO**
Are the tamper evident requirements met for OTC and Controlled Substances? (If quality review follows the chemistry-labeling MOU, obtain answer from Appendix D of chemistry review; if quality review does not follow the MOU, labeling reviewer is responsible for assessing for tamper evidence.) **NA**

For ophthalmic products:

Does this ophthalmic product cap color match the American Academy of Ophthalmology (AAO) packaging color-coding scheme? **CLICK HERE**

For parenteral products:

Is there text on the cap/ferrule overseal of this injectable product? **CLICK HERE**
If YES, does text comply with the recommendations in USP General Chapter <1>? **CLICK HERE**
What is the cap and ferrule color? **Click here to enter text.**
NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.

(b) (4)

(b) (4)

3.3 CALCULATIONS FOR CONTENTS IN LABELING

Is calculation of ingredient(s) required? **NO**
If YES, go to Table 10 and Reviewer Assessment below, if NO go to section 3.5.

We verified the calculation on the following content.

Table 10: Ingredients		
Ingredient	**Stated Content**	**Location of the Information**
Click here to enter text.	Click here to enter text.	Click here to enter text.

(Note: For Rx products, if chemistry review follows the MOU, chemistry reviewer will verify the accuracy of the active and inactive ingredient amount(s) if information is in the DESCRIPTION and HOW SUPPLIED sections for all products, and additionally, DOSAGE AND ADMINISTRATION section for parenteral products. See Chemistry-Labeling MOU, Appendix A, Miscellaneous section for discussion on calculations.)

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling MOU? **CLICK HERE**
Are the stated contents in the table above acceptable? **CLICK HERE**
Aluminum content in small volume parenterals, large volume parenterals, and pharmacy bulk packages, which are used in TPNs, need to be in the labeling per 21 CFR 201.323.
Did the chemistry reviewer verify the aluminum content? **CLICK HERE**
Are the labeling requirements met per 21 CFR 201.323? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.4 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

We evaluated the SPL data elements to ensure they are consistent with the information submitted in the ANDA.

Table 11: ANDA Tablet/Capsule Size and Imprint		
Tablet/Capsule Strength	**ANDA Tablet/Capsule Size (mm) and imprint code from SPL**	**ANDA Tablet/Capsule Size (mm) and imprint code (Cite source of information such as the chemistry review that follows the MOU, Product Specification in 3.2.P.5.1, Commercial Batch Record in 3.2.P.3.3. etc.)**
Click here to enter text.	Click here to enter text.	Click here to enter text.
Click here to enter text.	Click here to enter text.	Click here to enter text.

Reviewer Assessment:

For solid oral dosage forms: Do size and imprint code from the SPL data elements match the information provided in the quality submission? **NA**
Are all the other data elements (strength, inactive ingredients, product characteristics, packaging etc.) consistent with the information submitted in the ANDA labeling? **NO**

Reviewer Comments:
Not Acceptable. See section 1.

4. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments:

Appendix D: Chemistry Review Template – Labeling section

A. Labeling & Package Insert

a) DESCRIPTION section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer. *None*

b) HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No
If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No
If "No," explain.

c) DOSAGE AND ADMINISTRATION section, for injectable, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☒ N/A
If "No," explain.

d) For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No
If "No," explain.
N/A

e) Inhalation Gas

(b) (4)

f) Describe issue(s) sent to and/or received from the OGD Labeling Reviewer:

(b) (4)

- *Delivery system to introduce the medication to the patient.*

(b) (4)

1 Page has been withheld in full as b4 (CCI/TS) immediately following this page

(b) (4)

5. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other review discipline reviewer(s):

Reviewer Comments:
Bioequivalence review dated 7/7/2015 was adequate.

6. SPECIAL CONSIDERATIONS

This drug product has a lot of issues that need to be resolved before it can be approved. (b) (4)

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 12 and 13 provide a summary of recommendations for each labeling piece analyzed in this review.

Table 12: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Draft	100 ppm: (b) (4)	5/20/2014	Revise
Blister	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
Carton	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
(Other – specify)	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
Table 13 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Draft	07/2016	7/5/2016	Revise
Medication Guide	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
Patient Information	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
SPL Data Elements	Draft	05/2014	5/20/2014	Revise

Huijeong Jung

Digitally signed by Huijeong Jung
Date: 2/27/2017 04:47:55PM
GUID: 508da702000287c1e12e719fda6a6d14

Melaine Shin

Digitally signed by Melaine Shin
Date: 2/01/2017 02:43:17PM
GUID: 508da70900028c98567d39baedf7b37b

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA207141Orig1s000

PROPRIETARY NAME REVIEW(s)

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	January 26, 2018
Application Type and Number:	ANDA 207141
Product Name and Strength:	Noxivent (nitric oxide) gas for inhalation, 100 ppm and 800 ppm
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Praxair Distribution, Inc.
Panorama #:	2017-19602955
DMEPA Safety Evaluator:	Colleen Little, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

Contents

1 INTRODUCTION

This review evaluates the proposed proprietary name, Noxivent, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively. The Applicant submitted an external name study, conducted by [redacted] (b) (4) for this proposed proprietary name.

1.1 REGULATORY HISTORY

The Applicant previously submitted the proposed proprietary name, Noxivent, on July 9, 2014 and May 18, 2016. The Division of Medication Error Prevention and Analysis (DMEPA) found the name conditionally acceptable in OSE Review #2014-25811[a] and OSE Review #2016-8071454[b]. As requested by FDA, because of the amount of time elapsed since our last review conducted on July 7, 2016, the Applicant re-submitted a complete request for proprietary name review on December 12, 2017.

The external study conducted by [redacted] (b) (4) in the December 12, 2017 submission is the same study previously submitted and the [redacted] (b) (4) Proprietary Name Safety Summary for Noxivent is dated May 27, 2014.

1.2 PRODUCT INFORMATION

The following product information is provided in the July 9, 2014, the May 18, 2016, and the December 12, 2017 proprietary name submissions.

- Intended Pronunciation: 'näk-sə-vent
- Active Ingredient: nitric oxide
- Indication of Use: A vasodilator indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents.
- Route of Administration: Inhaled using a calibrated Nitric Oxide Delivery System.
- Dosage Form: Gas
- Strength: 100 ppm and 800 ppm
- Dose and Frequency: 20 ppm, maintained for up to 14 days or until the underlying oxygen desaturation has resolved.
- How Supplied:

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[a] Stewart, J. Proprietary Name Review for Noxivent (ANDA 207141). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 Dec 10. RCM No.: 2014-25811.

[b] Lowery, A. Proprietary Name Review for Noxivent (ANDA 207141). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 Jul 7. RCM No.: 2016-8071454

Size D	(b) (4)
Size 88	
Size AD	
Size AQ	

- Storage: Controlled Room Temperature
- Reference Listed Drug/Reference Product: INOmax (NDA 020845)

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that the proposed name would not misbrand the proposed product. The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Cardiovascular and Renal Products (DCRP) concurred with the findings of OPDP's assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proprietary name[c].

2.2.2 Components of the Proposed Proprietary Name

The Applicant indicated in their submission that the proposed name, Noxivent, connotes nitric oxide and breathing (vent, respiratory associated). This proprietary name is comprised of a single word that does not contain any components (i.e. a modifier, route of administration, dosage form, etc.) that are misleading or can contribute to medication error.

2.2.3 Comments from Other Review Disciplines at Initial Review

In response to the OSE December 22, 2018 e-mail, the Division of Division of Cardiovascular and Renal Products (DCRP) did not forward any comments or concerns relating to the proposed proprietary name at the initial phase of the review.

[c] USAN stem search conducted on January 19, 2018

2.2.4 FDA Name Simulation Studies

103 practitioners participated in DMEPA's prescription studies. The responses did not overlap with any currently marketed products nor did the responses sound or look similar to any currently marketed products or any products in the pipeline. Appendix B contains the results from the verbal and written prescription studies.

2.2.5 Phonetic and Orthographic Computer Analysis (POCA) Search Results

Our POCA search[d] identified 169 names with a combined phonetic and orthographic score of ≥55% or an individual phonetic or orthographic score ≥70%**.** %. We had identified and evaluated some of the names[a,b] in our previous proprietary name reviews. We re-evaluated the previously identified names of concern considering any lessons learned from recent post-marketing experience, which may have altered our previous conclusion regarding the acceptability of the name. We note that none of the product characteristics have changed and we agree with the findings from our previous review for the names evaluated previously. Therefore, we identified 47 names not previously analyzed. These names are included in Table 1 below.

2.2.6 Names Retrieved for Review Organized by Name Pair Similarity

Table 1 lists the number of names retrieved from our POCA search. These name pairs are organized as highly similar, moderately similar or low similarity for further evaluation.

Table 1. Similarity Category	**Number of Names**
Highly similar name pair: combined match percentage score ≥70%	2
Moderately similar name pair: combined match percentage score ≥55% to ≤ 69%	45
Low similarity name pair: combined match percentage score ≤54%	0

2.2.7 Safety Analysis of Names with Potential Orthographic, Spelling, and Phonetic Similarities

Our analysis of the 47 names contained in Table 1 determined none of the names will pose a risk for confusion as described in Appendices C through H.

3 CONCLUSION

The proposed proprietary name is acceptable.

If you have any questions or need clarifications, please contact Darrell Lyons, OSE project manager, at 301-796-4092.

[d] POCA search conducted on January 17, 2017 in version 4.2.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Noxivent, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your submission, received on December 12, 2017, are altered prior to approval of the marketing application, the name must be resubmitted for review.

Appears this way in original

4 REFERENCES

1. ***USAN Stems (http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page)***

   USAN Stems List contains all the recognized USAN stems.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

Drugs@FDA

Drugs@FDA is an FDA Web site that contains most of the drug products approved in the United States since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA-approved *brand name* and *generic drugs*; *therapeutic biological products*, *prescription* and *over-the-counter* human drugs; and *discontinued drugs* (see Drugs @ FDA Glossary of Terms, available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#ther_biological).

RxNorm

RxNorm contains the names of prescription and many OTC drugs available in the United States. RxNorm includes generic and branded:

- Clinical drugs – pharmaceutical products given to (or taken by) a patient with therapeutic or diagnostic intent
- Drug packs – packs that contain multiple drugs, or drugs designed to be administered in a specified sequence

Radiopharmaceuticals, contrast media, food, dietary supplements, and medical devices, such as bandages and crutches, are all out of scope for RxNorm (http://www.nlm.nih.gov/research/umls/rxnorm/overview.html#).

Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

3. ***Electronic Drug Registration and Listing System (eDRLS) database***

The electronic Drug Registration and Listing System (eDRLS) was established to supports the FDA's Center for Drug Evaluation and Research (CDER) goal to establish a common Structured Product Labeling (SPL) repository for all facilities that manufacture regulated drugs. The system is a reliable, up-to-date inventory of FDA-regulated, drugs and establishments that produce drugs and their associated information.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. **Misbranding Assessment**: For prescription drug products, OPDP assesses the name for misbranding concerns. . For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNDP. OPDP or DNDP evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. **Safety Assessment**: The safety assessment is conducted by DMEPA, and includes the following:

a. Preliminary Assessment: We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 2*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [e]

[e] National Coordinating Council for Medication Error Reporting and Prevention. http://www nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

***Table 2- Prescreening Checklist for Proposed Proprietary Name**

	Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.
Y/N	**Is the proposed name obviously similar in spelling and pronunciation to other names?**
	Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products.
Y/N	**Are there inert or inactive ingredients referenced in the proprietary name?**
	Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)).
Y/N	**Does the proprietary name include combinations of active ingredients?**
	Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).
Y/N	**Is there a United States Adopted Name (USAN) stem in the proprietary name?**
	Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem.
Y/N	**Is this proprietary name used for another product that does not share at least one common active ingredient?**
	Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name.
Y/N	**Is this a proprietary name of a discontinued product?**
	Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients.

b. Phonetic and Orthographic Computer Analysis (POCA): Following the preliminary screening of the proposed proprietary name, DMEPA staff evaluates the proposed name against potentially similar names. In order to identify names with potential similarity to the proposed proprietary name, DMEPA enters the proposed proprietary name in POCA and queries the name against the following drug reference databases, Drugs@fda, CernerRxNorm, and names in the review pipeline using a 55% threshold in POCA. DMEPA reviews the combined orthographic and phonetic matches and group the names into one of the following three categories:

- Highly similar pair: combined match percentage score ≥70%.
- Moderately similar pair: combined match percentage score ≥55% to ≤ 69%.
- Low similarity: combined match percentage score ≤54%.

Using the criteria outlined in the check list (Table 3-5) that corresponds to each of the three categories (highly similar pair, moderately similar pair, and low similarity), DMEPA evaluates the name pairs to determine the acceptability or non-acceptability of a proposed proprietary name. The intent of these checklists is to increase the transparency and predictability of the safety determination of whether a proposed name is vulnerable to confusion from a look-alike or sound-alike perspective. Each bullet below corresponds to the name similarity category cross-references the respective table that addresses criteria that DMEPA uses to determine whether a name presents a safety concern from a look-alike or sound-alike perspective.

- For highly similar names, differences in product characteristics often cannot mitigate the risk of a medication error, including product differences such as strength and dose. Thus, proposed proprietary names that have a combined score of ≥ 70 percent are at risk for a look-alike sound-alike confusion which is an area of concern (See Table 3).
- Moderately similar names are further evaluated to identify the presence of attributes that are known to cause name confusion.
    - Name attributes: We note that the beginning of the drug name plays a significant role in contributing to confusion. Additionally, drug name pairs that start with the same first letter and contain a shared letter string of at least 3 letters in both names are major contributing factor in the confusion of drug names[f]. We evaluate all moderately similar names retrieved from POCA to identify the above attributes. These names are further evaluated to identify overlapping or similar strengths or doses.
    - Product attributes: Moderately similar names of products that have overlapping or similar strengths or doses represent an area for concern for FDA. The dose and strength information is often located in close proximity to the drug name itself on prescriptions and medication orders, and the information can be an important factor that either increases or decreases the potential for confusion between similarly named drug pairs. The ability of other product characteristics to mitigate confusion (e.g., route, frequency, dosage form) may be limited when the strength or dose overlaps. DMEPA reviews such names further, to determine whether sufficient differences exist to prevent confusion. (See Table 4).

- Names with low similarity that have no overlap or similarity in strength and dose are generally acceptable (See Table 5) unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

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[f] Shah, M, Merchant, L, Characteristics That May Help in the Identification of Potentially Confusing Proprietary Drug Names. Therapeutic Innovation & Regulatory Science, September 2016

c. FDA Prescription Simulation Studies: DMEPA staff also conducts a prescription simulation studies using FDA health care professionals.

   Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

   In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

d. Comments from Other Review Disciplines: DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

   The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

   Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

   When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name.

Table 3. Highly Similar Name Pair Checklist (i.e., combined Orthographic and Phonetic score is ≥ 70%).

Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may render the names less likely to confusion, provided that the pair does not share a common strength or dose.			
Orthographic Checklist		Phonetic Checklist	
Y/N	Do the names begin with different first letters? *Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.*	**Y/N**	Do the names have different number of syllables?
Y/N	Are the lengths of the names dissimilar* when scripted? **FDA considers the length of names different if the names differ by two or more letters.*	**Y/N**	Do the names have different syllabic stresses?
Y/N	Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names?	**Y/N**	Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion?
Y/N	Is there different number or placement of cross-stroke or dotted letters present in the names?	**Y/N**	Across a range of dialects, are the names consistently pronounced differently?
Y/N	Do the infixes of the name appear dissimilar when scripted?		
Y/N	Do the suffixes of the names appear dissimilar when scripted?		

Table 4: Moderately Similar Name Pair Checklist (i.e., combined score is ≥55% to ≤69%).

Step 1	Review the DOSAGE AND ADMINISTRATION and HOW SUPPLIED/STORAGE AND HANDLING sections of the prescribing information (or for OTC drugs refer to the Drug Facts label) to determine if strengths and doses of the name pair overlap or are very similar. Different strengths and doses for products whose names are moderately similar may decrease the risk of confusion between the moderately similar name pairs. Name pairs that have overlapping or similar strengths or doses have a higher potential for confusion and should be evaluated further (see Step 2). Because the strength or dose could be used to express an order or prescription for a particular drug product, overlap in one or both of these components would be reason for further evaluation. For single strength products, also consider circumstances where the strength may not be expressed. For any i.e. drug products comprised of more than one active ingredient, consider whether the strength or dose may be expressed using only one of the components. To determine whether the strengths or doses are similar to your proposed product, consider the following list of factors that may increase confusion: • Alternative expressions of dose: 5 mL may be listed in the prescribing information, but the dose may be expressed in metric weight (e.g., 500 mg) or in non-metric units (e.g., 1 tsp, 1 tablet/capsule). Similarly, a strength or dose of 1000 mg may be expressed, in practice, as 1 g, or vice versa. • Trailing or deleting zeros: 10 mg is similar in appearance to 100 mg which may potentiate confusion between a name pair with moderate similarity. • Similar sounding doses: 15 mg is similar in sound to 50 mg
Step 2	Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may reduce the likelihood of confusion for moderately similar names **with** overlapping or similar strengths or doses.

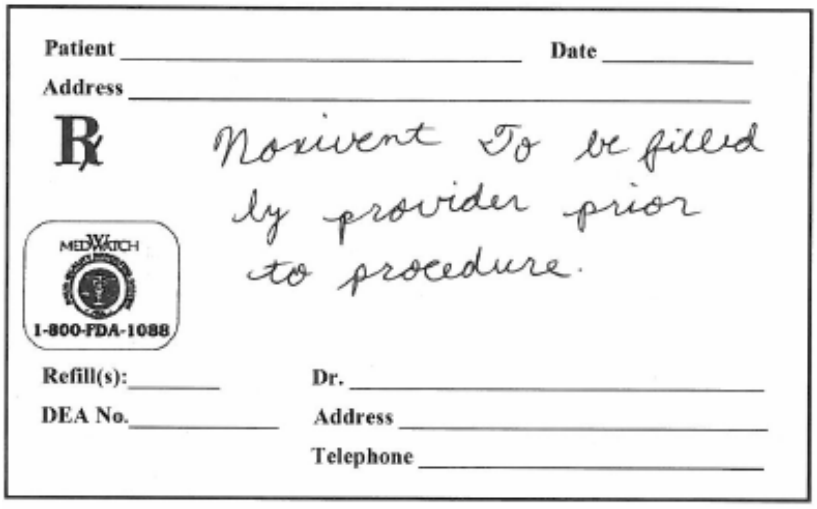
	Orthographic Checklist (Y/N to each question) • Do the names begin with different first letters? Note that even when names begin with different first letters, certain letters may be confused with each other when scripted. • Are the lengths of the names dissimilar* when scripted? *FDA considers the length of names different if the names differ by two or more letters. • Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names? • Is there different number or placement of cross-stroke or dotted letters present in the names? • Do the infixes of the name appear dissimilar when scripted? • Do the suffixes of the names appear dissimilar when scripted?	Phonetic Checklist (Y/N to each question) • Do the names have different number of syllables? • Do the names have different syllabic stresses? • Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion? • Across a range of dialects, are the names consistently pronounced differently?

Table 5: Low Similarity Name Pair Checklist (i.e., combined score is ≤54%).

Names with low similarity are generally acceptable unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

Appendix B: Prescription Simulation Samples and Results

Figure 1. Noxivent Study (Conducted on 1/22/2018)

Handwritten Medication Order/Prescription	Verbal Prescription
Medication Order: Noxivent 20 ppm continously Outpatient Prescription:  Patient _____ Date _____ Address _____ ℞ Noxivent To be filled by provider prior to procedure. MEDWATCH 1-800-FDA-1088 Refill(s):_____ Dr. _____ DEA No._____ Address _____ Telephone _____	Noxivent. To be filled by provider prior to procedure.

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

As of 1/22/2018

293 People Received Study
103 People Responded

Study Name: Noxivent

Total	**38**	**27**	**38**	
INTERPRETATION	**OUTPATIENT**	**VOICE**	**INPATIENT**	**TOTAL**
MOXIVENT	1	0	1	2
NAXEVENT	0	1	0	1
NORIVENT	2	0	1	3
NORIVENT FO	1	0	0	1
NOSEVET	0	1	0	1
NOSIVENT	0	0	1	1
NOXAVENT	0	5	0	5
NOXEVENT	0	1	0	1
NOXIVANT	0	1	0	1
NOXIVENT	34	18	35	87

Appendix C: Highly Similar Names (e.g., combined POCA score is ≥70%)

No.	**Proposed name:** Noxivent **Established name:** nitric oxide **Dosage form:** gas for inhalation **Strength(s):** 100 ppm and 800 ppm **Usual Dose:** 20 ppm continuously by inhalation via Nitric Oxide Delivery System, maintained for up to 14 days or until the underlying oxygen desaturation has resolved	POCA Score (%)	**Orthographic and/or phonetic differences in the names sufficient to prevent confusion** **Other prevention of failure mode expected to minimize the risk of confusion between these two names.**
1.	Noxivent	100	The names is the subject of this review.
2.	Dexilant	70	The prefixes and suffixes of this name pair have sufficient orthographic differences. Specifically, the first letters (‘N’ vs. ‘D’) are orthographically different, and Dexilant contains an upstroke letter “l” in the fifth position not present in Noxivent. The first syllables ('näk vs. Dek) and the last syllables (vent vs. lant) of this name pair sound different. The name pair has the following different product characteristics that further minimize the potential for confusion: Dosage form: gas for inhalation vs. capsule Route of administration: inhalation vs. oral Strengths: 100 ppm, 800 ppm vs. 30 mg, 60 mg Dosing frequency: continuously vs once daily

Appendix D: Moderately Similar Names (e.g., combined POCA score is ≥55% to ≤69%) with no overlap or numerical similarity in Strength and/or Dose

No.	Name	POCA Score (%)
3.	Cefoxitin	56
4.	Nexletol***	56
5.	Nexobrid***	56
6.	Vanoxide-Hc	57

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Appendix E: Moderately Similar Names (e.g., combined POCA score is ≥55% to ≤69%) with overlap or numerical similarity in Strength and/or Dose

No.	**Proposed name:** Noxivent **Established name:** nitric oxide **Dosage form:** gas for inhalation **Strength(s):** 100 ppm and 800 ppm **Usual Dose:** 20 ppm continuously by inhalation via Nitric Oxide Delivery System, maintained for up to 14 days or until the underlying oxygen desaturation has resolved	POCA Score (%)	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
7.	Jantoven	60	This name pair has sufficient orthographic and phonetic differences.
			(b) (4)
9.	Nintedanib	56	This name pair has sufficient orthographic and phonetic differences.
10.	Nitrogen	56	This name pair has sufficient orthographic and phonetic differences.
11.	Nolvadex	55	This name pair has sufficient orthographic and phonetic differences.
12.	oxidronate	58	This name pair has sufficient orthographic and phonetic differences.
13.	Trevyent	55	This name pair has sufficient orthographic and phonetic differences.
14.	Vonvendi	55	This name pair has sufficient orthographic and phonetic differences.

Appendix F: Low Similarity Names (e.g., combined POCA score is ≤54%)

No.	Name	POCA Score (%)
	N/A	

Appendix G: Names not likely to be confused or not used in usual practice settings for the reasons described**.**

No.	Name	POCA Score (%)	Failure preventions
15.	Evoxin	58	International product marketed in the United Kingdom.
16.	Inoven	56	International product marketed in the United Kingdom.
17.	Myoxin	55	Brand discontinued with no generic equivalent available.
18.	Noxythiolin	55	International product marketed in the United Kingdom and Ireland.
19.	Tenoxicam	56	International product market in various countries outside of the United States.
20.	Zoxin	56	International product marketed in the United Kingdom and Poland.

Appendix H: Names not likely to be confused due to absence of attributes that are known to cause name confusion[g].

No.	Name	POCA Score (%)
21.	Antizol-Vet	55
22.	Axitinib	56
23.	Dextenza***	56
24.	Edoxudine	56
25.	Eloxatin	58
26.	Exefen	55
27.	Idoxene	60
28.	Ketotifen	56
29.	Lexifen	60
30.	Mectizan	55
31.	Mexiletine	56
32.	Moctanin	56
33.	Motifene	56
34.	Moxonidine	56
35.	Onexton	57

[g] Shah, M, Merchant, L, Chan, I, and Taylor, K. Characteristics That May Help in the Identification of Potentially Confusing Proprietary Drug Names. Therapeutic Innovation & Regulatory Science, September 2016

No.	Name	POCA Score (%)
36.	Ostifen	56
37.	(b) (4)	
38.	Oxeladin	56
39.	Oxerutins	58
40.	Oxervate***	58
41.	Oxycontin	56
42.	Oxyfrin	56
43.	Oxytocin	55
44.	Perox-A-Mint	60
45.	Ruxience***	56
46.	Vectibix	57
47.	Xenon Xe 133-V.S.S.	56

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/s/

COLLEEN L LITTLE
01/26/2018

CHI-MING TU
01/26/2018

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	July 7, 2016
Application Type and Number:	ANDA 207141
Product Name and Strength:	Noxivent (nitric oxide) gas for inhalation, 100 ppm and 800 ppm
Product Type:	Single-ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Praxair Distribution, Inc.
Panorama #:	2016-8071454
DMEPA Primary Reviewer:	Ashleigh Lowery, PharmD, BCCCP
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

Contents

1 INTRODUCTION

This review evaluates the proposed proprietary name, Noxivent, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively. The Applicant submitted an external name study, conducted by [redacted] (b) (4) for this product.

1.1 REGULATORY HISTORY

The Applicant previously submitted the proposed proprietary name, Noxivent, on July 9, 2014. The Division of Medication Error Prevention and Analysis (DMEPA) found the name conditionally acceptable in OSE Review #2014-25811.[1] As requested by FDA, because of the amount of time elapsed since the review, the Applicant re-submitted a complete request for proprietary name review on May 18, 2016. The external study conducted by [redacted] (b) (4) in the May 18, 2016 submission is the same study previously submitted and the [redacted] (b) (4) Proprietary Name Safety Summary for Noxivent is dated May 27, 2014.

1.2 PRODUCT INFORMATION

The following product information is provided in the May 18, 2016 proprietary name submission and the July 5, 2016 submission.

- Intended Pronunciation: näk-sə-vent
- Active Ingredient: nitric oxide
- Indication of Use: Vasodilator agent for use in conjunction with ventilatory support and other appropriate agents in 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.
- Route of Administration: Inhalation via a Nitric Oxide Delivery System
- Dosage Form: Compressed Gas
- Strength: 100 ppm and 800 ppm concentrations
- Dose and Frequency: 20 ppm continuously maintained for up 14 days or until the underlying oxygen desaturation has resolved.

[1] Stewart, J. Proprietary Name Review for Noxivent ANDA 207141. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 Dec 10. RCM No.: 2014-25811.

- How Supplied:

Size AD	(b) (4) [redacted]
Size AD	
Size AQ	
Size AQ	

- Storage: Store at 25°C (77°F) with excursions permitted between 15–30°C (59–86°F) [see USP Controlled Room Temperature].
- Container and Closure Systems: Aluminum cylinders

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that the proposed name would not misbrand the proposed product. DMEPA and the Division of Cardiovascular and Renal Products (DCRP) concurred with the findings of OPDP's assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proprietary name[2].

2.2.2 Components of the Proposed Proprietary Name

The Applicant indicated in their submission that the proposed name, Noxivent, connotes nitric oxide and breathing (vent, respiratory associated). This proprietary name is comprised of a single word that does not contain any components (i.e. a modifier, route of administration, dosage form, etc.) that are misleading or can contribute to medication error.

2.2.3 FDA Name Simulation Studies

One hundred four (104) practitioners participated in DMEPA's prescription studies. The responses did not overlap with any currently marketed products nor did the responses

[2]USAN stem search conducted on May 27, 2016.

sound or look similar to any currently marketed products or any products in the pipeline. Eighty-three (83) participants interpreted the name correctly. Appendix B contains the results from the verbal and written prescription studies.

2.2.4 Comments from Other Review Disciplines at Initial Review

In response to the OSE June 21, 2016 e-mail, the Division of Cardiovascular and Renal Products (DCRP) did not forward any comments or concerns relating to the proposed proprietary name at the initial phase of the review.

2.2.5 Phonetic and Orthographic Computer Analysis (POCA) Search Results

Table 1 lists the number of names with the combined orthographic and phonetic score of ≥50% retrieved from our POCA search[3] organized as highly similar, moderately similar or low similarity for further evaluation. We identified 186 names in our POCA search. We had identified and evaluated 176 names in our previous proprietary name review.[1] We re-evaluated the previously identified names of concern considering any lessons learned from recent post-marketing experience, which may have altered our previous conclusion regarding acceptability of the name. We note that none of the product characteristics have changed and we agree with the findings from our previous review for the names evaluated previously. Table 1 consists of names not previously evaluated.

Table 1. POCA Search Results	**Number of Names**
Highly similar name pair: combined match percentage score ≥70%	1
Moderately similar name pair: combined match percentage score ≥50% to ≤ 69%	8
Low similarity name pair: combined match percentage score ≤49%	1

2.2.6 Safety Analysis of Names with Potential Orthographic, Spelling, and Phonetic Similarities

Our analysis of the ten names contained in Table 1 determined ten names will not pose a risk for confusion as described in Appendices C through H.

[3] POCA search conducted on May 27, 2016.

3 CONCLUSIONS

The proposed proprietary name is acceptable.

If you have any questions or need clarifications, please contact Darrell Lyons, OSE project manager, at 301-796-4092.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Noxivent, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your May 18, 2016 submission are altered prior to approval of the marketing application, the name must be resubmitted for review.

4 REFERENCES

1. ***USAN Stems (http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page)***

   USAN Stems List contains all the recognized USAN stems.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

Drugs@FDA

Drugs@FDA is an FDA Web site that contains most of the drug products approved in the United States since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA-approved *brand name* and *generic drugs*; *therapeutic biological products*, *prescription* and *over-the-counter* human drugs; and *discontinued drugs* (see Drugs @ FDA Glossary of Terms, available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#ther_biological).

RxNorm

RxNorm contains the names of prescription and many OTC drugs available in the United States. RxNorm includes generic and branded:

- Clinical drugs – pharmaceutical products given to (or taken by) a patient with therapeutic or diagnostic intent
- Drug packs – packs that contain multiple drugs, or drugs designed to be administered in a specified sequence

Radiopharmaceuticals, contrast media, food, dietary supplements, and medical devices, such as bandages and crutches, are all out of scope for RxNorm (http://www.nlm.nih.gov/research/umls/rxnorm/overview.html#).

Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

3. ***Electronic Drug Registration and Listing System (eDRLS) database***

The electronic Drug Registration and Listing System (eDRLS) was established to supports the FDA's Center for Drug Evaluation and Research (CDER) goal to establish a common Structured Product Labeling (SPL) repository for all facilities that manufacture regulated drugs. The system is a reliable, up-to-date inventory of FDA-regulated, drugs and establishments that produce drugs and their associated information.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. **Misbranding Assessment**: For prescription drug products, OPDP assesses the name for misbranding concerns. . For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNDP. OPDP or DNDP evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. **Safety Assessment**: The safety assessment is conducted by DMEPA, and includes the following:

a. Preliminary Assessment: We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 2*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [4]

[4] National Coordinating Council for Medication Error Reporting and Prevention. http://www nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

***Table 2- Prescreening Checklist for Proposed Proprietary Name**

	Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.
Y/N	**Is the proposed name obviously similar in spelling and pronunciation to other names?**
	Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products.
Y/N	**Are there medical and/or coined abbreviations in the proprietary name?**
	Proprietary names should not incorporate medical abbreviations (e.g., QD, BID, or others commonly used for prescription communication) or coined abbreviations that have no established meaning.
Y/N	**Are there inert or inactive ingredients referenced in the proprietary name?**
	Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)).
Y/N	**Does the proprietary name include combinations of active ingredients?**
	Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).
Y/N	**Is there a United States Adopted Name (USAN) stem in the proprietary name?**
	Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem.
Y/N	**Is this proprietary name used for another product that does not share at least one common active ingredient?**
	Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name.
Y/N	**Is this a proprietary name of a discontinued product?**
	Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients.

b. Phonetic and Orthographic Computer Analysis (POCA): Following the preliminary screening of the proposed proprietary name, DMEPA staff evaluates the proposed name against potentially similar names. In order to identify names with potential similarity to the proposed proprietary name, DMEPA enters the proposed proprietary name in POCA and queries the name against the following drug reference databases, Drugs@fda, CernerRxNorm, and names in the review pipeline using a 50% threshold in POCA. DMEPA reviews the combined orthographic and phonetic matches and group the names into one of the following three categories:

- Highly similar pair: combined match percentage score ≥70%.
- Moderately similar pair: combined match percentage score ≥50% to ≤ 69%.
- Low similarity: combined match percentage score ≤49%.

Using the criteria outlined in the check list (Table 3-5) that corresponds to each of the three categories (highly similar pair, moderately similar pair, and low similarity), DMEPA evaluates the name pairs to determine the acceptability or non-acceptability of a proposed proprietary name. The intent of these checklists is to increase the transparency and predictability of the safety determination of whether a proposed name is vulnerable to confusion from a look-alike or sound-alike perspective. Each bullet below corresponds to the name similarity category cross-references the respective table that addresses criteria that DMEPA uses to determine whether a name presents a safety concern from a look-alike or sound-alike perspective.

- For highly similar names, differences in product characteristics often cannot mitigate the risk of a medication error, including product differences such as strength and dose. Thus, proposed proprietary names that have a combined score of ≥ 70 percent are at risk for a look-alike sound-alike confusion which is an area of concern (See Table 3).
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- Names with low similarity that have no overlap or similarity in strength and dose are generally acceptable (See Table 5) unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

c. FDA Prescription Simulation Studies: DMEPA staff also conducts a prescription simulation studies using FDA health care professionals.

   Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

   In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

d. Comments from Other Review Disciplines: DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

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   When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name.

Table 3. Highly Similar Name Pair Checklist (i.e., combined Orthographic and Phonetic score is ≥ 70%).

Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may render the names less likely to confusion, provided that the pair does not share a common strength or dose.			
Orthographic Checklist		Phonetic Checklist	
Y/N	Do the names begin with different first letters? *Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.*	**Y/N**	Do the names have different number of syllables?
Y/N	Are the lengths of the names dissimilar* when scripted? **FDA considers the length of names different if the names differ by two or more letters.*	**Y/N**	Do the names have different syllabic stresses?
Y/N	Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names?	**Y/N**	Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion?
Y/N	Is there different number or placement of cross-stroke or dotted letters present in the names?	**Y/N**	Across a range of dialects, are the names consistently pronounced differently?
Y/N	Do the infixes of the name appear dissimilar when scripted?		
Y/N	Do the suffixes of the names appear dissimilar when scripted?		

Table 4: Moderately Similar Name Pair Checklist (i.e., combined score is ≥50% to ≤69%).

Step 1	Review the DOSAGE AND ADMINISTRATION and HOW SUPPLIED/STORAGE AND HANDLING sections of the prescribing information (or for OTC drugs refer to the Drug Facts label) to determine if strengths and doses of the name pair overlap or are very similar. Different strengths and doses for products whose names are moderately similar may decrease the risk of confusion between the moderately similar name pairs. Name pairs that have overlapping or similar strengths or doses have a higher potential for confusion and should be evaluated further (see Step 2). Because the strength or dose could be used to express an order or prescription for a particular drug product, overlap in one or both of these components would be reason for further evaluation. For single strength products, also consider circumstances where the strength may not be expressed. For any i.e. drug products comprised of more than one active ingredient, consider whether the strength or dose may be expressed using only one of the components. To determine whether the strengths or doses are similar to your proposed product, consider the following list of factors that may increase confusion: • Alternative expressions of dose: 5 mL may be listed in the prescribing information, but the dose may be expressed in metric weight (e.g., 500 mg) or in non-metric units (e.g., 1 tsp, 1 tablet/capsule). Similarly, a strength or dose of 1000 mg may be expressed, in practice, as 1 g, or vice versa. • Trailing or deleting zeros: 10 mg is similar in appearance to 100 mg which may potentiate confusion between a name pair with moderate similarity. • Similar sounding doses: 15 mg is similar in sound to 50 mg
Step 2	Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may reduce the likelihood of confusion for moderately similar names **with** overlapping or similar strengths or doses.

	Orthographic Checklist (Y/N to each question) • Do the names begin with different first letters? Note that even when names begin with different first letters, certain letters may be confused with each other when scripted. • Are the lengths of the names dissimilar* when scripted? *FDA considers the length of names different if the names differ by two or more letters. • Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names? • Is there different number or placement of cross-stroke or dotted letters present in the names? • Do the infixes of the name appear dissimilar when scripted? • Do the suffixes of the names appear dissimilar when scripted?	Phonetic Checklist (Y/N to each question) • Do the names have different number of syllables? • Do the names have different syllabic stresses? • Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion? • Across a range of dialects, are the names consistently pronounced differently?

Table 5: Low Similarity Name Pair Checklist (i.e., combined score is ≤49%).

In most circumstances, these names are viewed as sufficiently different to minimize confusion. Exceptions to this would occur in circumstances where, for example, there are data that suggest a name with low similarity is nonetheless misinterpreted as a marketed product name in a prescription simulation study. In such instances, FDA would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

Appendix B: Prescription Simulation Samples and Results

Figure 1. Noxivent Study (Conducted on 6/7/2016)

Handwritten Medication Order/Prescription	Verbal Prescription
Medication Order: Noxivent 20 ppm continuously Outpatient Prescription: Patient _____ Date _____ Address _____ ℞ Noxivent MEDWATCH 1-800-FDA-1088 To be filled by provider prior to procedure #1 Refill(s):_____ Dr. OSE DEA No._____ Address _____ Telephone _____	Noxivent. To be filled by provider prior to procedure.

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

Study Name: Noxivent

As of Date 6/13/2016

311 People Received Study
104 People Responded

Study Name: Noxivent

Total	33	37	34	
INTERPRETATION	**OUTPATIENT**	**VOICE**	**INPATIENT**	**TOTAL**
DOXIVANT	0	1	0	1
DOXIVENT	0	1	0	1
MOXIVENT	1	0	0	1
NOXAFENT	0	1	0	1
NOXAVENCE	0	1	0	1
NOXAVENT	0	9	0	9
NOXEVENT	0	2	0	2
NOXIFENT	0	1	0	1
NOXIVEN	0	0	1	1
NOXIVENT	29	21	33	83
NOXIVERET	1	0	0	1
NOXIVERIT	2	0	0	2

Appendix C: Highly Similar Names (e.g., combined POCA score is ≥70%)

No.	**Proposed name:** Noxivent **Established name:** nitric oxide for inhalation **Dosage form:** Gas **Strength(s):** 100 ppm, 800 ppm **Usual Dose:** 20 ppm continuously by inhalation via Nitric Oxide Delivery System	**POCA Score (%)**	**Orthographic and/or phonetic differences in the names sufficient to prevent confusion** **Other prevention of failure mode expected to minimize the risk of confusion between these two names.**
1.	NOXIVENT	100	This name is the subject of this review.

Appendix D: Moderately Similar Names (e.g., combined POCA score is ≥50% to ≤69%) with no overlap or numerical similarity in Strength and/or Dose

No.	Name	POCA Score (%)
1.	N/A	

Appendix E: Moderately Similar Names (e.g., combined POCA score is ≥50% to ≤69%) with overlap or numerical similarity in Strength and/or Dose

No.	**Proposed name:** Noxivent **Established name:** nitric oxide for inhalation **Dosage form:** Gas **Strength(s):** 100 ppm, 800 ppm **Usual Dose:** 20 ppm continuously by inhalation via Nitric Oxide Delivery System	**POCA Score (%)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
1.	DupixENT***	56	The prefixes and infixes of this name pair have sufficient orthographic differences. The second syllables sound different.
2.	Netupitant	60	The infixes of this name pair have sufficient orthographic differences. The second and third syllables sound different, and Netupitant contains an extra syllable.
3.	Nitrogen, Nf	50	The suffixes of this name pair have sufficient orthographic differences. When considering the modifier Nf, the infixes of this name pair have sufficient orthographic differences. The first and second syllables sound different. When considering the modifier Nf, Nitrogen Nf contains two extra syllables.
4.	Nitromist	51	The infixes of this name pair have sufficient orthographic differences. The first, second, and third syllables sound different.
5.	NIVEstym***	50	The suffixes of this name pair have sufficient orthographic differences. The first, second, and third syllables sound different.
6.	Novoeight	50	The suffixes of this name pair have sufficient orthographic differences. The second and third syllables sound different.

Appendix F: Low Similarity Names (e.g., combined POCA score is ≤49%)

No.	Name	POCA Score (%)
1.	N/A	

Appendix G: Names not likely to be confused or not used in usual practice settings for the reasons described**.**

No.	Name	POCA Score (%)	Failure preventions
1.	Mezavant	57	International product marketed in Australia, Belgium, Canada, Czech Republic, Denmark, Germany, Greece, Ireland, Norway, Spain, Sweden, and the United Kingdom.
2.	NIVEstim***	50	Proposed proprietary name withdrawn by the Applicant. New proprietary name, Nivestym***, is under review. (See failure preventions for Nivestym*** in Appendix E)

Appendix H: Names not likely to be confused due to notable spelling, orthographic and phonetic differences.

No.	Name	POCA Score (%)
1.	Volixibat***	50

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

/s/

ASHLEIGH V LOWERY
07/07/2016

CHI-MING TU
07/07/2016

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	December 10, 2014
Application Type and Number:	ANDA 207141
Product Name and Strength:	Noxivent (nitric oxide for inhalation) 100 ppm, and 800 ppm
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Praxair Distribution, Inc.
Submission Date:	July 9, 2014
Panorama #:	2014-25811
DMEPA Primary Reviewer:	Janine Stewart, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

Contents

1 INTRODUCTION

This review evaluates the proposed proprietary name, Noxivent, from a safety and misbranding perspective. The Reference Listed Drug for this product is INOmax NDA 020845. The Applicant submitted an external name study conducted by the (b) (4) The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively.

1.1 PRODUCT INFORMATION

The following product information is provided in the July 9, 2014 proprietary name submission.

- Intended Pronunciation: **näk-sə-vent**
- Active Ingredient: **nitric oxide**
- Indication of Use: Vasodilator agent for use in conjunction with ventilatory support and other appropriate agents in 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.
- Route of Administration: Inhalation via a Nitric Oxide Delivery System
- Dosage Form: Compressed Gas
- Strength: 100 ppm and 800 ppm concentrations
- Dose and Frequency: 20 ppm continuously maintained for up 14 days or until the underlying oxygen desaturation has resolved.
- How Supplied:

Size AD	(b) (4)
Size AD	
Size AQ	
Size AQ	

- Storage: Store at 25°C (77°F) with excursions permitted between 15–30°C (59–86°F) [see USP Controlled Room Temperature].
- Container and Closure Systems: Aluminum cylinders

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that the proposed name does not misbrand the proposed product. DMEPA and the Division of Cardiovascular and Renal Products (DCRP) concurred with the findings of OPDP's assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proprietary name[1].

2.2.2 Components of the Proposed Proprietary Name

The Applicant indicated in their submission that the proposed name, Noxivent, connotes nitric oxide and breathing (vent, respiratory associated). This proprietary name is comprised of a single word that does not contain any components (i.e. a modifier, route of administration, dosage form, etc.) that are misleading or can contribute to medication error.

2.2.3 FDA Name Simulation Studies

One hundred one practitioners participated in DMEPA's prescription studies. The responses did not overlap with any currently marketed products nor did the responses sound or look similar to any currently marketed products or any products in the pipeline. Common verbal misinterpretations identified in the prescription studies included omission of the second 'n' and mistaking the 'vent' for 'vit', 'vet', or 'mit'. In addition, some mistook the 'o' for an 'a' and the 'i' for an 'a'. Common written misinterpretations included mistaking the letter string 'iv' for 'w', the 'x' for 'v' and the 'v' for 'b'. Appendix B contains the results from the verbal and written prescription studies.

2.2.3 Comments from Other Review Disciplines at Initial Review

In response to the OSE, July 25, 2014 e-mail, the Office of Generic Drugs (OGD) did not forward any comments or concerns relating to the proposed proprietary name at the initial phase of the review.

2.2.4 Phonetic and Orthographic Computer Analysis (POCA) Search Results

Table 1 lists the number of names with the combined orthographic and phonetic score of ≥50% retrieved from our POCA search[2] organized as highly similar, moderately similar,

[1]USAN stem search conducted on October 8, 2014.

or low similarity for further evaluation. Table 1 also includes names identified from the FDA Prescription Simulation or by (b) (4) Inc.

Table 1. POCA Search Results	Number of Names
Highly similar name pair: combined match percentage score ≥70%	3
Moderately similar name pair: combined match percentage score ≥50% to ≤ 69%	189
Low similarity name pair: combined match percentage score ≤49%	13

2.2.5 Safety Analysis of Names with Potential Orthographic, Spelling, and Phonetic Similarities

Our analysis of the 205 names contained in Table 1 determined 205 names would not pose a risk for confusion as described in Appendices C through G.

3 CONCLUSIONS

The proposed proprietary name is acceptable.

If you have further questions or need clarifications, please contact Cherye Milburn, OSE project manager, at 301-796-2084.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Noxivent, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your July 9, 2014 submission are altered prior to approval of the marketing application, the name must be resubmitted for review.

[2] POCA search conducted on October 8, 2014.

4 REFERENCES

1. ***USAN Stems (http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page)***

   USAN Stems List contains all the recognized USAN stems.

2. ***Phonetic and Orthographic Computer Analysis (POCA)***

POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

Drugs@FDA

Drugs@FDA is an FDA Web site that contains most of the drug products approved in the United States since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA-approved *brand name* and *generic drugs*; *therapeutic biological products*, *prescription* and *over-the-counter* human drugs; and *discontinued drugs* (see Drugs @ FDA Glossary of Terms, available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#ther_biological).

RxNorm

RxNorm contains the names of prescription and many OTC drugs available in the United States. RxNorm includes generic and branded:

- Clinical drugs – pharmaceutical products given to (or taken by) a patient with therapeutic or diagnostic intent
- Drug packs – packs that contain multiple drugs, or drugs designed to be administered in a specified sequence

Radiopharmaceuticals, contrast media, food, dietary supplements, and medical devices, such as bandages and crutches, are all out of scope for RxNorm (http://www.nlm.nih.gov/research/umls/rxnorm/overview.html#).

Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. **Misbranding Assessment**: For prescription drug products, OPDP assesses the name for misbranding concerns. . For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNCE. OPDP or DNCE evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNCE provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. **Safety Assessment**: The safety assessment is conducted by DMEPA, and includes the following:

a. Preliminary Assessment: We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 2*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [3]

[3] National Coordinating Council for Medication Error Reporting and Prevention. http://www nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

***Table 2- Prescreening Checklist for Proposed Proprietary Name**

	Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.
Y/N	**Is the proposed name obviously similar in spelling and pronunciation to other names?**
	Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products.
Y/N	**Are there medical and/or coined abbreviations in the proprietary name?**
	Proprietary names should not incorporate medical abbreviations (e.g., QD, BID, or others commonly used for prescription communication) or coined abbreviations that have no established meaning.
Y/N	**Are there inert or inactive ingredients referenced in the proprietary name?**
	Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)).
Y/N	**Does the proprietary name include combinations of active ingredients?**
	Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).
Y/N	**Is there a United States Adopted Name (USAN) stem in the proprietary name?**
	Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem.
Y/N	**Is this proprietary name used for another product that does not share at least one common active ingredient?**
	Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name.
Y/N	**Is this a proprietary name of a discontinued product?**
	Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients.

b. Phonetic and Orthographic Computer Analysis (POCA): Following the preliminary screening of the proposed proprietary name, DMEPA staff evaluates the proposed name against potentially similar names. In order to identify names with potential similarity to the proposed proprietary name, DMEPA enters the proposed proprietary name in POCA and queries the name against the following drug reference databases, Drugs@fda, CernerRxNorm, and names in the review pipeline using a 50% threshold in POCA. DMEPA reviews the combined orthographic and phonetic matches and group the names into one of the following three categories:

- Highly similar pair: combined match percentage score ≥70%.
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Using the criteria outlined in the checklist (Table 3-5) that corresponds to each of the three categories (highly similar pair, moderately similar pair, and low similarity), DMEPA evaluates the name pairs to determine the acceptability or non-acceptability of a proposed proprietary name. The intent of these checklists is to increase the transparency and predictability of the safety determination of whether a proposed name is vulnerable to confusion from a look-alike or sound-alike perspective. Each bullet below corresponds to the name similarity category cross-references the respective table that addresses criteria that DMEPA uses to determine whether a name presents a safety concern from a look-alike or sound-alike perspective.

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   In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

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Y/N	Are the lengths of the names dissimilar* when scripted? **FDA considers the length of names different if the names differ by two or more letters.*	**Y/N**	Do the names have different syllabic stresses?
Y/N	Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names?	**Y/N**	Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion?
Y/N	Is there different number or placement of cross-stroke or dotted letters present in the names?	**Y/N**	Across a range of dialects, are the names consistently pronounced differently?
Y/N	Do the infixes of the name appear dissimilar when scripted?		
Y/N	Do the suffixes of the names appear dissimilar when scripted?		

Table 4: Moderately Similar Name Pair Checklist (i.e., combined score is ≥50% to ≤69%).

Step 1	Review the DOSAGE AND ADMINISTRATION and HOW SUPPLIED/STORAGE AND HANDLING sections of the prescribing information (or for OTC drugs refer to the Drug Facts label) to determine if strengths and doses of the name pair overlap or are very similar. Different strengths and doses for products whose names are moderately similar may decrease the risk of confusion between the moderately similar name pairs. Name pairs that have overlapping or similar strengths or doses have a higher potential for confusion and should be evaluated further (see Step 2). Because the strength or dose could be used to express an order or prescription for a particular drug product, overlap in one or both of these components would be reason for further evaluation. For single strength products, also consider circumstances where the strength may not be expressed. For any i.e. drug products comprised of more than one active ingredient, consider whether the strength or dose may be expressed using only one of the components. To determine whether the strengths or doses are similar to your proposed product, consider the following list of factors that may increase confusion: o Alternative expressions of dose: 5 mL may be listed in the prescribing information, but the dose may be expressed in metric weight (e.g., 500 mg) or in non-metric units (e.g., 1 tsp, 1 tablet/capsule). Similarly, a strength or dose of 1000 mg may be expressed, in practice, as 1 g, or vice versa. o Trailing or deleting zeros: 10 mg is similar in appearance to 100 mg which may potentiate confusion between a name pair with moderate similarity. o Similar sounding doses: 15 mg is similar in sound to 50 mg
Step 2	Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may reduce the likelihood of confusion for moderately similar names **with** overlapping or similar strengths or doses.

	Orthographic Checklist (Y/N to each question) • Do the names begin with different first letters? Note that even when names begin with different first letters, certain letters may be confused with each other when scripted. • Are the lengths of the names dissimilar* when scripted? *FDA considers the length of names different if the names differ by two or more letters. • Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names? • Is there different number or placement of cross-stroke or dotted letters present in the names? • Do the infixes of the name appear dissimilar when scripted? • Do the suffixes of the names appear dissimilar when scripted?	Phonetic Checklist (Y/N to each question) • Do the names have different number of syllables? • Do the names have different syllabic stresses? • Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion? • Across a range of dialects, are the names consistently pronounced differently?

Table 5: Low Similarity Name Pair Checklist (i.e., combined score is ≤49%).

In most circumstances, these names are viewed as sufficiently different to minimize confusion. Exceptions to this would occur in circumstances where, for example, there are data that suggest a name with low similarity is nonetheless misinterpreted as a marketed product name in a prescription simulation study. In such instances, FDA would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

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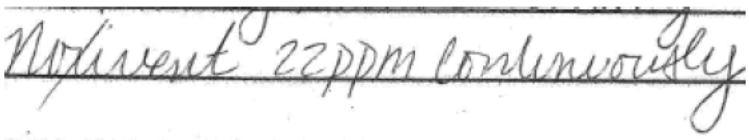
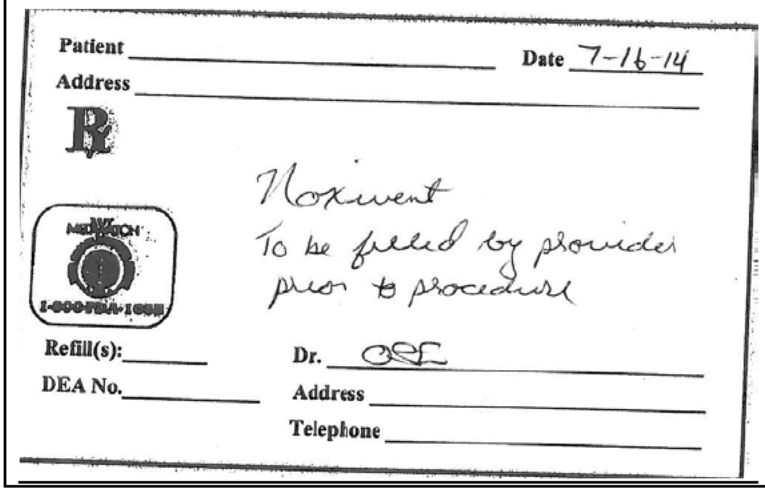
Appendix B: Prescription Simulation Samples and Results

Figure 1. Noxivent Study (Conducted on July 16, 2014)

Handwritten Requisition Medication Order	Verbal Prescription
Medication Order:  	Noxivent To be filled by the provider prior to the procedure.
Outpatient Prescription:  	

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

264 People Received Study

101 People Responded

Study Name: Noxivent

As of Date 10/8/2014

Total	37	30	34	
INTERPRETATION	**OUTPATIENT**	**VOICE**	**INPATIENT**	**TOTAL**
NAXAVENT	0	1	0	1
NOVIVENT	1	0	0	1
NOXAVENT	0	17	0	17
NOXAVET	0	1	0	1
NOXAVINT	0	1	0	1
NOXAVIT	0	1	0	1
NOXEVENT	0	1	0	1
NOXIBENT	0	0	1	1
NOXIMET	0	1	0	1
NOXIVENT	35	7	32	74
NOXWENT	1	0	0	1
NUXIVENT	0	0	1	1

Appendix C: Highly Similar Names (e.g., combined POCA score is ≥70%)

No.	**Proposed name: Noxivent** **Strength(s): 100 ppm , 800 ppm** **Usual Dose: 20 ppm by ventilation, maintained continuously for up to 14 days**	**POCA Score (%)**	**Orthographic and/or phonetic differences in the names sufficient to prevent confusion**
1.	Noxivent	100	The proprietary name that is the subject of this review.
2.	Oxivent (Phon-82; Orth- 88)	85	Name identified in RxNorm database. This is an international oxitropium product that is marketed in several countries. The prefixes of this name pair have sufficient orthographic differences. The first syllable of this name pair sounds different.
3.	Dexivant *** (Phon-90)	78	Name identified in Names Entered by SE database. This name was never reviewed. This product was approved under the name Dexilant in OSE RCM# 2010-151 under NDA 022287.

Appendix D: Moderately Similar Names (e.g., combined POCA score is ≥50% to ≤69%) with no overlap or numerical similarity in Strength and/or Dose

No.	Proposed Name	POCA Score (%)
1.	AmOXIcot	56
2.	ANTIVERT	56
3.	BACIGUENT	54
4.	BeNOXInate	52
5.	BenzodENT	58
6.	CINOXACIN	52
7.	CRIXIVAN	55
8.	CyclIVErt	52
9.	Dexaphen SA	50

No.	Proposed Name	POCA Score (%)
10.	DEXILANT (Phon- 81; Orth- 58)	67
11.	DibENT	52
12.	doconexENT	54
13.	DOXIdan	60
14.	DuraVENT	58
15.	Dura-VENT	58
16.	(b) (4)	52
17.	ENOXacin	58
18.	GuaIVENT	56
19.	G-VENT	50
20.	K-VescENT	55
21.	(b) (4)	50
22.	Mastic Dent	55
23.	MAXIDEX	56
24.	Maxifed	54
25.	Maxifed CD	54
26.	Maxifed DM	56
27.	Maxifed-G	58
28.	MedIVErt	52
29.	Mentadent	58
30.	MOXIlin	61
31.	MyciguENT	55
32.	Nafcillin	50

No.	Proposed Name	POCA Score (%)
33.	NALOXONE	50
34.	Nasopen PE	52
35.	Nasopen-CH	53
36.	(b) (4)	50
37.	NEBUPENT	57
38.	Neocidin	52
39.	Neutracett	50
40.	NEUTREXIN	50
41.	Nexa Select	54
42.	Nexafed	57
43.	NEXCEDE	52
44.	Nexiclon	58
45.	Nicomide-T	56
46.	NICORETTE (MINT)	52
47.	Nicotinex	53
48.	NIPENT	59
49.	(b) (4)	51
50.	NITROMIST	51
51.	(b) (4)	55
52.	Noctiva ***	58
53.	(b) (4)	50
54.	Nohist EXT	54
55.	NORCET	50

No.	Proposed Name	POCA Score (%)
56.	Norethin 1/50 M	50
57.	NORETHIN 1/50M-21	50
58.	NORETHIN 1/50M-28	50
59.	NOROXIN	54
60.	NORPLANT	56
61.	Novacet	56
62.	Novagest	60
63.	NovoseVEN	64
64.	OXIlan	53
65.	OXILAN-300	53
66.	OXILAN-350	53
67.	OXISTAT	56
68.	Pepsodent	58
69.	PHENAVENT	56
70.	PhenaVENT D	50
71.	Poly-VENT	61
72.	PrevidENT	50
73.	PseudoVENT	54
74.	PsorENT	54
75.	RespIVENT-D	52
76.	ROXICET	64
77.	ROXICET 5/500	64
78.	SinuVENT	57

No.	Proposed Name	POCA Score (%)
79.	Tri VENT DM	50
80.	Tri VENT HC	50
81.	UnIVErt	50
82.	VaNOXIde	50

Appears this way in original

Appendix E: Moderately Similar Names (e.g., combined POCA score is ≥50% to ≤69%) with overlap or numerical similarity in Strength and/or Dose

No.	**Proposed name: Noxivent** **Strength(s): 100 ppm , 800 ppm** **Usual Dose: 20 ppm by ventilation, maintained continuously for up to 14 days**	**POCA Score (%)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
1.	ATROVENT	59	The prefix and infix of this name pair have sufficient orthographic differences. The first and second syllables of this name pair sound different.
2.	BECLOVENT	64	The prefix and infix of this name pair have sufficient orthographic differences. The first and second syllables of this name pair sound different.
3.	BetaVENT	59	The prefix and infix of this name pair have sufficient orthographic differences. The first and second syllables of this name pair sound different.
4.	BLOXIVERZ	56	The prefix and suffix of this name pair have sufficient orthographic differences. The first and third syllables of this name pair sound different.
5.	COMBIVENT	66	The prefix and infix of this name pair have sufficient orthographic differences. The first and second syllables of this name pair sound different.
6.	[redacted] (b) (4)		
7.	Doxepin	53	The prefix and suffix of this name pair have sufficient orthographic differences. The first and third syllables of this name pair sound different.

No.	Proposed name: Noxivent Strength(s): 100 ppm , 800 ppm Usual Dose: 20 ppm by ventilation, maintained continuously for up to 14 days	POCA Score (%)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
8.	FLOVENT	54	The prefix of this name pair have sufficient orthographic differences. The first syllable of this name pair sound different. The name Noxivent has an additional syllable, thus the names sound different.
9.	LANOXIN	52	The prefix, infix, and suffix of this name pair have sufficient orthographic differences. The first, second and third syllables of this name pair sound different.
10.	LOXITANE	50	The prefix and suffix of this name pair have sufficient orthographic differences. The first and third syllables of this name pair sound different.
11.	LOXITANE C	52	The prefix and suffix of this name pair have sufficient orthographic differences. Loxitane C and Noxivent have a different number of syllables. The first and last syllables of each name sound different.
12.	Maxiphen	60	The suffix of this name pair has sufficient orthographic differences. The last syllable of each name sounds different.
13.	Maxiphen ADT	58	The suffix of this name pair has sufficient orthographic differences. Maxiphen ADT and Noxivent have a different number of syllables. The last syllable of each name sounds different.
14.	Maxiphen CD	58	The suffix of this name pair has sufficient orthographic differences. Maxiphen CD and Noxivent have a different number of syllables. The last syllable of each name sounds different.

No.	Proposed name: Noxivent Strength(s): 100 ppm , 800 ppm Usual Dose: 20 ppm by ventilation, maintained continuously for up to 14 days	POCA Score (%)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
15.	Maxiphen DM	60	The suffix of this name pair has sufficient orthographic differences. Maxiphen DM and Noxivent have a different number of syllables. The last syllable of each name sounds different.
16.	Maxiphen-G DM	52	The suffix of this name pair has sufficient orthographic differences. Maxiphen ADT and Noxivent have a different number of syllables. The last syllable of each name sounds different.
17.	MaXIVate (Phon-72)	62	Deactivated per RedBook but generic equivalent Betamethasone Diproprionate 0.5% creams, ointments and lotions are available. Since generic Betamethasone are available in multiple dosage forms, a dosage form needs to be specified on prescription before dispensing. Thus, providing differentiating product characteristics.
18.	NasalFENT ***	61	The prefix and infix of this name pair have sufficient orthographic differences. The first and second syllables of this name pair sound different.
19.	NEXAVAR	54	The suffix of this name pair has sufficient orthographic differences. The third syllable of this name pair sounds different.
20.	Nexavir	54	The suffix of this name pair has sufficient orthographic differences. The third syllable of this name pair sounds different.

No.	Proposed name: Noxivent Strength(s): 100 ppm , 800 ppm Usual Dose: 20 ppm by ventilation, maintained continuously for up to 14 days	POCA Score (%)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
21.	NEXIUM	50	The suffix of this name pair has sufficient orthographic differences. The third syllable of this name pair sounds different.
22.	Nexium 24R ***	50	The suffix of this name pair has sufficient orthographic differences. Nexium 24R and Noxivent have a different number of syllables. The last syllable of each name sounds different.
23.	NEXIUM IV	56	The suffix of this name pair has sufficient orthographic differences. Nexium IV and Noxivent have a different number of syllables. The last syllable of each name sounds different.
24.	Nexphen PD	63	The suffix of this name pair has sufficient orthographic differences. The third syllable of this name pair sounds different.
25.	NEXTERONE	51	The infix and suffix of this name pair have sufficient orthographic differences. The second and third syllables of this name pair sound different.
26.	novolin ***	50	The infix and suffix of this name pair have sufficient orthographic differences. The first, second and third syllables of this name pair sound different.

No.	Proposed name: Noxivent Strength(s): 100 ppm , 800 ppm Usual Dose: 20 ppm by ventilation, maintained continuously for up to 14 days	POCA Score (%)	Prevention of Failure Mode In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names
27.	NOVOLIN 70/30	50	The prefix, infix and suffix of this name pair have sufficient orthographic differences. The first, second and third syllables of this name pair sound different. The names Novolin 70/30 and Noxivent have a different number of syllables. The extra modifier provides differentiating sounds from Noxivent.
28.	NOVOLIN L	50	The infix and suffix of this name pair have sufficient orthographic differences. The first, second and third syllables of this name pair sound different. The names Novolin L and Noxivent have a different number of syllables. The extra modifier provides differentiating sounds from Noxivent.
29.	NOXAFIL	53	The suffix of this name pair has sufficient orthographic differences. The third syllable of this name pair sounds different.
30.	RespIVENT	62	The prefix and infix of this name pair have sufficient orthographic differences The first and second syllables of this name pair sound different.
31.	ROXIPRIN	51	The prefix and suffix of this name pair has sufficient orthographic differences. The first and third syllable of this name pair sounds different.
32.	SEREVENT	53	The prefix and infix of this name pair have sufficient orthographic differences The first and second syllables of this name pair sound different.

No.	**Proposed name: Noxivent** **Strength(s): 100 ppm , 800 ppm** **Usual Dose: 20 ppm by ventilation, maintained continuously for up to 14 days**	**POCA Score (%)**	**Prevention of Failure Mode** **In the conditions outlined below, the following combination of factors, are expected to minimize the risk of confusion between these two names**
33.	TamOXIfen	58	The prefix and infix this name pair have sufficient orthographic differences. The first, second and third syllables of this name pair sound different. The names Tamoxifen and Noxivent have a different number of syllables.
34.	THEOVENT	54	The prefix and infix of this name pair have sufficient orthographic differences The first and second syllables of this name pair sound different.
35.	VOTRIENT	57	The prefix and infix this name pair have sufficient orthographic differences. The first, second and third syllables of this name pair sound different.

Appendix F: Low Similarity Names (e.g., combined POCA score is ≤49%)

No.	Name	POCA Score (%)
1.	Aventyl	< 20
2.	Cymbalta	< 20
3.	Desipramine	< 20
4.	Duloxetine	44
5.	Effexor	< 20
6.	Gabapentin	34
7.	Lyrica	< 20
8.	Naproxen	49
9.	Neurontin	< 20
10.	Niaspan	< 20
11.	Nortriptyline	35
12.	pregabalin	< 20
13.	Sinequan	< 20

Appendix G: Names not likely to be confused or not used in usual practice settings for the reasons described.

No.	Name	POCA Score (%)	Failure preventions
1.	AmOXIdin	60	Name identified in RxNorm database. This is an international amoxicillin product.
2.	AmOXI-tabs	54	Name identified in RxNorm database. This is a veterinary amoxicillin product.
3.	ANTIOXIDANT 119	60	Name identified in RxNorm database. Unable to find product characteristics in commonly used drug databases.
4.	ciNOXate	50	Name identified in RxNorm database. This is an ingredient in sunscreen, but not the name of the sunscreen.
5.	[redacted]		(b) (4)
6.	ElOXIject	55	Name identified in RxNorm database. This is a veterinary meloxicam product.
7.	ENOXImone	56	Name identified in RxNorm database. Unable to find product characteristics in commonly used drug databases.
8.	EpridENT	52	Name identified in RxNorm database. Unable to find product characteristics in commonly used drug databases.
9.	[redacted]		(b) (4)

No.	Name	POCA Score (%)	Failure preventions
10.	(b) (4)		
11.	MOXIdectin	56	Name identified in RxNorm database. This is a veterinary anthelmintic product.
12.	Neovet	52	Name identified in RxNorm database. This is a veterinary neomycin product.
13.	(b) (4)		
14.			
15.	NiOXIn	56	Name identified in RxNorm database. This is a line of hair care and styling products.
16.	Noctamid	50	Name identified in RxNorm database. This is an international lormetazepam product.
17.	nonivamide	50	Name identified in RxNorm database. This is a food additive and active ingredient in pepper spray.

No.	Name	POCA Score (%)	Failure preventions
18.	Noscapine	51	Name identified in RxNorm database. This is an international drug product.
19.	(b) (4)		
20.	NOXyflex-S	57	Name identified in RxNorm database. Unable to find product characteristics in commonly used drug databases.
21.	Nystamont	56	Name identified in RxNorm database. This is an international nystatin product.
22.	NystavescENT	58	Name identified in RxNorm database. Unable to find product characteristics in commonly used drug databases.
23.	PoNOXylan	50	Name identified in RxNorm database. This is a preservative ingredient and antiseptic agent in topical antibacterial products.
24.	(b) (4)		

Appendix H: Names not likely to be confused due to notable spelling, orthographic and phonetic differences.

No.	Name	POCA Score (%)
1.	Amoxymed	52
2.	BESIVANCE	50
3.	CLOXAPEN	50
4.	DEXACEN-4	52
5.	DexaJect	52
6.	(b) (4)	54
7.	DexPhen M	50
8.	Dixlanta	51
9.	Doptelet ***	50
10.	DOSTINEX	50
11.	(b) (4)	58
12.	Doxazosin	50
13.	Doxy Lemmon	51
14.	DOXY-LEMMON	51
15.	Doxytex	52
16.	Edoxaban ***	50
17.	Exefen DM	50
18.	Exefen-PD	50
19.	FOSVESET	54
20.	icatibant	51
21.	MagneBind	50
22.	MagneBind 250/300	50

No.	Name	POCA Score (%)
23.	MagneBind 400/200	50
24.	Magnebind-200	50
25.	Magnebind-300	50
26.	MAGNEVIST	54
27.	Maxidone	52
28.	Maximet SR	54
29.	Maximum D3	50
30.	(b) (4)	52
31.	MOXATAG	50
32.	moxaverine	52
33.	Mycocide NS	55
34.	Otrivin	50
35.	Oxoject	56
36.	OxyBlend	62
37.	OXYCET	56
38.	Oxyfast	52
39.	Oxygen	54
40.	PROSTASCINT	52
41.	Quillivant ***	50
42.	Roxanol-T	50
43.	Roxybond ***	60
44.	TIROSINT	50
45.	TREXIMET	54

No.	Name	POCA Score (%)
46.	Viravan-T	52
47.	(b) (4)	50
48.	ZONTIVITY	50

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

/s/

JANINE A STEWART
12/11/2014

CHI-MING TU
12/11/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA207141Orig1s000

CHEMISTRY REVIEW(s)

CHEMISTRY REVIEW

A. Check List *(once you check a "Yes" from top down, skip the rest afterward):*

• First Generic?	Yes: ☒	No: ☐
• MR Product?	Yes: ☐	No: ☒
• Solid IR/Oral Sol. RPN > 60 or Inj. Q1/Q2 ≠ RLD?	Yes: ☐	No: ☒
• Major Formulation/ Mfg. Process Change?	Yes: ☐	No: ☒

B. Review Tier *(3 Tier if a "Yes" and 2 Tier if all "No" are checked in A)*: **3 Tier:** ☐ **2 Tier:** ☒

C. Approvability: – ***CMC is Adequate***

ANDA 207141

Noxivent (Nitric Oxide gas for Inhalation)

Praxair Distribution, Inc.
c/o Icon Clinical Research

Kadum Al Shareffi, Ph.D.
Office of Lifecycle Drug Products
Division of Immediate Release Products I
Branch 3

Table of Contents

Chemistry Review Data Sheet

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Chemistry Review Data Sheet

1. ANDA: 207141

2. REVIEW #: 3

3. REVIEW DATE: 12-04-2015 / 12-15-2015 / 01-22-2016 /01-28-2016 / 06-13-2016 / 07-21-2016/ 05-02-2017/06-30-2017/ 01-19-2018 / 02-26-2018/ 05-24-2018/09-20-2018; 9/24/2018

4. REVIEWER: Kadum Al Shareffi, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
Original submission	05-20-2014
Proprietary Name Request for review	07-09-2014
Quality response to Information Request/Patent &exclusivity	11-12-2014
Quality response to Information Request	12-08-2014
Administration change / Contact Information	08-27-2015
Correspondence	09-08-2015
Correction to previously submitted Patent certifications	05-05-2016
Notice of Certification of invalidity of a patent	05-06-2016
Request for Proprietary Name Review	05-18-2016
Patent Information	05-20-2016
Patent and Labeling	07-05-2016
Patent information	08-15-2016
Quality response to IR	08-22-2016
Patent & Exclusivity / Patent Certification	08-29-2016
Received the return receipts of the Notice Letter	09-15-2016
List of parties authorized to communicate with FDA	02-23-2017
Response to ECD letter (labeling)	03-15-2017
Quality response to IR letter dated 05-05-2017	05-26-2017
Quality response to IR letter dated 01-22-2018	02-01-2018
Gratuitous Amendment (verification statement) No quality	02-02-2018
Gratuitous Amendment (Labeling revision) No quality	02-28-2018

Amendment dated 10-23-2014, User fee. No CMC review.
Amendment dated 01-21-2015, conformation of delivery notice. No CMC review.
Amendment dated 08-04-2017 is dealing with labeling. No CMC review.
Amendment dated 09-11-2017 is dealing with labeling. No CMC review.
Amendment dated 10-02-2017 is dealing with labeling. No CMC review.
Amendment dated 12-11-2017 is dealing with labeling. No CMC review.
Amendment dated 12-12-2017 is dealing with labeling, proprietary name. No CMC review.
Amendment dated 02-02-2018 is dealing with verification statement of amendment dated 01-22-2018. No CMC review.
Amendment dated 02-28-2018 is dealing with New Patent Certification and Corresponding Updated Labeling. No CMC review.
Amendment dated 03-27-2018 is dealing with Certified Mail Return Receipts of Notice Letter. No CMC review.

Chemistry Review Data Sheet

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Patent amendment	08-20-2018
Response to DRL (labeling) dated 08-13-2018	08-21-2018
Response to FDA request on 09-11-2018 – Nitric Oxide Lots compatibility testing for NOxBOxi device	09-19-2018

Amendment dated 08-21-2018 is dealing with labeling. No CMC review.

7. NAME & ADDRESS OF APPLICANT:

Name:	**Praxair Distribution, Inc.**
Address:	10 Riverview Drive^ Danbury, CT 06810 USA
Tel: Fax: email	330-949-3324 636-680-3453 Mike_skrjanc@praxair.com
Representative*:	**ICON Clinical Research LLC** Amy Kneifel / Director, Regulatory Affairs 79 T.W. Alexander Drive 4401 Research Commons, Suite 300 Durham, NC 27709 – 4353 919-294-2241 (b) (4) amy.kneifel@iconplc.com

*US Agent has been changed per Amendment dated 09-15-2016.

^Amendment dated 03-15-2017.

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: Noxivent
Non-Proprietary Name (USAN): Nitric oxide

9. LEGAL BASIS FOR SUBMISSION:

Innovator Product: INOmax® (nitric oxide), 800 ppm, 100ppm
Innovator Company: INO Therapeutics (NDA # 020845)

Patents Related Amendments:

Amendment dated 08-20-2018 (Sequence 0029)

Patent Amendment and Responses to Other Requests for Information

1) In accordance with 21 C.F.R. § 314.107(e), Praxair is providing a copy of the judgment entered on September 5, 2017, as well as the corresponding memorandum opinion.

2) The judgment was appealed to the Federal Circuit, is fully briefed, and is awaiting scheduling for the oral argument (see the enclosed appeal docket report). Mallinckrodt opted not to appeal the district court's non-infringement judgment for the '9794 patent, so that aspect of the district court's judgment is final. *See* Mallinckrodt's Appeal Brief at p. 21, n.6 (enclosed).

3) There is no pending litigation with regard to the '904 and '210 patents because

Mallinckrodt dropped those patents from its case shortly before trial. *See* District Court's Minute Order dated January 25, 2017 requiring Mallinckrodt to reduce the number of asserted patents and claims for trial, and subsequent e-mail correspondence dated January 27, 2017 from Mallinckrodt's counsel David Callahan of Latham & Watkins LLP responding to the Court's Order identifying the remaining patents and claims that would be tried, and which does not mention the '904 or '210 patents (both documents enclosed).

Amendment dated 09-15-2016 (Sequence 0016)

Praxair has received the return receipts of the Notice Letter sent on August 30, 2016 via certified mail to the NDA Holder for NDA No. N020845, the owner of the related patents listed in the Orange Book, and counsel for the NDA Holder for NDA No. N020845.

Amendment dated 08-29-2016 (Sequence 0015)

New Patent Certifications

Corrections to Previously Submitted Patent Certifications

New patent certifications for U.S. Patent No. 9,408,993 that is newly listed in the Orange Book, as well as revisions to previously submitted patent certifications for U.S. Patent No. 9,265,911 and U.S. Patent No. 9,295,802 The patent certifications include:

- New Patent Certification for US Patent No. 9,408,993 (Drug Product Claims);
- New Patent Certification for US Patent No. 9,408,993 (Method of Use Claims);
- Revised Patent Certification for US Patent No. 9,265,911 (Method of Use Claims); and
- Revised Patent Certification for US Patent No. 9,295,802 (Method of Use Claims).

Paragraph IV Patent Certification for US Patent No. 9,408,993 (Drug Product Claims); Section viii statement for US Patent No. 9,408,993 (Method of Use Claims); Section viii statement for US Patent No. 9,265,911 (Method of Use Claims); and Section viii statement for US Patent No. 9,295,802 (Method of Use Claims).

Amendment dated 08-15-2016 (Sequence 0013)

Corrections to two previously submitted patent certifications:

- Patent Certification for US Patent No. 8,573,210 (Drug Product Claims); and
- Patent Certification for US Patent No. 8,431,163.

These two patent certifications now indicate the correct patent number. Paragraph IV certification for each is included.

No scientific review, or manufacturing or facilities changes.

Amendment dated 07-05-2016

Patent and Labeling amendment:

In October 2015, more than one year after Praxair's original ANDA submission on May 20, 2014, INO Therapeutics updated the reference listed drug ("RLD") label primarily to change the method of use (10/2015). The change to the RLD label in October 2015 has necessitated this amendment to Praxair's ANDA submission. Specifically, Praxair wishes to revise the Section VIII statements for U.S. Patent Nos. 8,291,904, 8,573,210, 8,776,794, and 8,776,795.

In this sequence, Praxair encloses with this cover letter, a signed Form FDA 356h, Section VIII statements for U.S. Patent Nos. 8,291,904; 8,573,210; 8,776,794; and 8,776,795; the October 2015 RLD label, a redlined version of the October 2015 RLD label comparing it to the updated proposed labeling for ANDA 207141, and clean versions (MS Word and pdf) of the updated proposed labeling for ANDA 207141.

Changes to the RLD label are made to reflect the different manufacturers and proprietary names,

and to omit methods of use that are protected by patent. *See* 21 C.F.R. § 314.94(a)(8)(iv).

Amendment dated 05-20-2016

Patent Information- Certified Mail Return Receipts of Notice Letter:
In accordance with 21 C.F.R. § 314.95, please be advised that Praxair has received the return receipts of the Notice Letter sent via certified mail to the NDA Holder for NDA No. N020845, the owner of the related patents listed in the Orange Book, and counsel for the NDA Holder for NDA No. N020845. Copies of the front and back of the certified mail return receipts are provided in this sequence.

Amendment dated 05-18-2016

Request for Proprietary name Review:
Reference is made to the Request for Proprietary Name Review previously submitted in Sequence 0001 to the AND A. The proprietary name review was conducted by the Agency and a conditionally acceptable proprietary name letter was issued on 18 December 2014.
As requested by the Agency in their email dated 13 May 2016, because of the amount of time that has elapsed since FDA' s review of the proprietary name, the Sponsor is submitting a complete request for proprietary name review again as found in Section 1.12.4.

Amendment dated 05-06-2016

Notice of Certification of Invalidity or Noninfringement of a Patent ("Notice Letter"):
Praxair Distribution, Inc. ("Praxair") sent the Notice of Certification of Invalidity or Noninfringement of a Patent ("Notice Letter") via certified mail to the NDA Holder for NDA No. N020845, the owner of the related patents listed in the Orange Book, and counsel for the NDA Holder for NDA No. N020845.
Pursuant to§ 314.95(b), Praxair certifies that the Notice Letter has been provided to each person identified under § 314.95(a) and that the notice met the content requirements under § 314.95(c).

Amendment dated 05-05-2016

Corrections to Previously Submitted Patent Certifications / Administrative information:
The purpose of this submission is to provide the following patent certifications:
• Patent Certification for US Patent No. 9,265,911 Paragraph IV (Drug Product Claims)
• Patent Certification for US Patent No. 9,295,802 Paragraph IV (Drug Product Claims)
• Patent Certification for US Patent No. 9,265,911 Section viii Statement
• Patent Certification for US Patent No. 9,295,802 Section viii Statement
• Patent Certification for US Patent No. 9,279,794 Paragraph IV Certification
In addition, we are herein providing corrections to previously submitted patent certifications:
• Patent Certification for US Patent No. 6,125,846
The initially submitted certification states the patent expiration date instead of the pediatric exclusivity date (May 16, 2017 instead of November 16, 2017). The corrected certification indicates the correct pediatric exclusivity date.
• Patent Certification for US Patent No. 5,732,693
The previously filed certification appears to have a duplicate page added to it that is not needed. The corrected version removes the unnecessary page and also indicates the correct exclusivity dates.
• Patent Certification for US Patent No. 5,752,504
The initially submitted certification states the patent expiration date as that of the pediatric exclusivity elate (June 13, 2017 instead of December 13, 20 16). The corrected certification indicates the correct exclusivity dates.

Chemistry Review Data Sheet

Patent Certification for US Patent No. 5,873,359, 5,485,827
Paragraph II Certification
Pursuant to 21 CFR 314.94(a)(12)(i)(2) and in its opinion and to the best knowledge of Praxair Distribution, Inc., U.S. Patent No. 5,873,359, 5,485,827 are now expired.

Patent Certification for US Patent No. 5,558,083, 5,732,693, 5,752,504, 6,125,846
Paragraph III Certification
Pursuant to 21 CFR 314.94(a)(12)(i)(3) and in its opinion and to the best knowledge of Praxair Distribution, Inc., U.S. Patent No. 5,558,083, 5,732,693, 5,752,504, and 6,125,846 shall expire on May 22, 2014, June 13, 2017, June 13, 2017, May 16, 2017 respectively.

Patent Certification for US Patent No. 8,431,163, 8,573,209, 8,293,284, 8,291,904, and 8,537,210
Paragraph IV Certification
Pursuant to 21 U.S.C. § 355(j)(vii) and 21 C.F.R. § 314.94(a)(12)(i)(4) Praxair Distribution, Inc., certifies that U.S. Patent No. 8,431,163 ("the 163 patent"), 8,573,209 ("the '209 Patent"), 8,293,284 ("the '284 Patent"), 8,291,904 ("the '904 Patent") are invalid, unenforceable, or will not be infringed by the manufacture, use or sale of Noxivent™ for which this application is submitted.
Praxair Distribution, Inc., certifies that claims 1 through 11 U.S. Patent No. 8,537,210 ("the '210 Patent"), are invalid, unenforceable, or will not be infringed by the manufacture, use or sale of Noxivent™ for which this application is submitted.
Praxair will comply with the requirements under 21 C.F.R. § 314.95(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved application for the listed drug, and with the requirements under 314.95(c) with respect to the content of the notice.

Patent Certification for US Patent No. 8,291,904, 8,282,966, and 8,537,210:
None Required for the Method of Use Claims (Section viii Statement)

10. PHARMACOL. CATEGORY: Treatment of term and near-term neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension. It is an FDA Orphan Designation, indicated for rare diseases (prevalence <200,000 in U.S.).

11. DOSAGE FORM: **Compressed Gas**

12. STRENGTH/POTENCY: **800 ppm, and 100 ppm**

13. ROUTE OF ADMINISTRATION: **Inhalation**

14. Rx/OTC DISPENSED: **_x_ Rx __ OTC**

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

☐ SPOTS product – Form Completed
☒ Not a SPOTS product

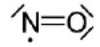
15b. NANOTECHNOLOGY PRODUCT TRACKING:

☐ NANO product – Form Completed (See Appendix A.4)

Chemistry Review Data Sheet

☒ Not a NANO product

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

Chemical name: Nitric oxide
CAS: 10102-43-9
Molecular formula: NO
Molecular weight: 30.01 g mol^{-1}
Molecular Structure: 
Elemental composition: (b) (4)
Odor threshold: 0.3 – 1.0 ppm
Relative gas density (air=1): 1.04

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
*		Praxair Distribution	Drug Substance: Nitric oxide	6	Adequate	06/23/2017	Reviewed by DMF team (Li Mu, and Wei Liu) as part of ANDA
(b) (4)	III	(b) (4)		3	Adequate	06-10-2016	Xing Wang
	III			3	Adequate	06-10-2016	Wei Liu
	III			3	Adequate	06-10-2016	Xing Wang

*API information is provided as part of ANDA. There is no separate Type II DMF for API is filed.

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
NDA for INOmax (Nitric oxide)	INO Therapeutics (NDA 20845)	Reference Listed Drug (RLD)

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
Methods Validation	N/A		
EES	Approve	04-16-2017	Delaram Moshkelani
Labeling	Acceptable	09/12/2018	A. Jung
Bioequivalence	Adequate	07-07-2015	Diana Vivian
EA	Acceptable	11-28-2015	Kadum Al Shareffi
Radiopharmaceutical	N/A		
Samples Requested	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ☒ Yes ☐ No If no, explain reason(s) below:

20. EES INFORMATION

Drug Substance and Product			
Function	**Site Information**	**FEI/CFN#** (b) (4)	**Status**
			Approve
			Approve

Chemistry Review for ANDA 207141

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

CMC is Adequate.

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

N/A

II. Summary of Chemistry Assessments

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

a. Drug Substance: Nitric oxide gas, There is no USP monograph for Nitric Oxide gas drug substance.

b. Drug Product: There is no USP monograph for Nitric Oxide gas drug product.
It is an Admixture of Nitric oxide and Nitrogen gas (0.01% and 99.99%) for 100 ppm, and 0.08% and 99.92% respectively for 800 ppm). The drug product is supplied in aluminum cylinders as a compressed gas under high pressure and is administered by inhalation in combination with a breathing gas.

(ii) Components of drug product

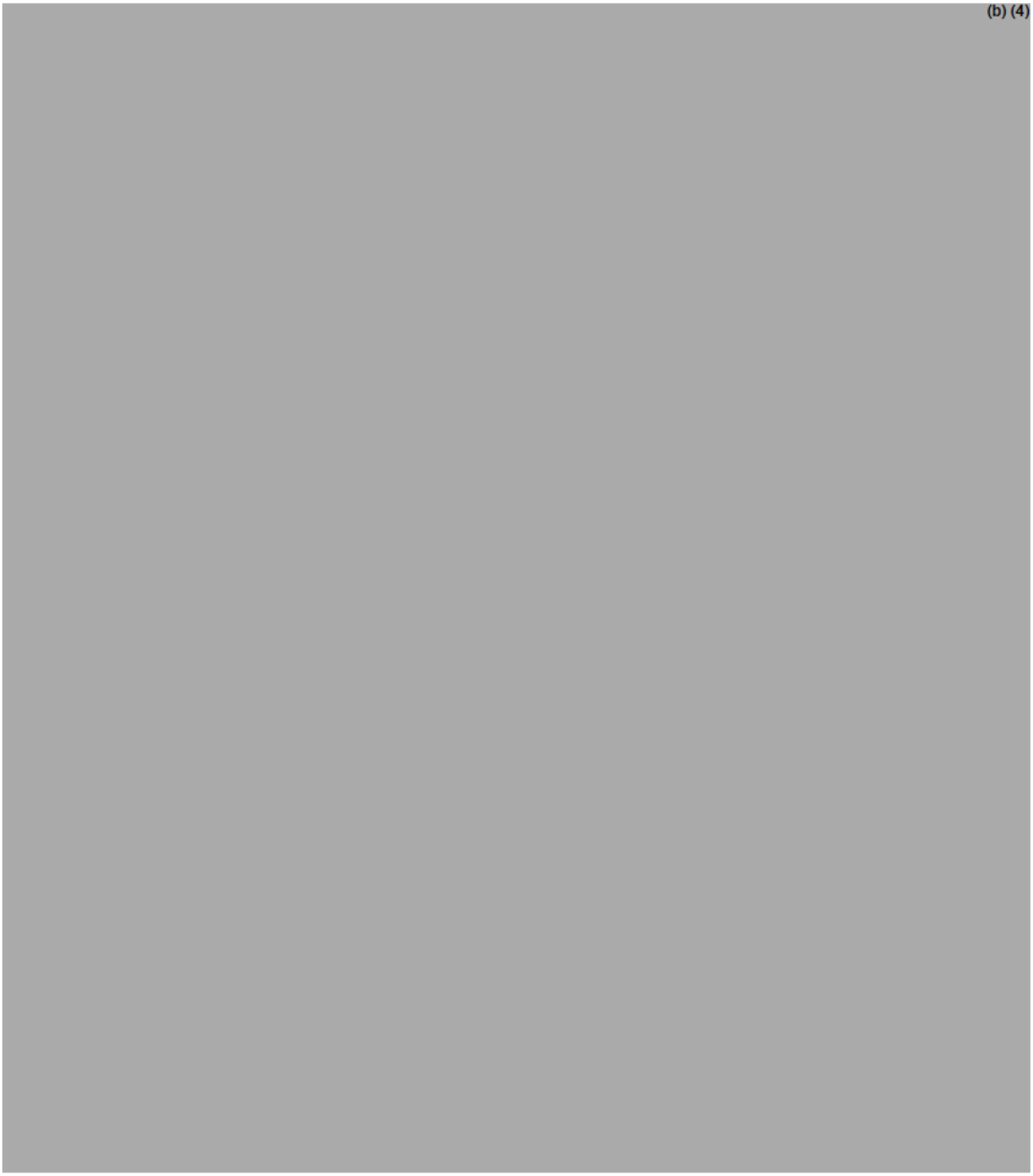
Active ingredients: Nitric oxide gas

(b) (4)

(b) (4)

(v) Executed batch and proposed production batches

The manufacturing process of the exhibit batch is at commercial scale.
Twelve exhibit batches were manufactured for the process validation and registration stability programs from Drug substance batch numbers NO917307701, NO917307901, and NO917308101. (b) (4)



*(vi) Packaging**

Strength	Size	Description
800 ppm	AD	Portable aluminum cylinders containing 362 liters at STP of nitric oxide gas in **800 ppm** concentration in nitrogen (delivered volume **323 liters**) (NDC 59579-102-02)
	AQ	Aluminum cylinders containing 2154 liters at STP of nitric oxide gas in **800 ppm** concentration in nitrogen (delivered volume **2082 liters**) (NDC 59579-102-01)
100 ppm	AD	Portable aluminum cylinders containing 362 liters at STP of nitric oxide gas in **100 ppm** concentration in nitrogen (delivered volume **323 liters**) (NDC 59579-101-02)
	AQ	Aluminum cylinders containing 2154 liters at STP of nitric oxide gas in **100 ppm** concentration in nitrogen (delivered volume **2082 liters**)

		(NDC 59579-101-01)

*Updated by amendment dated 08-21-2018.

(vii) Storage conditions

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.

(b) (4)

Occupational Exposure

The exposure limit set by the Occupational Safety and Health Administration (OSHA) for nitric oxide is 25 ppm, and for NO2 the limit is 5 ppm.

(viii) Expiration Date

(b) (4) dating period is proposed, based on available data of 6 months accelerated conditions, and 12 months (amendment dated 08-22-2016) at room temperature, which will be confirmed by real-time room temperature stability data.

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

INDICATIONS

Nitric oxide 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.

The recommended dose is 20 ppm and is achieved using an approved nitric oxide delivery system that allows for operator-determined concentrations of nitric oxide in the breathing gas. The system must not cause the generation of excessive inhaled nitrogen dioxide (NO2) and precise monitoring of inspired nitric oxide and NO2 is required using a properly calibrated analysis device with alarms.

Oxygen (O2) levels are also measured. Treatment is maintained up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from NO therapy.

Monitor for **PaO_2**, **methemoglobin**, and inspired **NO2** during *Noxivent*™ administration.

*HOW SUPPLIED**

Strength	Size	Description	NDC
800 ppm	AD	Portable aluminum cylinders containing 362 liters at STP of nitric oxide gas in **800 ppm** concentration in nitrogen (delivered volume **323 liters**)	NDC 59579-102-02
	AQ	Aluminum cylinders containing 2154 liters at STP of nitric oxide gas in **800 ppm** concentration in nitrogen (delivered volume **2082 liters**)	NDC 59579-102-01
100 ppm	AD	Portable aluminum cylinders containing 362 liters at STP of nitric oxide gas in **100 ppm** concentration in nitrogen (delivered volume **323 liters**)	NDC 59579-101-02

	AQ	Aluminum cylinders containing 2154 liters at STP of nitric oxide gas in **100 ppm** concentration in nitrogen (delivered volume **2082 liters**)	NDC 59579-101-01

*Updated by amendment dated 08-21-2018.

RLD:

Strength	Size	Description
800 ppm	**Size D**	Portable aluminum cylinders containing 353 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen
800 ppm	**Size 88**	Aluminum cylinders containing 1963 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen
100 ppm	**Size D**	Portable aluminum cylinders containing 353 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen
100 ppm	**Size 88**	Aluminum cylinders containing 1963 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen

C. Initial Risk Assessment for Drug Product

Risk calculation tables are not available for gas based drug products.

D. Basis for Approvability or Not-Approval Recommendation

CMC is Adequate. Bioequivalence is Adequate. EES is Approved.

109 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

ENVIRONMENTAL IMPACT ANALYSIS STATEMENT

A categorical exclusion from the requirements of preparing an environmental assessment is claimed for this Abbreviated New Drug Application pursuant to 21 C.F.R. 25.31(a). Namely, the action that is claimed does not increase the use of the active moiety.

A APPENDICES

A.1	***Facilities and Equipment (biotech only)***	***N/A***
A.2	***Adventitious Agents Safety Evaluation***	***N/A***
A.3	***Novel Excipients*** The proposed formulation does not contain novel excipients.	
A.4	***Nanotechnology Product Information***	***N/A***
R	**REGIONAL INFORMATION**	
R.1	***Executed Batch Records***	*Provided in Module 3.2.R*
R.2	***Comparability Protocols*** *Drug substance and Drug product are Not Applicable.* *Provided in Module 3.2.R*	
R.3	***Methods Validation Package***	*Refer to Module 3.2.P.5.3*

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Documents

Patent Certification:	Provided in Module 1.3.5
Exclusivity:	Exclusivity statement is provided in Module 1.3.5
Debarment Certification:	Provided in Module 1.3.3
cGMP Statement:	Provided in Module 3.2.P.3.1

Reprocessing Statement: Provided in Module 3.2.P.3.3

Letters of Authorization: Provided in Module 1.4.1

Request for Bio-waiver: Provided in Module 1.12.15

Citizen Petition and/or Control Request Linked to the Application: N/A

Environmental Impact Considerations/Categorical Exclusions:
Provided in Module 1.12.14

Appendix D: Chemistry Review Template – Labeling section
A. Labeling & Package Insert

a) DESCRIPTION section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer. *None*

b) HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No
If "No," explain.
ii) Are the storage conditions acceptable? ☒ Yes ☐ No
If "No," explain.

c) DOSAGE AND ADMINISTRATION section, for injectable, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☒ N/A
If "No," explain.

d) For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No
If "No," explain.
N/A

e) Inhalation Gas

Strength	Size	Description
800 ppm	AD	Portable aluminum cylinders containing 362 liters at STP of nitric oxide gas in **800 ppm** concentration in nitrogen (delivered volume **323 liters**) (NDC 59579-102-02)
	AQ	Aluminum cylinders containing 2154 liters at STP of nitric oxide gas in **800 ppm** concentration in nitrogen (delivered volume **2082 liters**) (NDC 59579-102-01)
100 ppm	AD	Portable aluminum cylinders containing 362 liters at STP of nitric oxide gas in **100 ppm** concentration in nitrogen (delivered volume **323 liters**) (NDC 59579-101-02)
	AQ	Aluminum cylinders containing 2154 liters at STP of nitric oxide gas in **100 ppm** concentration in nitrogen (delivered volume **2082 liters**) (NDC 59579-101-01)

f) Describe issue(s) sent to and/or received from the OGD Labeling Reviewer:

. (b) (4)

III. List of Deficiencies To Be Communicated: *(None)*

Drug substance:

None (Drug substance is adequate on 06-23-2017, by Li Mu, and Wei Liu).

Drug Product:

None

Administrative

A. Reviewer's Signature

B. Endorsement Block

WO - 75/ Kadum Al Shareffi, Ph.D. - Reviewer / 07-27-2015/12-04-2015/ 12-15-2015/01-22-2016/01-28-2016/06-13-2016 / 07-21-2016/05-02-2017/ 06-30-2017/01-19-2018/ 02-26-2018/ 05-24-2018 / 09-20-2018; 9/24/2018

WO - 75/ Laxma Nagavelli, Ph.D./Branch Chief 3; 12/14/2015; 1/23/2016; 1/30/2016; 2/3/2016; 6/14/2016; 7/21/2016; 5/3/2016; 7/7/2017; 1/22/2018; 2/26/2018; 5/24/2018; 9/20/2018; 9/24/2018

WO - 75/ Jonee Mearns - PM/

TYPE OF LETTER: *CMC is Adequate.*

Laxma Nagavelli

Digitally signed by Laxma Nagavelli
Date: 9/24/2018 02:08:29PM
GUID: 508da705000289ae28a00999ca07b9c4

Kadum Al Shareffi

Digitally signed by Kadum Al Shareffi
Date: 9/24/2018 02:12:46PM
GUID: 51ddb2d90000e277a1c514807a095a4e

ANDA 207141

Noxivent (Nitric Oxide for Inhalation)

PRAXAIR DISTRIBUTION INC
C/O ICON CLINICAL RESEARCH

Primary Reviewer: Li Mu, Ph.D.
Team Leader: Wei Liu, Ph.D.
Division of Lifecycle API
Branch 2, Team 4

Drug Substance Chemistry Review Data Sheet

1. ANDA 207141:

2. REVIEW #: 3

3. REVIEW DATE: 06/12/2017

4. REVIEWER: Primary Reviewer: Li Mu, Ph.D.
Team Leader: Wei Liu, Ph.D.

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed	SD#	Document Date
Original-1, New/ANDA; Form 3674	1	05/20/2014
Proprietary Name/Request for Review	2	07/09/2014
User Fee/Coversheet	3	10/23/2014
Patent & Exclusivity/Patent Certification; Quality/Response To Information Request; Form 3674	4	11/11/2014
Quality/Response To Information Request	5	12/08/2014
Patent & Exclusivity/Patent Information	6	01/21/2015
Patent & Exclusivity/Patent Information	7	02/19/2015
Administrative Change/Contact Information	8	08/27/2015
Correspondence	9	09/08/2015
Patent & Exclusivity/Patent Certification	10	05/05/2016
Patent & Exclusivity/Patent Certification	11	05/06/2016
Proprietary Name/Request for Review	12	05/18/2016
Patent & Exclusivity/Patent Certification	13	05/20/2016
Labeling/Package Insert Draft; Patent & Exclusivity/Patent Information; Patent & Exclusivity/Patent Certification	14	07/05/2016
Patent & Exclusivity/Patent Certification	15	08/15/2016
Quality/Response To Information Request	16	08/22/2016
Patent & Exclusivity/Patent Certification	17	08/29/2016
Patent & Exclusivity/Patent Information	18	09/15/2016
Administrative Change/Contact Information	19	02/23/2017

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	SD#	Document Date
Patent & Exclusivity/Patent Certification; Patent & Exclusivity/Exclusivity Information; Response to ECD/Labeling	20	03/15/2017
Quality/Response To Information Request	21	05/26/2017

7. NAME & ADDRESS OF APPLICANT:

Name:	Praxair Distribution, Inc.
Address:	39 Old Ridgebury Road, Danbury, CT 06810, USA
Representative:	Robert S. Cormack, Ph.D., Director, Regulatory Affairs
Telephone:	330-949-3324

8. DRUG PRODUCT NAME/CODE/TYPE:
Proprietary Name: Noxivent
Non-Proprietary Name (USAN): nitric oxide

9. LEGAL BASIS FOR SUBMISSION:

10. PHARMACOL. CATEGORY: Hypoxemic Respiratory Failure in the Term and near-Term Newborn

11. DOSAGE FORM: gas

12. STRENGTH/POTENCY: 800 ppm, 100 ppm

13. ROUTE OF ADMINISTRATION: inhalation

14. Rx/OTC DISPENSED: _x_ Rx __ OTC

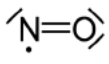
15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
☐ SPOTS product – Form Completed

☒ Not a SPOTS product
15b. NANOTECHNOLOGY PRODUCT TRACKING:
☐ NANO product – Form Completed (See Appendix A.4)

☒ Not a NANO product

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

Chemical Name: nitric oxide / nitrogen monoxide / nitrogen oxide / nitrogen (II) oxide

Structural formula: 

Molecular Formula: NO
Molecular weight: 30.01 g/mole
CAS Registry Number: 10102-43-9

17. RELATED/SUPPORTING DOCUMENTS:

A. DRUG SUBSTANCEs:

DRUG SUBSTANCE #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
207141	ANDA	Praxair Distribution, Inc.		1			N/A

[1] Action codes for DRUG SUBSTANCE Table:
1 – DRUG SUBSTANCE Reviewed.
Other codes indicate why the DRUG SUBSTANCE was not reviewed, as follows:
2 –Type 1 DRUG SUBSTANCE
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DRUG SUBSTANCE not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DRUG SUBSTANCE did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
Methods Validation			
Labeling			
Bioequivalence			
Toxicology/Clinical			
EA			
Radiopharmaceutical			
Samples Requested			

19. ORDER OF REVIEW
The application submission(s) covered by this review was taken in the date order of receipt. ☒ Yes ☐ No If no, explain reason(s) below:

20. EES INFORMATION

Drug Substance			
Function	**Site Information**	**FEI/CFN#**	**Status**
(b) (4)			

Drug Product			
Function	**Site Information**	**FEI/CFN#**	**Status**
[i.e. manufacturer, contract lab, etc.]	*[Location, address, etc.]*		

Drug Substance Risk-based-Review Summary

(A) RISK ASSESSMENT:

Critical Attributes pertaining to DS quality	Previous Risk Ranking	Comments	Updated Risk Ranking	Comments*
SM Designation	45	(b) (4)	45	(b) (4)
Manufacturing Process	9		9	
ID/Characterization	15		15	
Impurities	80		36	
Residual Solvents/ Elemental Impurities	15		15	
Stability	36		36	

(B) EXECUTIVE SUMMARY

MDD	RT	IT	QT	TTC
20 ppm				

Background Information

- Hypoxemic Respiratory Failure in the Term and near-Term Newborn
- No USP monograph for the Nitric Oxide DS. EP monograph is available
- RLD: NDA20845
- Nitric oxide is a colorless, odorless, toxic gas

(b) (4)

***(ii)* Controls.**

- Release specifications comply with the EP monograph/RLD (b) (4)
- The nitric oxide DS itself demonstrates genotoxicity in vitro/in vivo, the impurity could be controlled at the level of ICH Q3A and M7

(b) (4)

(b) (4)

(v) **Hidden Facility.**
N/A

(C) REVIEW CONCLUSION

Adequate

28 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

III. List Of Comments/Deficiencies To Be Communicated to The Applicant

ANDA: 207141
APPLICANT: Praxair Distribution, Inc.
DRUG PRODUCT: Noxivent (Nitric Oxide for Inhalation)

Appears this way in original

Administrative

A. Reviewer's Signature
Li Mu

B. Endorsement Block

Chemist Name/Date: Li Mu / 06/12/2017
Chemistry Team Leader Name/Date: Wei Liu 4/6/2017
Project Manager Name/Date:

TYPE OF LETTER:

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A. Check List *(once you check a "Yes" from top down, skip the rest afterward):*

- First Generic? Yes: ☒ No: ☐
- MR Product? Yes: ☐ No: ☒
- Solid IR/Oral Sol. RPN > 60 or Inj. Q1/Q2 ≠ RLD? Yes: ☐ No: ☒
- Major Formulation/ Mfg. Process Change? Yes: ☐ No: ☒

B. Review Tier *(3 Tier if a "Yes" and 2 Tier if all "No" are checked in A):* **3 Tier:** ☐ **2 Tier:** ☒

C. Approvability: – ***No, IR/CR letter***

ANDA 207141

Noxivent (Nitric Oxide gas for Inhalation)

Praxair Distribution, Inc.
c/o Icon Clinical Research

Kadum Al Shareffi, Ph.D.
Office of Life Cycle Drug Products
Division of Immediate Release Products I
Branch 3

Table of Contents

Chemistry Review Data Sheet

Appears this way in original

Chemistry Review Data Sheet

1. ANDA: **207141**

2. REVIEW #: **1**

3. REVIEW DATE: **12-04-2015 / 12-15-2015 / 01-22-2016 / 01-28-2016 / 06-13-2016**

4. REVIEWER: **Kadum Al Shareffi, Ph.D.**

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Correspondence	09-08-2015
Administration change / Contact Information	08-27-2015
Quality response to Information Request	12-08-2014
Quality response to Information Request/Patent &exclusivity	11-11-2014
Proprietary Name Request for review	07-09-2014
Original submission	05-20-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	**Praxair Distribution, Inc**
Address:	39 Old Ridgebury Road Danbury CT 06810 USA
Tel:	330-949-3324
Fax:	636-680-3453
Representative:	**ICON Clinical Research** Amy Kneifel / Director, Regulatory Affairs 2100 Pennbrook Parkway North Wales PA 19454 USA
Telephone:	919-294-2241
Fax	215-789-9557
e-mail	amy kneifel@iconplc.com

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name: Noxivent
Non-Proprietary Name (USAN): Nitric oxide

9. LEGAL BASIS FOR SUBMISSION:

Innovator Product: INOmax® (nitric oxide), 800 ppm, 100ppm

Chemistry Review Data Sheet

Innovator Company: INO Therapeutics (NDA # 20845)

(b) (4)

[redacted]

10. PHARMACOL. CATEGORY: Treatment of term and near-term neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension. It is an FDA Orphan Designation, indicated for rare diseases (prevalence <200,000 in U.S.).

11. DOSAGE FORM: Compressed Gas

12. STRENGTH/POTENCY: 800 ppm, and 100 ppm

13. ROUTE OF ADMINISTRATION: Inhalation

14. Rx/OTC DISPENSED: _x_ Rx __ OTC

Chemistry Review Data Sheet

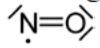
15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

☐ SPOTS product – Form Completed
☒ Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

☐ NANO product – Form Completed (See Appendix A.4)
☒ Not a NANO product

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

Chemical name: Nitric oxide
CAS: 10102-43-9
Molecular formula: NO
Molecular weight: 30.01 g mol^{-1}
Molecular Structure: 
Elemental composition: (b) (4)
Odor threshold: 0.3 – 1.0 ppm
Relative gas density (air=1): 1.04

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
207141	ANDA	Praxair Distribution		6	Inadequate	11/30/2015	Reviewed by DMF team as part of ANDA
(b) (4)	III	(b) (4)		3	Adequate	03-07-2016	Xing Wang
	III			3	Adequate	05-26-2016	Wei Liu
	III			3	Adequate	06-10-2016	Xing Wang

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
NDA for INOmax (Nitric oxide)	INO Therapeutics (NDA 20845)	Reference Listed Drug (RLD)

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
Methods Validation	N/A		
EES	Pending		
Labeling	Pending		
Bioequivalence	Adequate	07-07-2015	Diana Vivian
Toxicology/Clinical	N/A		
EA	Acceptable	11-28-2015	Kadum Al Shareffi
Radiopharmaceutical	N/A		
Samples Requested	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ☒ Yes ☐ No If no, explain reason(s) below:

20. EES INFORMATION

Drug Substance and Product			
Function	**Site Information**	**FEI/CFN#**	**Status**
		(b) (4)	Pending
			Pending

Chemistry Review for ANDA 207141

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA is not approvable. An IR/CR is recommended with CMC deficiencies

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

N/A

II. Summary of Chemistry Assessments

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

a. Drug Substance: Nitric oxide gas, There is no USP monograph for Nitric Oxide gas drug substance.

b. Drug Product: There is no USP monograph for Nitric Oxide gas drug product.
It is an Admixture of Nitric oxide and Nitrogen gas (0.01% and 99.99%) for 100 ppm, and 0.08% and 99.92% respectively for 800 ppm). The drug product is supplied in aluminum cylinders as a compressed gas under high pressure and is administered by inhalation in combination with a breathing gas.

(ii) Components of drug product

Active ingredients: Nitric oxide gas

(b) (4)

(b) (4)

(v) Executed batch and proposed production batches

The manufacturing process of the exhibit batch is at commercial scale.
Twelve exhibit batches were manufactured for the process validation and registration stability programs from Drug substance batch numbers NO917307701, NO917307901, and NO917308101. The batches were produced at commercial scale on the commercial equipment.

(b) (4)

(vi) Packaging

Size	Description
AD	(b) (4)
AD	
AQ	
AQ	

(vii) Storage conditions

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.

(b) (4)

Occupational Exposure

The exposure limit set by the Occupational Safety and Health Administration (OSHA) for nitric oxide is 25 ppm, and for NO2 the limit is 5 ppm.

(viii) Expiration Date

(b) (4) dating period is proposed, based on available data of 6 months accelerated conditions, and 6 months at room temperature, which will be confirmed by real-time room temperature stability data.

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

INDICATIONS

Nitric oxide 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.

The recommended dose is 20 ppm and is achieved using an approved nitric oxide delivery system that allows for operator-determined concentrations of nitric oxide in the breathing gas. The system must not cause the generation of excessive inhaled nitrogen dioxide (NO2) and precise monitoring of inspired nitric oxide and NO2 is required using a properly calibrated analysis device with alarms.

Oxygen (O2) levels are also measured. Treatment is maintained up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from NO therapy.

Monitor for **PaO_2**, **methemoglobin**, and inspired **NO2** during *Noxivent*™ administration.

HOW SUPPLIED

Size	Description	NDC
AD	(b) (4)	NDC XXXXX-XXX-XX
AD		NDC XXXXX-XXX-XX
AQ		NDC XXXXX-XXX-XX
AQ		NDC XXXXX-XXX-XX

RLD:

Strength	Size	Description
800 mg	Size D	Portable aluminum cylinders containing 353 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen
800 mg	Size 88	Aluminum cylinders containing 1963 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen
100 mg	Size D	Portable aluminum cylinders containing 353 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen
100 mg	Size 88	Aluminum cylinders containing 1963 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen

C. Initial Risk Assessment for Drug Product

Risk calculation tables are not available for gas based drug products.

D. Basis for Approvability or Not-Approval Recommendation

CMC of this ANDA is not acceptable. Bioequivalence is Adequate. Labeling is pending. EES is pending. This ANDA is not approvable.

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(b) (4)

[redacted]

ENVIRONMENTAL IMPACT ANALYSIS STATEMENT

A categorical exclusion from the requirements of preparing an environmental assessment is claimed for this Abbreviated New Drug Application pursuant to 21 C.F.R. 25.31(a). Namely, the action that is claimed does not increase the use of the active moiety.

A	APPENDICES		
	A.1	***Facilities and Equipment (biotech only)***	***N/A***
	A.2	***Adventitious Agents Safety Evaluation***	***N/A***
	A.3	***Novel Excipients*** The proposed formulation does not contain novel excipients.	
	A.4	***Nanotechnology Product Information***	***N/A***
R	**REGIONAL INFORMATION**		
	R.1	***Executed Batch Records***	*Provided in Module 3.2.R*
	R.2	***Comparability Protocols***	*Provided in Module 3.2.R*
	R.3	***Methods Validation Package***	*Refer to Module 3.2.P.5.3*

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Documents

Patent Certification: Provided in Module 1.3.5

Exclusivity: Exclusivity statement is provided in Module 1.3.5

Debarment Certification: Provided in Module 1.3.3

cGMP Statement: Provided in Module 3.2.P.3.1

Reprocessing Statement: Provided in Module 3.2.P.3.3

Letters of Authorization: Provided in Module 1.4.1

Request for Bio-waiver: Provided in Module 1.12.15

Citizen Petition and/or Control Request Linked to the Application: N/A

Environmental Impact Considerations/Categorical Exclusions: Provided in Module 1.12.14

Appendix D: Chemistry Review Template – Labeling section

A. Labeling & Package Insert

a) DESCRIPTION section

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer. *None*

b) HOW SUPPLIED section

i) Is the information accurate? ☒ Yes ☐ No
If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No
If "No," explain.

c) DOSAGE AND ADMINISTRATION section, for injectable, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No ☒ N/A
If "No," explain.

d) For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No
If "No," explain.
N/A

e) Inhalation Gas

ANDA 207141 Strength	Size	Imprint Code for the commercial batches
100ppm	AD	(b) (4)
	AQ	
800ppm	AD	
	AQ	

f) Describe issue(s) sent to and/or received from the OGD Labeling Reviewer:
. (b) (4)
. *Delivery system to introduce the medication to the patient.*

III. List of Deficiencies To Be Communicated

(Next page)

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ADMINISTRATIVE

A. Reviewer's Signature

B. Endorsement Block

WO - 75/ Kadum Al Shareffi, Ph.D. - Reviewer / 07-27-2015/12-04-2015/ 12-15-2015/01-22-2016/01-28-2016/06-13-2016
WO - 75/ Laxma Nagavelli, Ph.D./Branch Chief 3/12/14/2015; 1/23/2016; 1/30/2016; 2/3/2016; 6/14/2016
WO - 75/ Jonee Mearns - PM/

TYPE OF LETTER: IR/CR Letter

ANDA #	**Product Name and dosage form**	**Review start date**	**Net review days**	**PMAP goal days allowed** (Originals only)	**Comments: If goal not met**	**Amount of OT used if any** (hours)
207141	Noxivent (Nitric oxide gas for Inhalation)	07-27-2015 11-27-2015	10	10		20

ANDA 207141

Noxivent (Nitric Oxide for Inhalation)

PRAXAIR DISTRIBUTION INC
C/O ICON CLINICAL RESEARCH

Primary Reviewer: Li Mu, Ph.D.
Team Leader: Wei Liu, Ph.D.
Division of Lifecycle API
Branch 2, Team 4

Table of Contents

Drug Substance Chemistry Review Data Sheet

1. ANDA 207141:

2. REVIEW #: 1

3. REVIEW DATE: 10/08/2015

4. REVIEWER: Primary Reviewer: Li Mu, Ph.D.
Team Leader: Wei Liu, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Document(s)	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original-1, New/ANDA; Form 3674, SD#1	05/20/2014
Proprietary Name/Request for Review, SD#2	07/09/2014
User Fee/Coversheet, SD#3	10/23/2014
Patent & Exclusivity/Patent Certification; Quality/Response To Information Request; Form 3674, SD#4	11/11/2014
Quality/Response To Information Request, SD#5	12/08/2014
Patent & Exclusivity/Patent Information, SD#6	01/21/2015
Patent & Exclusivity/Patent Information, SD#7	02/19/2015
Administrative Change/Contact Information, SD#8	08/27/2015
Correspondence, SD#9	09/08/2015

7. NAME & ADDRESS OF APPLICANT:

Name:	Praxair Distribution, Inc.
Address:	39 Old Ridgebury Road, Danbury, CT 06810, USA
Representative:	Robert S. Cormack, Ph.D., Director, Regulatory Affairs
Telephone:	330-949-3324

8. DRUG PRODUCT NAME/CODE/TYPE:
Proprietary Name: Noxivent
Non-Proprietary Name (USAN): nitric oxide

9. LEGAL BASIS FOR SUBMISSION:

10. PHARMACOL. CATEGORY: Hypoxemic Respiratory Failure in the Term and near-Term Newborn

11. DOSAGE FORM: gas

12. STRENGTH/POTENCY: 800 ppm, 100 ppm

13. ROUTE OF ADMINISTRATION: inhalation

14. Rx/OTC DISPENSED: _x_ Rx __ OTC

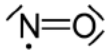
15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
☐ SPOTS product – Form Completed

☒ Not a SPOTS product
15b. NANOTECHNOLOGY PRODUCT TRACKING:
☐ NANO product – Form Completed (See Appendix A.4)

☒ Not a NANO product

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

Chemical Name: nitric oxide / nitrogen monoxide / nitrogen oxide / nitrogen (II) oxide

Structural formula: 

Molecular Formula: NO
Molecular weight: 30.01 g/mole
CAS Registry Number: 10102-43-9

17. RELATED/SUPPORTING DOCUMENTS:

A. DRUG SUBSTANCEs:

DRUG SUBSTANCE #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
207141	ANDA	Praxair Distribution, Inc.		1			N/A

[1] Action codes for DRUG SUBSTANCE Table:
1 – DRUG SUBSTANCE Reviewed.
Other codes indicate why the DRUG SUBSTANCE was not reviewed, as follows:
2 –Type 1 DRUG SUBSTANCE
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DRUG SUBSTANCE not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DRUG SUBSTANCE did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
Methods Validation			
Labeling			
Bioequivalence			
Toxicology/Clinical			
EA			
Radiopharmaceutical			
Samples Requested			

19. ORDER OF REVIEW
The application submission(s) covered by this review was taken in the date order of receipt. ☒ Yes ☐ No If no, explain reason(s) below:

20. EES INFORMATION

Drug Substance			
Function	**Site Information**	**FEI/CFN#**	**Status**
(b) (4)			

Drug Product			
Function	**Site Information**	**FEI/CFN#**	**Status**
[i.e. manufacturer, contract lab, etc.]	*[Location, address, etc.]*		

Drug Substance Risk-based-Review Summary

(A) RISK ASSESSMENT:

Critical Attributes pertaining to DS quality	Previous Risk Ranking	Comments	Updated Risk Ranking after CR #X	Comments*
SM Designation	45	(b) (4)		
Manufacturing Process	9			
ID/Characterization	15			
Impurities	80			
Residual Solvents/ Elemental Impurities	15			
Stability	36			

(B) EXECUTIVE SUMMARY

MDD	RT	IT	QT	TTC
20 ppm				

Background Information

- Hypoxemic Respiratory Failure in the Term and near-Term Newborn
- No USP monograph for the Nitric Oxide DS. EP monograph is available
- RLD: NDA20845
- Nitric oxide is a colorless, odorless, toxic gas

(b) (4)

***(ii)* Controls.**

- Release specifications comply with the EP monograph/RLD with the exception (b) (4)
- The nitric oxide DS itself demonstrates genotoxicity in vitro/in vivo, the impurity could be controlled at the level of ICH Q3A and M7

(b) (4)

(b) (4)

[redacted]

(v) **Hidden Facility.**

N/A

(C) REVIEW CONCLUSION

Not adequate

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data

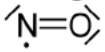
S.1 General Information

S.1.1 Nomenclature

USAN, generic, compendial, or INN name: Nitric Oxide
Manufacturer's code (if applicable): N/A
Chemical name: Nitric Oxide
CAS number: 10102-43-9

S.1.2 Structure

Structural formula, including stereochemistry



Molecular formula: NO
Molecular weight: 30.01 g/mole
Pharmacologic Class: Hypoxemic Respiratory Failure in the Term and near-Term Newborn

S 1.3 General Properties

Elemental composition	(b) (4)
Physical state at 20°C	Gaseous
Color	Colorless
Odor threshold	0.3-1.0 ppm
Relative gas density (air=1)	1.04

Water Solubility 7.4 mL/100 mL (0°C, 1 atm)

Nitric oxide forms a NO-H_2O hydrate with water that has a dissociation pressure of approximately 140 psi (9.7 bars) at 0°C.

Nitric oxide is a powerful oxidizing agent that combines with air (oxygen) to form nitrogen dioxide that hydrolyses in the presence of water (moisture) to form nitrous and nitric acids.

At high temperatures it can act as an oxidizing agent and at low temperatures, a reducing agent, with a range of compounds.

(b) (4)

[redacted]

Boiling Point (1 atm)

Temperature	Latent heat	Liquid volume mass	Vapor
-151.75°C	110.2 kcal·kg^{-1}	1300 kg·m^{-3}	3.02 7kg·m^{-3}

Critical Point

Temperature	Pressure	Volume mass
- 93°C	64.85 bar	520 kg·m^{-3}

(b) (4)

[redacted]

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R REGIONAL INFORMATION

R1 Executed Batch Records

Reviewer's Assessment (Review #):
Submitted in 3.2.R, including all detailed information about the manufacture, analysis, validation and packaging.

R2 Comparability Protocols

R3 Methods Validation Package

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Label

See section 3.2.S.6 above.

B. Environmental Assessment Or Claim Of Categorical Exclusion

The Environmental Impact Analysis Statement is submitted in section 1.12.14.

3 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

Administrative

A. Reviewer's Signature
Li Mu

B. Endorsement Block

Chemist Name/Date: Li Mu / 10/08/2015
Chemistry Team Leader Name/Date: Wei Liu/Nov 30, 2015
Project Manager Name/Date:

TYPE OF LETTER: CR Letter

1 Page has been withheld in full as b4 (CCI/TS) immediately following this page

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA207141Orig1s000

BIOEQUIVALENCE REVIEW(s)

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	207141
Drug Product Name	Nitric Oxide Gas for Inhalation
Strength(s)	100 PPM[1] and 800 PPM
Applicant Name	Praxair Distribution, Inc.
Address	39 Old Ridgebury Road Danbury, CT 06810
Applicant's Point of Contact	Robert S. Cornack, Ph.D., Director, Regulatory Affairs, ICON Clinical Research 2100 Pennbrook Parkway North Wales, PA 19454
Contact's Telephone Number	(b) (6)
Contact's Fax Number	215-789-9557
Original Submission Date(s)	05/20/2014
Submission Date(s) of Amendment(s) Under Review	--
First Generic (Yes or No)	No
Reviewer	Diana Vivian, Ph.D.

OSIS Status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☒ **Complete**	**Year 3 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection**
OVERALL REVIEW RESULT	**ADEQUATE**	
REVISED/NEW DRAFT GUIDANCE INCLUDED	**NO**	
COMMUNICATION	☐ **ECD** ☐ **IR** ☒ **NOT APPLICABLE**	

BIOEQUIVALENCE STUDY TRACKING/SUPPORTING DOCUMENT #	**STUDY/TEST TYPE**	**STRENGTH**	**REVIEW RESULT**
1	**Waiver**	**100 PPM**	**ADEQUATE**
1	**Waiver**	**800 PPM**	**ADEQUATE**

[1] PPM: parts per million (i.e. 100 PPM corresponds to 0.01%)

1 EXECUTIVE SUMMARY

This application contains the waiver request of *in vivo* bioequivalence study requirements for Praxair Distribution, Inc.'s proposed test product, Nitric Oxide Gas for Inhalation, 100 PPM and 800 PPM under 21 CFR § 320.22(b)(2). The reference listed drug (RLD) is INO Therapeutics Inc.'s INOmax® (Nitric Oxide Gas) for Inhalation, 100 PPM and 800 PPM (NDA #020845).

The drug product meets the requirements set forth in 21 CFR §320.22(b)(2) in that 1) the drug product is administered by inhalation as a gas and 2) contains an active ingredient in the same dosage form as the RLD. In addition, the formulation of the test product is qualitatively and quantitatively (Q1/Q2) the same as the RLD.

Bioequivalence is self-evident, and therefore, the Division of Bioequivalence II (DB II) deems the test product Nitric Oxide Gas for Inhalation, 100 PPM and 800 PPM bioequivalent to the corresponding reference product, INO Therapeutics' INOMAX® (nitric oxide gas) for Inhalation, 100 PPM and 800 PPM based on criteria set forth in 21 CFR §320.22(b)(2).[2]

No OSIS inspection is pending or necessary.

The application is **adequate**.

[2] See also Memorandum on Abbreviated New Drug Application (ANDA) 207141, Praxair Distribution, Inc., (Praxair) for Nitric Oxide Gas, For Inhalation, 100 ppm and 800 ppm, for a discussion of bioequivalence in the context of therapeutic equivalence for Praxair's ANDA 207141.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information[3,4]

Test Product	Nitric Oxide Gas for Inhalation, 100 PPM and 800 PPM
Reference Product	INOMAX® (nitric oxide gas) for Inhalation, 100 PPM and 800 PPM
RLD Manufacturer	INO Therapeutics, Inc.
NDA No.	020845
RLD Approval Date	December 23, 1999 for both strengths
Indication	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. Monitor for PaO_2, methemoglobin, and inspired NO_2 during INOmax administration. [redacted] (b) (4)

3.2 PK/PD Information[3,5]

Bioavailability	Approximately 90% of nitric oxide is absorbed during steady state inhalation. Nitric oxide is absorbed into the pulmonary vasculature, but systemic exposure is limited by rapid inactivation in blood cells (the half-life is a few seconds). 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.
Food Effect	N/A
Tmax	The average time to reach peak methemoglobin was 10.0 ± 9 hrs (median, 8 hrs) in a clinical study with 13 patients.
Metabolism	Methemoglobin and nitrate are the end products of nitric oxide metabolism present in the systemic circulation. Nitrate has been identified as the predominant nitric oxide metabolite excreted in the urine, accounting for >70% of the nitric oxide dose inhaled.
Excretion	Nitrate is cleared from the plasma by the kidney at rates approaching the rate of glomerular filtration.

[3] Electronic Orange Book. Search: nitric oxide; Last accessed 7/6/2015.
[4] Drugs@FDA. Search: nitric oxide. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020845s014lbl.pdf. Last accessed: 7/6/2015.
[5] Clinical Pharmacology; Search: nitric oxide. http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph.aspx?cpnum=2515&sec=monphar&t=0. Last accessed 7/6/2015.

Dosage and Administration	The recommended dose of INOMAX is 20 PPM, maintained for up to 14 days or until the underlying oxygen desaturation has resolved. Administration: ○ Use only with an INOmax DS$_{IR}$®, INOmax® DS, (b) (4) operated by trained personnel. ○ Wean from INOmax gradually.

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	N/A

Analytes to measure (in plasma/serum/blood):	N/A	
Bioequivalence based on:	N/A	
Waiver request of in-vivo testing:	100 PPM and 800 PPM	
Source of most recent recommendations or provide the link to the current draft guidance:	21 CFR §320.22(b)(2). The drug product meets the requirements set forth that 1) the drug product is administered by inhalation as a gas and 2) contains an active ingredient in the same dosage form as the RLD.	
Summary of OGD or DB History	Pending ANDAs (Not Yet Reviewed)	No
	Approved ANDAs	No
	Previously Reviewed ANDAs	(b) (4)
	Protocols[6]	No
	Controls[7]	Yes, CC #12-0677 is from the current applicant seeking clarification of the ANDA process for a medical gas, including eligibility for a waiver under 21 CFR 320.22(b)(2).

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	---	---
Single-dose fed	---	---
Steady-state	---	---
In vitro dissolution	---	---
Waiver requests	Yes	2
BCS Waivers	---	---
Clinical Endpoints	---	---
Failed Studies	---	

[6] OGD-DB Protocols Tracking Database: http://fdswv04385/seltrack/Protocols.ASP. Last accessed 7/6/2015.
[7] OGD Control Documents Database: http://cdsogd1/controls. Last accessed 7/6/2015.

Amendments	---	---

3.5 Waiver Request(s)

Strengths for which waivers are requested, if applicable	100 PPM and 800 PPM
Waiver regulation cited?	21 C.F.R. 320.22(b)(2)
Strengths considered for 21 CFR 320.24 (b)(6)	N/A
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	**WAIVERS GRANTED**
If not then why?	N/A

3.6 Deficiency Comments

None

3.7 Recommendations

The Division of Bioequivalence II (DB II) agrees that the information submitted by Praxair Distribution, Inc. demonstrates that Nitric Oxide Gas for Inhalation, 100 PPM and 800 PPM, meets the requirements specified under Section 21 CFR § 320.22 (b) (2). The DB II recommends that the waiver of in vivo bioequivalence testing requirements be granted for the test product.

3.8 Comments for Other OGD Disciplines

Discipline	Comment
--	--

3 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

(b) (4)

Are the amounts of all inactive ingredients based on Maximum Daily Dose (MDD) within IIG (per unit) limits?	YES
If no, are they all above/within IIG (per day) limits?	N/A
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)?	N/A
Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	YES

Comments:

1. The drug product is administered by inhalation as a gas and is available in two strengths (100 and 800 ppm).
2. The drug product contains an active ingredient in the same dosage form as the RLD.
3. It contains no inactive ingredient or other change in formulation from RLD formulation that may significantly affect the inhalation of the active moiety from the drug product, as a result, the systemic absorption of the active ingredient through the lungs can be expected to be the same as the RLD.
4. All inactive ingredients are the same as the amounts used in RLD. Therefore, the formulation of the test and reference products are qualitatively (Q1) and quantitatively (Q2) the same.
5. Nitric oxide (NO) is the active ingredient and the drug product is a gaseous blend of nitric oxide and nitrogen (N_2) (0.01% and 99.99%, for 100 ppm; and 0.08% and 99.92%, respectively, for 800 ppm). The drug product is supplied in aluminum cylinders as a compressed gas under high pressure and is administered by inhalation in combination with a breathing gas.

The test formulation is acceptable.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 207141

APPLICANT: Praxair Distribution, Inc.

DRUG PRODUCT: Nitric Oxide Gas for Inhalation, 100 PPM and 800 PPM

The Division of Bioequivalence II (DBII) has completed its review and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Ethan M. Stier, Ph.D.
Director, Division of Bioequivalence II
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.2 Outcome Page

ANDA 207141

Completed Assignment for 207141 ID: 26202

Reviewer: Vivian, Diana **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Nitric Oxide Gas for Inhalation Waiver, 100 PPM and 800 PPM, Praxair Distribution Inc.

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
26202	5/20/2014	Other (REGULAR)	Waiver Oral Solution	2	2
				Total:	2

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA207141Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ANDA 207141

DISCIPLINE REVIEW LETTER

ICON Clinical Research LLC
U.S. Agent for: Praxair Distribution, Inc.
79 TW Alexander Drive
4401 Research Commons, Suite 300
Durham, NC 27709

Attention: Amy Kneifel
Director, Regulatory Affairs, ICON Clinical Research

Dear Ms. Kneifel:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on May 20, 2014, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Nitric Oxide Gas for Inhalation, 100 ppm and 800 ppm.

We have concluded the Labeling review of this ANDA and have identified the following initial deficiencies:

Labeling Deficiencies determined on September 6, 2018 based on your submission(s) received August 21, 2018:

1. CONTAINER LABEL
    a. When addressing the Labeling deficiencies communicated to you through the discipline review letter dated August 13, 2018, it appears that you used the original version of the container labels rather than the most recent container labels. Therefore, some of the previous corrections you made based on previous agency comments have been lost in your container labels submitted on August 21, 2018. Therefore, we ask that you readdress the following deficiencies which were communicated to you on March 2, 2017:
        i. Increase the prominence of "for inhalation" from "nitric oxide for inhalation" to be in line with the reference listed drug label. (b) (4)
        ii. Increase the prominence of the middle portion of the NDC number to help differentiate each product within this product line (i.e 59579-101-02) and relocate it to the top of the label.
        iii. Add the barcode according to the 21 CFR 201.25.
    b. (b) (4)

2. PRESCRIBING INFORMATION

(b) (4)

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

If you would like to respond to these initial deficiencies before the end of this review-cycle, we request a complete written response to this discipline review letter as soon as possible. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
LABELING

If you do not submit a complete written response by September 21, 2018, these initial deficiencies may be incorporated in a complete response letter.

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application As contemplated in the

Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified as we complete our review of your entire application.

If you respond to these issues during this review cycle, depending on the timing of your response, we may not be able to consider your response before taking action on your application.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, please contact Julie Call, Labeling Project Manager, at julie.call@fda.hhs.gov or 240-402-8598.

Sincerely,

{See appended electronic signature page}

Julie Call, PharmD
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

Julie Call

Digitally signed by Julie Call
Date: 9/07/2018 02:13:58PM
GUID: 525d9e9d00038c406bce70608a211ab1

ANDA 207141

DISCIPLINE REVIEW LETTER

ICON Clinical Research LLC
U.S. Agent for: Praxair Distribution, Inc.
79 TW Alexander Drive
4401 Research Commons, Suite 300
Durham, NC 27709

Attention: Amy Kneifel
Director, Regulatory Affairs, ICON Clinical Research

Dear Ms. Kneifel:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on May 20, 2014, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Nitric Oxide Gas for Inhalation, 100 ppm and 800 ppm.

Reference is also made to any amendments submitted prior to the issuance of this letter.

We also refer you to the communication sent today, August 13, 2018, by Rinku Patel from the Patent and Exclusivity Team in regards to the patent information.

We have concluded the Labeling review of this ANDA and have identified the following initial deficiencies:

Labeling Deficiencies determined on August 8, 2018 based on your submission(s) dated August 4, 2017, September 11, 2017, October 2, 2017, December 11, 2017, and February 28, 2018:

1. CONTAINER LABELS
   a. (b) (4) Please change the statement to "USE IN ACCORDANCE WITH APPROPRIATE SDS" or provide justification on using a different statement from the RLD.
   b. (b) (4) Please revise the first WARNING statement (b) (4) to "CAUTION: HIGH PRESSURE…".
   c. (b) (4)

2. PRESCRIBING INFORMATION
    a. HIGHLIGHTS OF PRESCRIBING INFORMATION, Limitation statement and Title: We recommend that you use all upper case letters for the proposed proprietary name, NOXIVENT, for this section, only. For example, please see the RLD labeling. (b) (4)
    b. (b) (4)
    c. HOW SUPPLIED: (b) (4) Please change to your own NDC numbers. Please note that your NDC numbers in HOW SUPPLIED need to match the NDC numbers on the CONTAINER LABELS.
    d. (b) (4)

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

If you would like to respond to these initial deficiencies before the end of this review-cycle, we request a complete written response to this discipline review letter as soon as possible. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
LABELING

If you do not submit a complete written response by August 27, 2018, these initial deficiencies may be incorporated in a complete response letter.

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified as we complete our review of your entire application.

If you respond to these issues during this review cycle, depending on the timing of your response, we may not be able to consider your response before taking action on your application.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

If you have any questions, please contact Julie Call, Labeling Project Manager, at julie.call@fda.hhs.gov or 240-402-8598.

Sincerely,

{See appended electronic signature page}

Julie Call, PharmD
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

Julie Call

Digitally signed by Julie Call
Date: 8/13/2018 01:40:26PM
GUID: 525d9e9d00038c406bce70608a211ab1

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 207141

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Praxair Distribution, Inc.
c/o ICON Clinical Research LLC
79 TW Alexander Dr.
4401 Research Commons, Suite 300
Durham, NC 27709

ATTENTION: Amy Kneifel
Director, Regulatory Affairs, ICON Clinical Research

Dear Ms. Kneifel:

Please refer to your Abbreviated New Drug Application (ANDA) dated and received May 20, 2014, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nitric Oxide Gas for Inhalation.

We also refer to your correspondence, dated and received December 12, 2017, requesting review of your proposed proprietary name, Noxivent.

We have completed our review of the proposed proprietary name, Noxivent and have concluded that it is conditionally acceptable.

If your application receives a complete response and six months or more has elapsed between the date you were notified of our decision on your proposed proprietary name and the date you respond to the application deficiencies, please submit a new request for review of your proposed proprietary name when you respond to the application deficiencies. See the Guidance for Industry, Contents of a Complete Submission for the Evaluation of Proprietary Names, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf

If any of the proposed product characteristics as stated in your December 12, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Darrell Lyons, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4092. For any other information regarding this application, contact Joe Shin, Regulatory Project Manager in the Office of Generic Drugs, at (240) 402-6259.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
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/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
01/30/2018

Approval Type: ☒ **FULL APPROVAL** ☐ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)**

RPM: Joe Shin Team Leader: Joe Shin

☐ **PI** ☒ **PII** ☐ **PIII** ☒ **PIV** (*eligible for 180 day exclusivity* ☒ **Yes** ☐ **No**) ☒ **MOU** ☒ **RX or** ☐ **OTC**

ANDA #: 207141 Applicant: Praxair Distribution, Inc.
Established Product Name: Nitric Oxide Gas for Inhalation, 100 ppm and 800 ppm / Proprietary name: Noxivent

Basis of Submission (RLD): N020845; INOmax for Inhalation, 100 ppm and 800 ppm; Mallinckrodt Hospital Products IP Limited

Basis Of Submission Discontinued? Yes ☒ **(For 100 ppm strength only)** No ☐

If yes, has FR published indicating the Agency determined the product was not withdrawn for reasons of safety or effectiveness?

Yes ☒ FR Notice dated **1/21/2016**; Document Citation **81**; FR. **3430** (Example: 78 FR 67365)

No ☐ Consult completed but not yet published in FR

(Is ANDA based on an approved Suitability Petition? ☐ Yes ☒ No, if yes, use SP language in template)

Does the ANDA contain REMS? ☐ Yes ☒ No *(If YES, initiate approval action 6 weeks prior to target action date)*

Regulatory Project Manager Evaluation: **Date: 9/18/2018**

☒ Date (Received) Acceptable for Filing -- Date **5/20/2014**

☐ Date last Complete Response (CR) letter was issued -- Date **N/A**

☐ Previously reviewed and tentatively approved (if applicable) --- Date **N/A**

YES	NO		
☐	☐	All submissions have been reviewed and relevant disciplines are adequate and finalized in the platform (Date or N/A)	
		Date of Acceptable Bioequivalence **9/17/2018** • Date of BE Guidance (if any) **N/A** Date of Acceptable Labeling **9/28/2018** • Date of last RLD labeling update **10/9/2015** Date of Acceptable Quality **9/24/2018** • DMF No(s). **See notes section below** Date(s) Acceptable **N/A** • No outstanding DMF review amendments ☒ • Date of Acceptable Overall Manufacturing Inspection **4/16/2017**	If applicable: Date of Acceptable Microbiology **N/A** Date of Acceptable Clinical Review **N/A** Date of Acceptable Dissolution **N/A** Date of Acceptable REMS **N/A**
☒	☐	**MMA:** All amendments submitted to the Agency on or after December 5, 2016 contain (1) a patent certification or section viii statement, (2) a recertification, or (3) a verification statement per 21 CFR 314.96(d).	
☐	☒	Are consults pending for any discipline?	
☒	☐	OSIS Clinical Endpoint and Bioequivalence Site Inspections are acceptable? **N/A, Waiver**	
☒	☐	Is there a pending legal or regulatory issue (refer to Policy Alert Tracker)? If YES → OGD Policy Lead confirmed ANDA may proceed ☒; Memo uploaded (if applicable) ☒	
☐	☒	Has there been an amendment providing for a major change in formulation or new strength since filing? If YES→Verify a second filing review was completed (if applicable) and that all disciplines completed new reviews ☐	
☒	☐	Is ANDA a Priority Approval (First generic, drug shortage, PEPFAR, other OGD Communications priorities)? If YES → Email OGD Communications Staff or Division liaison 30 to 60 days prior to approval, Date emailed **8/22/2018**	

Review Discipline/Division and RPM TL Endorsements

☒	☐	Applicable review discipline/division endorsements completed
☒	☐	RPM Team Leader endorsement completed

Additional Notes (if applicable)

Drug substance not available-Was reviewed as part of ANDA. DMF IIIs (3): (b) (4)

(b) (4)-ADQ 6/10/2016, PNR 1/26/2018 Adequate, Proprietary Granted Letter dated 1/30/2018

ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION

1. Division of Legal and Regulatory Support Endorsement

Date: 9/25/2018
Name: RTP

Patent/Exclusivity Certification:
☐ **PI** ☐ **PII** ☐ **PIII** ☒ **PIV** ☒ **section viii**

If Paragraph IV Certification- did applicant:

Notify patent holder/NDA holder:	Yes ☒	No ☐
Was applicant sued w/in 45 days:	Yes ☒	No ☐
Has case been settled:	Yes ☒	No ☐
Applicant addressed all listed exclusivities	Yes ☒	No ☐
Do the patent and exclusivity certifications align?	Yes ☒	No ☐
Have there been any revisions to the use code since the original submission?	Yes ☐	No ☒

RLD = **Inomax** NDA# **20845** ☒ **RX or** ☐ **OTC**
Date Checked in Orange Book#: **9/25/2018**

Type of Letter:
☒ APPROVAL
☐ TENTATIVE APPROVAL
☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH)

LETTER RECOMMENDED FOR DRUGS@FDA Yes ☒ No ☐

Forfeiture Information
Is a forfeiture memo needed for the first applicant: Yes ☒ No ☐
If yes, the date forfeiture memo was completed
Date _____ ANDA # _____

180 Day Exclusivity Information
Is applicant eligible for 180 day exclusivity Yes ☒ No ☐
☒ Sole
☐ Shared
ANDA Exclusivity for each strength: Yes ☐ No ☐
Which strength(s) eligible _____

Comments: BOS=Inomax NDA 20845. ANDA submitted on 5/20/2014 with a split certification with respect to the '904 patent, PIV (drug product, claims 1-10 and 16) and section viii statement associated with U-1226 [A method of providing a predetermined concentration of NO to a patient], split certification with respect to the '210 patent, PIV (drug product, claims 1-11) and section viii statement associated with U-1453 [A method of treating hypoxic respiratory failure by verifying gas information of NO prior to delivery to a patient], PIV the '284 patent, which only has a method of use claims associated with U-1286 [A method of reducing the risk of pulmonary edema in patients in need of treatment with inhaled NO]), PIV the '163 patent, which contains method of use claims associated with U-1286 [A method of reducing the risk of pulmonary edema in patients in need of treatment with inhaled NO]) and PIV the '209 patent (only listed as containing drug product claims) and PIII certifications to the '083 patent (expired on 5/22/2014), '693 patent (expired on 6/13/2017), '504 patent (expired on June 13, 2017), and '846 patent (expired on May 16, 2017), PII certification to the '359 patent and '827 patent, section viii statement to the '966 patent associated with U-1286 [A method of reducing the risk of pulmonary edema in patients in need of treatment with inhaled NO].
ANDA ack for filing with a PIV on 5/20/2014 for Nitric Oxide for Inhalation, 100 ppm and 800 ppm (LO dated 12/18/2014). [Tentative Approval Date needed in order to secure 180 day exclusivity : 11/20/2016]

Patent amendment rec'd on 11/12/2014 (pre-filing): In response to an email communication dated 10/31/2014 from Division of Filing Review, Praxair updated their patent amendments to include all patents listed in Orange Book. ***New*** PIV certification to the '741 patent and '112 patents (both listed as method of use patents only) associated with U-1286 [A method of reducing the risk of pulmonary edema in patients in need of treatment with inhaled NO]; ***new*** split certification with respect to the '6794, PIV (drug product) and section viii statement associated with U-1226 [A method of providing a predetermined concentration of NO to a patient], and ***new*** split certification to '795 patent, PIV (drug product) and section viii statement associated with U-1226 [A method of providing a predetermined concentration of NO to a patient]. Addressed unexpired pediatric exclusivity that expired on June 21, 2014 and M-132 (revisions to the clinical trials section in the inomax label to reflect results from the pediatric study reports) expired on December 21, 2013. Additionally, in response to a deficiency "your patent certification to

the '966, '284, and '163 patents are not congruent as they share the same use code, U-1286. Please revise." Praxair ***revised*** from a section viii statement to PIV with respect to the '966 patent associated with U-1286 [A method of reducing the risk of pulmonary edema in patients in need of treatment with inhaled NO]

Patent amendment rec'd on 1/21/2015: In accordance with 21 CFR 314.95(e), Praxair provides the USPS certified mail receipts to document receipt of notice to INO Therapeutics in Hampton, NJ signed and delivered on 1/9/2015; (b) (4) signed and delivered on 1/9/2015 in (b) (4) signed and delivered on 1/7/2015. [30 month stay: 7/9/2017]

Patent amendment rec'd on 2/19/2015 (paper submission): On 2/19/2015 suit filed by INO Therapeutics LLC, Ikaria Inc with respect to the '966, '284, '163, '741, '112, '904, '209, '6794, '795 and '210 patents in the United States District Court of District of Delaware, civil action no 15-170-GMS. A copy of compliant was provided. Note, the '741, '112, '6794, '795 patents were not listed at the time of Praxairs's original submission, therefore these patents did not give rise to the statutory 30-month stay of approval of this ANDA, but a stay was in effect due to the timely filed litigation on the '966, '284, '163, '904, '209 and '210 patents.

Patent amendment rec'd on 5/5/2016: Praxair provides corrections to previously submitted patent certifications with respect to the '504, '693 and '846 patents, certifications were revised to denote the correct expiration date. ***New*** split certification with respect to the '802 (only for the 800 ppm strength), PIV (drug product, claims 1-9) and section viii statement associated with U-1226 [A method of providing a predetermined concentration of NO to a patient], ***new*** split certification with respect to the '911 (only for the 800 ppm strength), PIV (drug product, claims 1-9) and section viii statement associated with U-1824 [A method of providing NO therapy to a patient by verifying gas information of NO prior to delivery to a patient], ***new*** PIV certification to the '9794 patent (for the 800 ppm strength only) associated with U-1823 [A method of providing NO therapy to a patient by compensating long-term sensitivity drift of electrochemical gas sensors used in systems for delivering therapeutic NO to a patient].

Patent amendment rec'd on 5/6/2016: Notification that notice letter has been provided to each person identified under 314.95(a) and that the notice met the content requirements under 314.95(c).

Patent amendment rec'd on 5/20/2016: In accordance with 21 CFR 314.95(e), Praxair provides the USPS certified mail receipts to document receipt of notice for the '802, '911, '9794 patents to INO Therapeutics in Hampton, NJ signed and delivered on a 5/10/2016; Mallinckrodt Hospital Products, signed and delivered on 5/16/16 in St. Louis, MO, to Mallinckrodt Pharmaceuticals in Hampton, NJ signed and delivered on 5/10/2016.

Patent amendment rec'd on 7/5/2016: To address an RLD label change from October 2015, Praxair submitted updated labeling and revised the section viii statements for '904 [U-1226], '210 [U-1453], '6794 [U-1226], and '795 [U-1226]. OGDP concluded that updates to the section viii statement did not constitute a revision to patent certifications pursuant to 314.94(a)(12)(viii).

Patent amendment rec'd on 8/15/2016: Praxair provides corrections to previously submitted patent certifications. The initial submitted certification for '210 patent had a transcription error in the listed patent number (original stated 85**3**7210, ***revised*** to 85**7**3210). Also, the initial submission certification for the '163 patent misidentified the listed patent number in the body of the certification. OGDP concluded that while these errors were not minor in nature, the compliant ensures that notice was sent to the correct patent holder/NDA holder.

Patent amendment rec'd on 8/29/2016: ***New*** split certification with respect to the '993 (only for the 800 ppm strength), PIV (drug product, claims 1-5) and section viii statement associated with U-1824 [A method of providing NO therapy to a patient by verifying gas information of NO prior to delivery to a patient]. The ***revised*** patent certifications include the section viii statement with proposed label carve-outs for the method of use claims in '911 patent and the '802 patent to track the current Inomax label. OGDP concluded that updates to the section viii statement for the '802 and '911 patents did not constitute a revision to patent certifications pursuant to 314.94(a)(12)(viii).

Patent amendment rec'd on 9/15/2016: In accordance with 21 CFR 314.95(e), Praxair provides the USPS certified mail receipts to document receipt of notice for the '993 patent to INO Therapeutics in Hampton, NJ signed and delivered on a 5/10/2016; Mallinckrodt Hospital Products, signed and delivered on 9/6/16 in St. Louis, MO, to Mallinckrodt Pharmaceuticals in Hampton, NJ signed and delivered on 9/1/2016 (x2) (b) (4) delivery confirmations were also provided, to INO Therapeutics in Hampton, NJ signed and delivered on an 8/31/2016; Mallinckrodt Hospital Products, signed and delivered on 8/31/2016 in Hazelwood, MO, to Mallinckrodt Pharmaceuticals in Hampton, NJ signed and delivered on 8/31/2016 (x2)

Patent amendment rec'd on 3/5/2017: In response to an easily correctable deficiency (ECD) letter dated 10/31/2014 from

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[redacted]

entered a judgment on September 5, 2017 in Praxair's favor on all issues in the patent litigation brought against by Mallinckrodt. Specifically, the court determined that all patents at issue in the litigation were either invalid or had not been infringed. Accordingly, section viii statements would no longer be required for the patents that are referenced in Question 1, and omission of any language associated with these use codes in Praxair's ANDA labeling is not required.

Patent amendment rec'd on 2/28/2018: New PIV certification with respect to the '570 (only for the 800-ppm strength), PIV certification (listed as method of use patent only) to claims associated with [U-2148 A method of providing NO therapy to a patient by measuring and displaying an indication of the calculated delivery concentration of nitric oxide as compared to the desired delivery concentration of NO]. Praxair's submitted proposed labeling same as the RLD labeling except for changes Praxair stated were permitted pursuant to 314.94(a)(8)(iv) (allowing the applicant's proposed labeling to differ from the RLD labeling by omitting aspects of the RLD labeling protected by patent). Specifically, Praxair updated its proposed labeling to delete any reference to the INOmax DSIR device, which is the subject of the newly listed '570 patent.

Patent amendment rec'd on 3/27/2018: In accordance with 21 CFR 314.95(e), Praxair provides the USPS certified mail receipts to document receipt of notice to INO Therapeutics in Hampton, NJ signed and delivered on a 5/10/2016; Mallinckrodt Hospital Products, signed and delivered on 3/5/2018 in St. Louis, MO, Mallinckrodt Hospital Products, signed and delivered on 3/5/2018 in Hazelwood, MO (x2), to Mallinckrodt Pharmaceuticals in Bedminster, NJ signed and but no documentation of delivery, to

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[redacted] signed but no documentation of delivery. It's permissible not to request documentation of delivery as this patent does not give rise to 30 month stay.

Email communication to Mike Skrjanc from Rinku Patel on 8/13/2018: In short, the Patent and Exclusivity Team requested (1) a copy of the judgment that was entered on September 5, 2017 in the United States District Court of District of Delaware, case no. 15-170-GMS; (2) notification as to whether or not that judgment was appealed; and (3) the status of the patent litigation regarding the '904 and '210 patents. (4) FDA acknowledgement that although Praxair stated that they intended to withdraw their section viii statements indicating that they are seeking approval for the methods of use described in the '904 (U-1226), '6794 (U-1226), '795 (U-1226), '802 (U-1226), '210 (U-1453), '9794* (U-1823), '911 (U-1824), and '993 (U-1824) patents, FDA noted that this has not occurred because they did not submit updated patent certification statements to this effect. Upon further review of the ANDA, Praxair's current proposed labeling, and the relevant record, the Agency determined that section viii statements are appropriate for addressing the method-of-use claims associated with the U-1226, U-1453, and U-1824 use codes for the above-referenced patents. Accordingly, we asked Praxair to amend or revise their August 4, 2017 and September 11, 2017 communications to indicate that they do not intend to withdraw their section viii statements for these patent use codes.

(please refer to Memo to File re: Nitric Oxide for Inhalation Patent Certification dated 8/16/2018) *We acknowledged that on May 5, 2016, Praxair submitted to their ANDA a paragraph IV certification certifying that the '9794 patent, which expires July 06, 2031 was "invalid, unenforceable, or will not be infringed by the manufacture, use or sale of NoxiventTM for which this application is submitted." This patent was erroneously identified by FDA in the above-referenced July 28, 2017, communication as one to which Praxair provided a section viii statement. (5) Under unique circumstances of their ANDA and these use codes, it is appropriate to submit a revised patent amendment with section viii statements for the '570 patent and for the method-of-use claims of the '9794 patent. We asked Praxair to submit a revised patent certification in light of these circumstances. (please refer to Memo to File re: Nitric Oxide for Inhalation Patent Certification dated 8/16/2018)
Patent amendment rec'd on 8/20/2018: In accordance with 21 CFR 314.107(e), Praxair provided a copy of the judgment entered on September 5, 2017 for 1:15-cv-00170 finding the '966, '284, '741, '163, and '112 are invalid under 35 USC 101, Praxair does not infringe, patents '209, '6794, '795, '911, and '802 and does not infringe the '9794 patent. A copy of the corresponding memorandum opinion dated September 5, 2017 was also submitted. Praxair confirmed with suitable documentation denoting there is no pending litigation with regard to the '904 and '210 patents because Mallinckrodt dropped those patents from its case shortly before trial. A copy of District Court's Minute Order dated January 25, 2017 requiring Mallinckrodt to reduce the number of asserted patents and claims for trial, and subsequent e-mail correspondence dated January 27, 2017 from Mallinckrodt's counsel David Callahan of Latham & Watkins LLP responding to the Court's Order identifying the remaining patents and claims that would be tried, and which does not mention the '904 or '210 patents were enclosed. Lastly, Praxair notes that the judgment was appealed to the Federal Circuit and is awaiting scheduling for the oral argument, Mallinckrodt opted not to appeal the district court's non-infringement judgment for the '9794 patent, so that aspect of the district court's judgment is final. Copies of the appeal docket dated October 10, 2017 and Mallinckrodt's appeal brief dated January 25, 2018 were enclosed. Additionally, Praxair amended its communications on August 4, 2017 and September 11, 2017 to clarify that Praxair does not intend to withdraw its section viii statements for the '904, '6794, '795, '802, '210, '9794, '911, and '993 patents. Therefore, the original split certifications to these patents remain intact. Lastly, Praxair submitted section viii statements for the '570 patent and for the method-of-use claims of the '9794 patent pursuant to 314.94(a)(12)(iii). With regard to the '9794 patent, Praxair confirms that it maintains the paragraph IV certification for the non-method-of-use claims as stated in its May 5, 2016 and March 15, 2017 submissions.

The Agency has determined that Mallinckrodt's Nitric Oxide 100 ppm for Inhalation, was not withdrawn from sale for reasons of safety or effectiveness. FDA published this determination in the Federal Register (81 FR 3430; January 21, 2016).

Praxair was the first applicant to file a PIV certification for these drug products on 5/20/2014. To retain eligibility for 180-day exclusivity this ANDA must have been TA'd within 30 months of ANDA submission, on November 20, 2016. This ANDA was not tentatively approved or approved within this time.

Praxair has addressed all unexpired patents and exclusivities by providing a section viii statement to '570 patent, PIV certifications to '966 (U-1286), '284 (U-1286), '163 (U-1286), '741 (U-1286), '112 (U-1286) and '209; split certification to '802 (U-1226), '904 (U-1226), '6794 (U-1226), '795 (U-1226), '993 (U-1824), '911 (U-1824), '9794 (U-1823), and '210 (U-1453). Judgment was entered on September 5, 2017 for 1:15-cv-00170 on Praxair's original suit and litigation finding the '966, '284, '741, '163, and '112 are invalid under 35 USC 101, Praxair does not infringe, patents '209, '6794, '795, '911, and '802 and does not infringe the '9794 patent. Note, the '741, '112, '6794, '795, '802, '9794, '911, '993, patents were not listed at the time of Praxairs's original submission, therefore these patents did not give rise to a statutory 30-month stay of approval of this ANDA.

Based on the foregoing reasons, this ANDA is eligible for immediate Full Approval with punt language regarding eligibility for 180-day exclusivity.

180 Day Exclusivity Status/Landscape: Praxair was the first applicant to file a PIV certification for these drug products on 5/20/2014 to '209, '210, '966, '904, '284, and '163 patents. To retain eligibility for 180-day exclusivity this ANDA must have

been TA'd within 30 months of ANDA submission, by November 20, 2016. This ANDA was not tentatively approved or approved within this time. Therefore, this ANDA will be approved with punt language regarding eligibility for 180-day exclusivity.
Citizen Petitions Impact: none
First Legally Approvable Date: 8/20/2018, the date corresponding to submission court decision in patent litigation.
If Tentative Approval, anticipated full approval date:

Appears this way in original

2. Final Decision

Date: 10/2/2018
Name: VSS/ODD

ANDA received on **5/20/2014** for the **100 ppm and 800 ppm** strengths
RTR'd? Yes ☐ No ☒ If yes, RTR'd on Enter date
Priority Status? Yes ☒ No ☐ If yes, prioritization factor is **first generic**
Basis of Submission (RLD)

Drug Name **INOmax**
NDA # **20845**
Applicant Name **INO Therapeutics**

☒ Verified the following:

1. Completion of the following endorsement tasks, if applicable:
   a. Division of Legal and Regulatory Support Endorsement
   b. Paragraph IV Evaluation
   c. REMS Endorsement
   d. Quality Endorsement
   e. Bioequivalence Endorsement
   f. Clinical-Bioequivalence Endorsement
   g. Labeling Endorsement
   h. RPM Team Leader Endorsement
2. All applicable endorsement tasks are completed in the platform within 30 days of potential approval.
3. No updates to patents and/or exclusivities in Orange Book since the Division of Legal and Regulatory Support Endorsement
4. No Reference Listed Drug updates at Drugs@FDA since the Labeling Endorsement
5. No issues listed on the current version of the Policy alert list since the RPM Team Leader Endorsement
6. No new alerts in the Submission Facility Status View since the Quality Endorsement
7. Overall Inspection Recommendation of Approve of the current project (see screenshot below)

T

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REFERENCES / ASSOCIATED DOCUMENTS

4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA

REVISION HISTORY

Version	Effective date	Name	Role	Summary of changes
01	10/1/2014	Heather Strandberg	Author	New Form
02	10/03/2017	Kevin Denny	Reviser	• Update form to reflect revisions to SOP 4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA, Version 04 • Remove content adequately captured in the platform • Update information captured in the Division of Legal and Regulatory Support Endorsement section • Other minor administrative corrections to format and content
03	1/24/18	Kevin Denny	Reviser	• Update Final Decision section

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 207141

INFORMATION REQUEST

ICON Clinical Research LLC
Attention: Amy Kneifel
U.S. Agent for Praxair Distribution, Inc.
Director, Regulatory Affairs
79 TW Alexander Dr.
4401 Research Commons, Suite 300
Durham, NC 27709

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated 05/20/2014, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Noxivent, Nitric Oxide, 800 ppm and 100 ppm.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than **02/01/2018** in order to continue our evaluation of your ANDA.

Comments and information requests:

A. Drug Product

1. Information describing your approach to the control of elemental impurities as per ICH Q3D could not be located. Please provide a summary of your risk assessment, any test data relied upon, and your conclusions regarding any necessary control. The risk assessment summary should include a discussion of the observed (or projected) levels of elemental impurities compared to the relevant PDEs and the control Thresholds ((b) (4)% of the corresponding PDE). Please refer to ICH Q3D, Section 5, "Risk Assessment and Control of Elemental Impurities" for additional information. You may also consult the ICH Q3D Training Module 5, "Risk Assessment," Slide 17, for a summary of the risk assessment documentation recommended for submission in the Application. The training module are available at www.ich.org.

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently

identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

If you have any questions, please contact Jonee Mearns, Regulatory Business Process Manager, at 240-402-0910.

Sincerely,

{See appended electronic signature page}

Jonee Mearns, MSN, RN
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Jonee Mearns

Digitally signed by Jonee Mearns
Date: 1/22/2018 12:07:13PM
GUID: 558850a9004db76de4202aba3846e509

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 14, 2017

FROM: Joe Shin
Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

TO: Abbreviated New Drug Application (ANDA) 207141, Praxair Distribution, Inc., for Nitric Oxide Gas for Inhalation

This memorandum documents certain facts that form the basis for the denial of Mallinckrodt Pharmaceuticals's citizen petition dated July 19, 2017 (FDA-2017-P-4360). As of December 14, 2017, ANDA 207141 for Nitric Oxide Gas for Inhalation remains pending.

ANDA 207141 was received for review on May 20, 2014. As of December 14, 2017, the drug product and labeling discipline-specific reviews remain pending and must be completed before a review of the application can be completed. In addition, as of December 14, 2017, the bioequivalence and drug substance discipline-specific reviews of this application have been completed. Based on current information, the review of the application will not be completed when the petition response is due under section 505(q) of the Federal Food, Drug, and Cosmetic Act.[1]

[1] The completion of a review cycle and the issuance of a Complete Response or discipline review letter do not indicate that review of the application has been completed for purposes of determining whether it is appropriate to respond substantively to a petition governed by section 505(q) raising an issue that is directly applicable to the pending ANDA.

Joe Shin

Digitally signed by Joe Shin
Date: 12/14/2017 01:46:19PM
GUID: 548b4db50000100809e4a9b42a823e26

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 12/07/2017 07:54:01 AM
To: mike_skrjanc@praxair.com
CC: amy.kneifel@iconplc.com
BCC: joe.shin@fda.hhs.gov
Subject: MMA Verification for ANDA 207141

ANDA 207141

ICON Clinical Research LLC
U.S. Agent for Praxair Distribution, Inc.
79 TW Alexander Dr.
4401 Research Commons, Suite 300
Durham, NC 27709

Dear Mr. Skrjanc,

This is in reference to your abbreviated new drug application (ANDA) 207141 for Nitric Oxide Gas for Inhalation, 100 ppm and 800 ppm. Your amendments dated March 15, May 26, August 4, September 11, and October 2, 2017, were submitted to the Agency on or after December 5, 2016, the effective date of the final rule on Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule, 81 FR 69580 (Oct. 6, 2016). This rule revised 21 CFR 314.96(d), which concerns amendments to unapproved ANDAs. In part, the rule now requires an amendment to an unapproved ANDA to contain an appropriate patent certification or section viii statement described in 21 CFR 314.94(a)(12), or a recertification for a previously submitted paragraph IV certification, if approval is sought for changes described in any of the following types of amendments:

(i) To add a new indication or other condition of use;
(ii) To add a new strength;
(iii) To make other than minor changes in product formulation; or
(iv) To change the physical form or crystalline structure of the active ingredient.

If an amendment to an unapproved ANDA does not contain a patent certification or section

viii statement, or a recertification, the applicant must verify that the proposed change described in the amendment is not one of the types of amendments described above.

Your amendment is deficient under 21 CFR 314.96(d). It currently does not contain (1) a patent certification or section viii statement, (2) a recertification, or (3) a verification statement. As appropriate, please submit a patent certification or section viii statement, a recertification, or a verification statement (referencing your amendments dated March 15, May 26, August 4, September 11, and October 2, 2017). If you intend to submit a patent certification or section viii statement, or a recertification, any such submission should bear prominent identification as to its contents, e.g. “Patent Information.” If you intend to submit a verification statement with regard to this amendment, please submit a correspondence to the unapproved ANDA titled "Amendment Verification Statement."

For future reference, to comply with the requirement of 21 CFR 314.96(d), we recommend that a patent certification or section viii statement, or recertification be referenced in the cover letter of an amendment to an unapproved ANDA and included in module 1.3 of such unapproved ANDA. Each submission of such patent information should bear prominent identification as to its contents, e.g. “Patent Information.” We recommend that a verification statement be included in the cover letter of an amendment to an unapproved ANDA. For inquiries related to this requirement please contact the Patent and Exclusivity Team at CDER-OGDPET@fda.hhs.gov.

If you have any questions, call Regulatory Project Manager, Joe Shin, at (240) 402-6259.

Sincerely,

Joe Shin, PharmD
Division of Project Management
Office of Regulatory Operations
OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

EASILY CORRECTABLE DEFICIENCY

ANDA 207141

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Praxair Distribution, Inc.
U.S. AGENT: ICON Clinical Research LLC

TEL: 919-294-2241

ATTN: Amy Kneifel

EMAIL: amy.kneifel@iconplc.com

FROM: Sunny Pyon

FDA CONTACT EMAIL:
Sunny.Pyon@fda.hhs.gov

Dear Ms. Kneifel:

This communication is in reference to your abbreviated new drug application (ANDA) dated May 20, 2014, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nitric Oxide Gas For Inhalation, 100 ppm and 800 ppm.

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies within ten (10) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
LABELING
REFERENCE # 16614221

If you do not submit a complete response within ten (10) U.S. business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments.

If you are unable to submit a complete response within ten (10) U.S. business days, please contact the Labeling Project Manager immediately so a complete response may be issued if appropriate.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review.

1 Page has been withheld in full as b4 (CCI/TS) immediately following this page

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

If you have questions regarding these deficiencies or would like acknowledgement of receipt of your amendment upon submission, please contact the Labeling Project Manager, Sunny Pyon, at Sunny.Pyon@fda.hhs.gov.

Sincerely,

Sunny Pyon, Pharm.D.
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 207141

INFORMATION REQUEST

ICON Clinical Research LLC
U.S. Agent for Praxair Distribution, Inc.
Attention: Amy Kneifel
Director, Regulatory Affairs, ICON Clinical Research
79 TW Alexander Dr.
4401 Research Commons
Suite 300
Durham, North Carolina 27709

Dear Amy Kneifel:

Please refer to your Abbreviated New Drug Application (ANDA) dated May 20, 2014, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Nitric Oxide 800 ppm, 100 ppm.

We also refer to your submission dated August 22, 2016, August 29, 2016, September 15, 2016, February 23, 2017, and March 15, 2017.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later **June 4, 2017** in order to continue our evaluation of your ANDA.

Drug Substance Deficiencies:

1. (b) (4)

2.

Drug Product Deficiencies:

1. We acknowledge your response in your amendment dated 08-22-2016, for the assay specification for release and stability of your drug product. The Agency recommends you to revise the assay specification range for the release and stability of your drug product per earlier deficiency and provide response with justification based on available data.

2. You mentioned in your Amendment dated 08-22-2016 that the stability data for 9 12-18 month test points was not obtained due to contract testing laboratory's equipment failure and a root cause of the failure was ultimately identified and resolved following the 18-month test point. Please provide the investigation report with your analysis for the root cause and any corrective actions and preventive actions (CAPA) that you have implemented to mitigate the risk.

If you do not submit a complete response by June 4, 2017, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

Please note, submitting unsolicited information in your response to this Information Request may have an impact on your Target Action Date.

All items listed on this Information Request shall be addressed in its entirety, any partial or incomplete response will not be reviewed and the same deficiency list will be issued to you again as part of the Complete Response Letter issued by OGD. Please note that a commitment to address an item in the future is not considered satisfying the Information Request.

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
Drug Product

If you have any questions, please contact me, Regulatory Business Process Manager, at 240-402-0910.

Sincerely,

{See appended electronic signature page}

Jonee Mearns, MSN, RN
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality

Center for Drug Evaluation and Research

Appears this way in original

Jonee Mearns

Digitally signed by Jonee Mearns
Date: 5/05/2017 01:28:43PM
GUID: 558850a9004db76de4202aba3846e509

EASILY CORRECTABLE DEFICIENCY

ANDA 207141

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Praxair Distribution, Inc. TEL: 919-294-2241

ATTN: Amy Kneifel EMAIL: amy.kneifel@iconplc.com

FROM: Danielle Russell FDA CONTACT EMAIL: Danielle.Russell@fda.hhs.gov

Dear Amy Kneifel:

This communication is in reference to your abbreviated new drug application (ANDA) dated 5/20/2014 & 7/5/2016, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nitric Oxide Gas For Inhalation, 100 ppm and 800 ppm .

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies within ten (10) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
LABELING
REFERENCE # 13471401

If you do not submit a complete response within ten (10) U.S. business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments.

If you are unable to submit a complete response within ten (10) U.S. business days, please contact the Labeling Project Manager immediately so a complete response may be issued if appropriate.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review.

We have completed our review and have the following comments:

LABELING:

Labeling Deficiencies determined based on your submissions dated 5/20/2014 & 7/5/2016:

1. GENERAL COMMENTS

   a. Please provide most current patent certifications to all patents listed in the orange book. If you are doing a split certification to a single patent, we ask that you indicate your intention clearly in the same document.

   b. We ask that you address the marketing exclusivity associated with M-167 (APPROVED FOR REVISIONS TO THE LABELING BASED ON THE CLINICAL STUDY ENTITLED 'BRONCHOPULMONARY DYSPLASIA (BPD) IN PRETERM INFANTS REQUIRING MECHANICAL VENTILATION OR POSITIVE PRESSURE SUPPORT ON DAYS 5 TO 14 AFTER BIRTH') expiring October 9, 2018.

   c. On December 27, 2016, Mallinckrodt Pharmaceuticals submitted a citizen petition to FDA (Docket No. FDA-2016-P-4587), regarding applications that reference Inomax (Nitric Oxide) for Inhalation. The issues raised by this petition are currently under review by the Agency, and FDA has not made a final decision on the issues the petition raises. These deficiency comments included in this communication reflect only our current thinking and this communication does not represent a final decision by the Agency on the issues raised in the pending citizen petition. As such, your labeling may be subject to further revision as we complete our review of the issues the petition raises.

2. CONTAINER LABEL

   a. Increase the prominence of "for inhalation" from "nitric oxide for inhalation" to be in line with the reference listed drug label.

   b. 

   c. Increase the prominence of the middle portion of the NDC number to help differentiate each product within this product line (i.e xxxx-XXX-xxx) and relocate it to the top of the label.

   d. Add the barcode according to the 21 CFR 201.25.

3. PRESCRIBING INFORMATION

4. STRUCTURED PRODUCT LABELING

We note that there is a discrepancy between the package description and the total volume listed in your HOW SUPPLIED section of your package insert labeling. Please revise and/or clarify.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

If you have questions regarding these deficiencies or would like acknowledgement of receipt of your amendment upon submission, please contact the Labeling Project Manager, Danielle Russell, at Danielle.Russell@fda.hhs.gov.

Sincerely,

Danielle Russell, Pharm.D.
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 207141

INFORMATION REQUEST

ICON Clinical Research
Attention: Amy Kneifel
Director, Regulatory Affairs, ICON Clinical Research
U.S. Agent for Praxair Distribution, Inc.
2100 Pennbrook Parkway
North Wales, PA 19454
U.S.A.

Dear Amy Kneifel:

Please refer to your Abbreviated New Drug Application (ANDA) dated May 20, 2014, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Noxivent (Nitric oxide gas for inhalation), 100 ppm and 800 ppm.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than **August 22, 2016** in order to continue our evaluation of your ANDA.

List of the deficiencies:

Chemistry deficiencies:

1. (b) (4)
2.
3.
4.

2 Psges have been withheld in full as b4 (CCI/TS) immediately following this page

3. (b) (4)

4.

5.

6.

If you do not submit a complete response by August 22, 2016, the review will be closed and the listed deficiencies will be incorporated in a COMPLETE RESPONSE correspondence.

All items listed on this Information Request shall be addressed in its entirety, any partial or incomplete response will not be reviewed and the same deficiency list will be issued to you again as part of the Complete Response Letter issued by OGD. Please note that a commitment to address an item in the future is not considered satisfying the Information Request.

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
Chemistry
REFERENCE # 9214257

If you have any questions, please contact Jonee Mearns, Regulatory Business Project Manager, at (240) 402-0910.

Sincerely,

Jonee Mearns, MSN, RN
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 207141

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Praxair Distribution, Inc.
c/o ICON Clinical Research
2100 Pennbrook Parkway
North Wales, PA 19454

ATTENTION: Amy Kneifel
Director, Regulatory Affairs, ICON Clinical Research

Dear Ms. Kneifel:

Please refer to your Abbreviated New Drug Application (ANDA) dated and received May 20, 2014, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nitric Oxide Gas for Inhalation, 100 ppm and 800 ppm.

We also refer to your correspondence, dated and received May 18, 2016, requesting review of your proposed proprietary name, Noxivent.

We have completed our review of the proposed proprietary name, Noxivent and have concluded that it is conditionally acceptable.

If your application receives a complete response and six months or more has elapsed between the date you were notified of our decision on your proposed proprietary name and the date you respond to the application deficiencies, please submit a new request for review of your proposed proprietary name when you respond to the application deficiencies. See the Guidance for Industry, Contents of a Complete Submission for the Evaluation of Proprietary Names, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf

If any of the proposed product characteristics as stated in your May 18, 2016, submission is altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Darrell Lyons, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4092. For any other information regarding this application, contact CAPT Aaron Sigler, Deputy Director in the Division of Project Management, Office of Generic Drugs, at (240) 402-8786.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
07/14/2016

MANDATORY: Send a copy of the consult request form to the Office of Combination Products (OCP) as follows:
--Originating Center: When the consult request is initiated.
--Consulting Center: When the consult is completed.
Email: combination@fda.gov or FAX: 301-847-8619

For additional information: Contact OCP by email or by telephone (301-796-8930) or refer to OCP's intranet page http://inside.fda.gov:9003/ProgramsInitiatives/CombinationProducts/ReviewerTools/default.htm.

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 GHB
Division: Drug and Device combination
Mail Code: HF
Consulting Reviewer Name: Tamara Brewton
Building/Room #:
Phone #: 240-402-2875
Fax
Email Address: Tamara.Brewton@fda.hhs.gov
RPM/CSO Name and Mail Code:

From (Originating Center):
Center: CDER
Division: OLDP/DIRP1
Mail Code: HF 630
Requesting Reviewer Name: Kadum Al Shareffi
Building/Room #: WO75/Rm 5528
Phone#: 240-402-8878
Fax #: 301-595-1275
Email Address: kadum.alshareffi@fda.hhs.gov
RPM/CSO Name and Mail Code: Steven Yang
Requesting Reviewer's Concurring Supervisor's Name: Laxma Nagavelli

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: 12-24-2015

Requested Completion Date: TAD 1-15-2016

Submission/Application Number: ANDA 207141
(Not Barcode Number)

Submission Type: ANDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: ☒Drug-device combination ☐Drug-biologic combination ☐Device-biologic combination ☐Drug-device-biologic combination ☐Not a combination product

Submission Receipt Date: 05-20-2014

Official Submission Due Date: 01-16-2016

Name of Product: Nitric oxide gas

Name of Firm: PRAXAIR

(b) (4)

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

To evaluate the generic applicant (ANDA 207141) gas cylinder valve against the RLD (NDA 20845) valve for their compatibility and inter changeability in the hospital setting. Details and diagrams for both valves are provided in the susbmission as well as shown here.

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

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: ☒ Consultative Review ☐ Collaborative Review

4 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

Reference ID: 3866522

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/s/

KADUM A AL SHAREFFI
12/29/2015

LAXMA R NAGAVELLI
12/29/2015

STEVEN W YANG
01/04/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 09/18/2015 05:37:01 AM
To: amy.kneifel@iconplc.com
CC:
BCC: joe.shin@fda.hhs.gov
Subject: TARGET ACTION DATE NOTIFICATION on ANDA 207141

ANDA 207141

NOTIFICATION --
TARGET ACTION DATE

ICON Clinical Research
U.S. Agent for Praxair Distribution, Inc.
2100 Pennbrook Parkway
North Wales, PA 19454
Attention: Amy B. Kneifel
Director, Regulatory Affairs

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated May 20, 2014, received May 20, 2014, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Noxivent (Nitric Oxide for Inhalation), 100 ppm and 800 ppm.

The Office of Generic Drugs (OGD), Center for Drug Evaluation and Research, Food and Drug Administration (FDA), is notifying you of our internal, administrative TARGET ACTION DATE for the above indicated ANDA.

The Target Action Date is the date by which FDA will strive to provide a communication on this ANDA. A TAD will be considered met if the applicant receives an Approval, Tentative Approval, Complete Response (CR) or a complete set of Informational Requests (IRs) by the action date. A complete set of IRs means that each pending discipline communicated

its comments to the applicant. In that case, the TAD will be met if the last discipline communicates its IR by the action date.

We note that FDA is not required to inform applicants of Target Action Dates, but is providing Target Action Dates at this time as a courtesy to help applicants ascertain when communications may occur for their applications as we implement the Generic Drug User Fee Amendments of 2012 (GDUFA). Notification of a Target Action Date does not constitute a commitment or guarantee that we will take action on your application by the Target Action Date. Any amendments submitted after this notification will affect whether FDA will provide a communication on the application by the Target Action Date.

GDUFA establishes goal dates for the review of ANDAs submitted beginning October 1, 2014. Target Action Dates are not GDUFA goal dates.

The Target Action Date for this ANDA is January 15, 2016.

Please contact your Regulatory Project Manager, Joe Shin at (240) 402-6259 for an additional status update of your application.

Sincerely,

Joe Shin
OFFICE OF GENERIC DRUGS
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 207141

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Praxair Distribution, Inc.
c/o ICON Clinical Research
2100 Pennbrook Parkway
North Wales, PA 19454

ATTENTION: Robert S. Cormack, Ph.D.
Director, Regulatory Affairs

Dear Dr. Cormack:

Please refer to your Abbreviated New Drug Application (ANDA) dated and received May 20, 2014, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Nitric Oxide for Inhalation 100 ppm, and 800 ppm.

We also refer to your correspondence, dated and received July 9, 2014, requesting review of your proposed proprietary name, Noxivent.

We have completed our review of the proposed proprietary name, Noxivent and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your July 9, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact CAPT Louis Flowers, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3158. For any other information regarding this application, contact CAPT Aaron Sigler, Deputy Director in the Division of Project Management, Office of Generic Drugs, at (240) 402-8786.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

LOUIS R FLOWERS
12/18/2014

TODD D BRIDGES
12/18/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 207141

ACKNOWLEDGEMENT
ANDA RECEIPT

ICON Clinical Research
U.S. Agent for: Praxair Distribution, Inc.
2100 Pennbrook Parkway
North Wales, PA 19454
Attention: Robert Cormack, Ph.D.

Dear Robert Cormack:

We acknowledge receipt of your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act.

NAME OF DRUG: Nitric Oxide for Inhalation, 100 ppm and 800 ppm

DATE OF APPLICATION: May 20, 2014

DATE (RECEIVED) ACCEPTABLE FOR REVIEW: May 20, 2014

Reference is made to the information requests dated October 31 and November 25, 2014 and your responses dated November 11 and December 8, 2014.

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

1) Each owner of the patent or the representative designated by the owner to receive the notice

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).
- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.
- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet “PATENT AMENDMENT” with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(5)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.
- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

You must submit a copy of a court order or judgment or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application. If you have further questions you may contact Martin Shimer, Deputy Director (Acting), Division of Legal and Regulatory Support at 240-402-8783.

This application is subject to the provisions of the Generic Drug User Fee Amendments of 2012 (GDUFA). Please identify any related communications with the ANDA number referenced above. If you have any questions, contact Heather Strandberg, Project Manager Team Leader, at Heather.Strandberg@FDA.HHS.GOV or 240-402-9096.

Sincerely,

Ted Palat
Team Leader
Division of Filing Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration