LungFit PH Intended Use and Nitric Oxide Prescribing Information*

Intended Use

The LungFit® PH is intended to deliver nitric oxide (NO), a vasodilator, generated by the device into the inspiratory limb of the patient breathing circuit of a ventilator in a way that provides a constant concentration of nitric oxide, as set by the user, to the patient throughout the inspired breath.

The LungFit® PH provides continuous integrated monitoring of inspired oxygen (O2), nitrogen dioxide (NO2) and nitric oxide (NO), and a comprehensive alarm system.

The LungFit® PH includes an integrated backup NO delivery system that is a completely independent backup NO generating system; it has its own NO generator and gas flow delivery system. The backup flow is delivered at 1 L/min at 220ppm NO to either a ventilator circuit or to a bagging system, depending upon the user selected setting.

The NO from the LungFit PH System 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. (23.0)

Initial U.S. Approval: 2022

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FULL PRESCRIBING INFORMATION: CONTENTS†

DRUG INTERACTIONS

Nitric oxide donor agents such as prilocaine, sodium nitroprusside and nitroglycerine may increase the risk of developing methemoglobinemia. (28.0)

To report SUSPECTED ADVERSE REACTIONS, contact Beyond Air at 1-855-586-4359 and http://www.beyondair.net/contact/, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

*The full Prescribing Information contained within this document is from sections 23 to 34.3 of the LungFit® PH System Operator's Manual. Garden City, NY: Beyond Air, Inc. 2022.

†Sections or subsections omitted from the full Prescribing Information are not listed.

LungFit® PH

23. INDICATIONS FOR USE

The NO from the LungFit PH System 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.

24. CONTRAINDICATIONS

The NO from the LungFit PH is contraindicated in neonates dependent on right-to-left shunting of blood.

25. DOSAGE AND ADMINISTRATION

25.1 Dosage

Term and near-term neonates with hypoxic respiratory failure.

The recommended dose of inhaled nitric oxide gas 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 inhaled nitric oxide therapy.

Doses greater than 20 ppm are not recommended.

25.2 Administration

Measure methemoglobin within 4-8 hours after initiation of treatment with the LungFit PH and periodically throughout treatment.

Monitor for PaO_2 and inspired NO_2 during NO administration.

Avoid abrupt discontinuation of NO. To wean NO down-titrate in several steps, pausing several hours at each step to monitor for hypoxemia.

26. WARNINGS AND PRECAUTIONS ASSOCIATED WITH NITRIC OXIDE (NO)

26.1 Rebound Pulmonary Hypertension Syndrome following Abrupt Discontinuation

Abrupt discontinuation of NO 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 NO therapy immediately.

WARNING: Avoid abrupt discontinuation of NO. To wean NO down, titrate in several steps, pausing several hours at each step to monitor for hypoxemia.

WARNING: Abrupt discontinuation of NO 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 NO therapy immediately.

26.2 Hypoxemia from Methemoglobinemia

Nitric oxide combines with hemoglobin to form methemoglobin, which does not transport oxygen. Methemoglobin levels increase with the dose of NO; it can take 8 hours or more before steady-state methemoglobin levels are attained. Monitor methemoglobin and adjust the dose of NO to optimize oxygenation.

If methemoglobin levels do not resolve with decrease in dose or discontinuation of NO, additional therapy may be warranted to treat methemoglobinemia

26.3 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, assess the delivery system in accordance with the troubleshooting section, and recalibrate the NO_2 sensor. Adjust the dose of NO and/or FiO_2 as appropriate.

26.4 Worsening Heart Failure

Patients with left ventricular dysfunction treated with NO may experience pulmonary edema, increased pulmonary capillary wedge pressure, worsening of left ventricular dysfunction, systemic hypotension, bradycardia and cardiac arrest. Discontinue NO while providing symptomatic care.

27. ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the label:

Hypoxemia [see Warnings and Precautions (26.2)]

Worsening Heart Failure [see Warnings and Precautions (26.4)]

27.1 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. Mortality was similar in the two groups.

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.

27.2 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.

28. DRUG INTERACTIONS

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

29. USE IN SPECIFIC POPULATIONS

29.1 Pregnancy

Pregnancy Category C Animal reproduction studies have not been conducted with LungFit PH. It is not known if nitric oxide gas from the LungFit PH can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. NO is not indicated for use in adults.

29.2 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.

29.3 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. Additional studies conducted in premature neonates for the prevention of bronchopulmonary dysplasia have not demonstrated substantial evidence of efficacy. No information about its effectiveness in other age populations is available.

29.4 Geriatric Use

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

30. OVERDOSAGE

Overdosage with NO 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, NO.

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.

31. DESCRIPTION

Nitric oxide gas generated by the LungFit PH is a drug administered by inhalation. Nitric oxide is a pulmonary vasodilator. Nitric oxide from the LungFit PH is a gaseous blend of nitric oxide and room air (main constituents: nitrogen (78.08%), oxygen (20.95%), argon (0.93%) and carbon dioxide (0.03%).

The generation of NO gas results in the conversion of small amounts of nitrogen and oxygen. The amount of this conversion is dependent on the concentration of nitric oxide, and will be a maximum of 0.08% of nitrogen and oxygen when set to 80 ppm at ventilator flow rates above 50 L/min. This will result in the decrease of nitrogen to approximately 78.00% and oxygen to 20.87% in the carrier gas.

32. CLINICAL PHARMACOLOGY

32.1 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. Nitric oxide 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.

32.2 Pharmacodynamics

<u>Effects on Pulmonary Vascular Tone in PPHN</u>

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, NO improves oxygenation (as indicated by significant increases in PaO_2).

32.3 Pharmacokinetics

The pharmacokinetics of nitric oxide has been studied in adults.

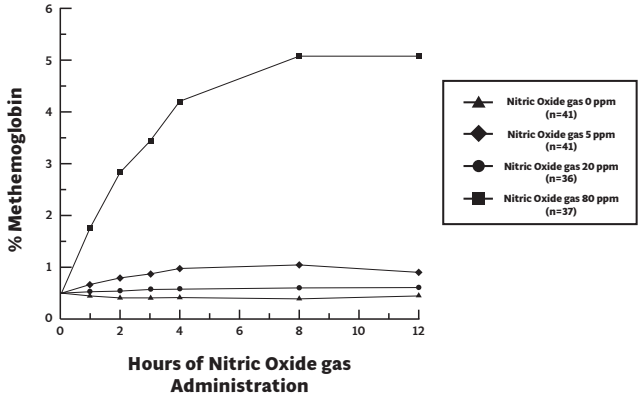
Absorption and Distribution

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 NO are shown in *Figure 54*.

***Figure 54*: Methemoglobin Concentration–Time Profiles**
Neonates Inhaling 0, 5, 20, or 80 ppm Nitric Oxide gas



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 NO groups, but reached approximately 5% in the 80 ppm NO 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.

33. NONCLINICAL TOXICOLOGY

33.1 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.

34. CLINICAL STUDIES

34.1 Treatment of Hypoxic Respiratory Failure (HRF)

The efficacy of NO has been investigated in term and near-term newborns with hypoxic respiratory failure resulting from a variety of etiologies. Inhalation of NO 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.

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.[1] 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*: Sumary 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%)	0.06
ECMO	66 (55%)	44 (39%)	0.014

* Extracoporeal 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 (27.1)*]. 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 248 term and near-term neonates with pulmonary hypertension and hypoxic respiratory failure.[2]

The primary objective of the study was to determine whether NO would reduce the receipt of ECMO in these patients. Hypoxic respiratory failure was caused by MAS (34% in each group), idiopathic PPHN (iNO 25%; control 20%), pneumonia (21% in each group), or RDS (9% in each group). 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 NO (n=126) or nitrogen gas (placebo; n=122) 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 NO or placebo. The primary results from the CINRGI study are presented in *Table 2*.

***Table 2*: Summary of Clinical Results from CINRGI Study**

	Placebo	**NO**	**P value**
ECMO*†	78/122 (64%)	48/126 (38%)	0.001
Death before discharge	13/122 (11%)	10/126 (8%)	0.82

* Extracoporeal membrane oxygenation
† ECMO was the primary end point of this study

Significantly fewer neonates in the NO group required ECMO compared to the control group (38% vs. 64%, $p<0.001$). While the number of deaths before discharge were similar in both groups (NO, 8%; placebo, 11%), the combined incidence of death and/or receipt of ECMO was decreased in the NO group (iNO 50/126 (40%) vs. control 80/122 (66%), $p<0.001$).

Of the 126 patients treated with NO, 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 (27.1)*].

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).

34.2 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 NO (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 NO 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). NO is not indicated for use in ARDS.

34.3 Ineffective in Prevention of Bronchopulmonary Dysplasia (BPD)

The safety and efficacy of NO for the prevention of chronic lung disease [bronchopulmonary dysplasia, (BPD)] in neonates ≤ 34 weeks gestational age requiring respiratory support has been studied in four large, multi-center, double-blind, placebo-controlled clinical trials in a total of 2,600 preterm infants. Of these, 1,290 received placebo, and 1,310 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.

NO for prevention of BPD in preterm neonates ≤ 34 weeks gestational age is not recommended.

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