BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Inhaled Nitric Oxide

Policy #: 440
Latest Review Date: May 2024
Category: Medicine

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000, which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Blue Advantage will treat **inhaled nitric oxide** as a **covered** benefit as a component of treatment of hypoxic respiratory failure in neonates born at more than 34 weeks of gestation.

Blue Advantage will treat **other indications for inhaled nitric oxide** as a **non-covered** benefit and as **investigational**, including, but not limited to:

- Treatment of premature neonates born at less than or equal to 34 weeks of gestation with hypoxic respiratory failure;
- Treatment of adults and children with acute hypoxemic respiratory failure;
- Postoperative use in adults and children with congenital heart disease;
- In lung transplantation, during and/or after graft reperfusion.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

Inhaled nitric oxide (INO), a treatment for neonates who have hypoxic respiratory failure is intended to improve oxygenation, reduce mortality rates, and reduce the need for invasive extracorporeal membrane oxygenation (ECMO). It is also proposed as a treatment for premature infants, critically ill children, adults with respiratory failure, in the postoperative management of children undergoing repair of congenital heart disease and in lung transplantation to prevent or reduce reperfusion injury.

Hypoxic Respiratory Failure

Hypoxic respiratory failure may result from respiratory distress syndrome (RDS), persistent pulmonary hypertension, meconium aspiration, pneumonia, or sepsis.

Treatment

Treatment consists of oxygen support, mechanical ventilation, and induction of alkalosis, neuromuscular blockade, or sedation.

Extracorporeal membrane oxygenation (ECMO) is an invasive technique that may be considered in neonates when other therapies fail. Inhaled nitric oxide (INO) is both a vasodilator and a mediator in many physiologic and pathologic processes. INO has also been proposed for use in preterm infants less than 34 weeks of gestation and in adults.

Also, there are several potential uses in surgery. One is the proposed use of INO to manage pulmonary hypertension after cardiac surgery in infants and children with congenital heart

disease. In congenital heart disease patients, increased pulmonary blood flow can cause pulmonary hypertension. Cardiac surgery can restore the pulmonary vasculature to normal, but there is the potential for complications, including postoperative pulmonary hypertension, which can prevent weaning from ventilation and is associated with substantial morbidity and mortality. Another potential surgical application is the use of INO in lung transplantation to prevent or reduce reperfusion injury.

KEY POINTS:

The most recent literature update was performed through April 1, 2024.

Summary of Evidence

For individuals who are neonates, are term or late preterm at birth, and have hypoxic respiratory failure who receive inhaled nitric oxide (INO), the evidence includes randomized controlled trials (RCTs) and a systematic review. Relevant outcomes are overall survival (OS), hospitalizations, resource utilization, and treatment-related morbidity. Evidence from RCTs and a meta-analysis have supported the use of INO in term or late preterm infants. Pooled analyses of RCT data have found that use of INO significantly reduced the need for extracorporeal membrane oxygenation (ECMO) and the combined outcome of ECMO or death. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are neonates, are premature at birth, and have hypoxic respiratory failure who receive INO, the evidence includes RCTs and systematic reviews. Relevant outcomes are OS, hospitalizations, resource utilization, and treatment-related morbidity. A large number of RCTs have evaluated INO for premature neonates, and most trials have reported no significant difference for primary endpoints such as mortality and bronchopulmonary dysplasia (BPD). Meta-analyses of these RCTs have not found better survival rates in patients who received INO compared with a control intervention. Most meta-analyses also did not report improvements in other outcomes with INO (eg, BPD, intracranial hemorrhage). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are adults or children in acute hypoxemic respiratory failure who receive INO, the evidence includes RCTs and systematic reviews. Relevant outcomes are OS, hospitalizations, resource utilization, and treatment-related morbidity. A large number of RCTs have evaluated INO for treatment of acute hypoxemic respiratory failure. Meta-analyses of these RCTs have not found that INO significantly reduced mortality or shortened the duration of mechanical ventilation. Some evidence from a meta-analysis of 4 RCTs, a cohort study, and a separate meta-analysis has suggested that INO may be associated with an increased risk of renal impairment in patients with acute respiratory distress syndrome (ARDS). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are adults or children with congenital heart disease who have had heart surgery who receive INO, the evidence includes RCTs and a systematic review. Relevant outcomes are OS, hospitalizations, resource utilization, and treatment-related morbidity.

Evidence from a number of small RCTs and a systematic review of these trials did not find a significant benefit for INO on mortality and other health outcomes in the postoperative management of children with congenital heart disease. There is less evidence on INO for adults with congenital heart disease. One RCT found that treatment with INO did not improve the postoperative outcomes of adults with congestive heart failure. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have a lung transplant who receive INO, the evidence includes RCTs and a systematic review. Relevant outcomes are OS, hospitalizations, resource utilization, and treatment-related morbidity. Several small RCTs have evaluated INO after lung transplantation; none found statistically significant improvements in health outcomes with INO. A systematic review of RCTs and observational studies concluded that available evidence did not support the routine use of INO after lung transplant. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American Academy of Pediatrics

In 2014, the American Academy of Pediatrics provided the following recommendations on the use of INO in premature infants (Table 1).

Table 1. Guidelines on Use of INO for Premature Infants

Recommendation	QOE	GOR
"Neither rescue nor routine use of iNO improves survival in preterm infants with respiratory failure."	A	Strong
"The preponderance of evidence does not support treating preterm infants who have respiratory failure with INO for the purpose of preventing/ameliorating BPD, severe intraventricular hemorrhage, or other neonatal morbidities."	A	Strong
"The incidence of cerebral palsy, neurodevelopmental impairment, or cognitive impairment in preterm infants treated within INO is similar to that of control infants."	A	NR

BPD: bronchopulmonary dysplasia; GOR: grade of recommendation; INO: inhaled nitric oxide; NR: not reported; QOE: quality of evidence.

American Heart Association/American Thoracic Society

The American Heart Association and American Thoracic Society (2015) published guidelines on the management of pediatric pulmonary hypertension. Relevant recommendations related to INO included:

- "Inhaled nitric oxide (iNO) is indicated to reduce the need for extracorporeal membrane oxygenation (ECMO) support in term and near-term infants with persistent pulmonary

hypertension of the newborn (PPHN) or hypoxemic respiratory failure who have an oxygenation index that exceeds 25 (Class I; Level of evidence A)."

- "iNO can be beneficial for preterm infants with severe hypoxemia that is due primarily to PPHN physiology rather than parenchymal lung disease, particularly if associated with prolonged rupture of membranes and oligohydramnios (Class IIa; Level of evidence B)."

National Institute for Health and Care Excellence
In April 2019, NICE issued a guidance on specialist neonatal respiratory care for preterm infants. The guidance recommends against the routine use of INO for preterm infants who need respiratory support for respiratory distress syndrome, unless there are other indications such as pulmonary hypoplasia or pulmonary hypertension.

National Institutes of Health
The National Institutes of Health (2011) published a consensus development conference statement on INO for premature infants, which was based on the Agency for Healthcare Research and Quality–sponsored systematic review of the literature, previously described. Conclusions included:

"Taken as a whole, the available evidence does not support use of INO (inhaled NO) in early-routine, early-rescue, or later-rescue regimens in the care of premature infants of <34 weeks' gestation who require respiratory support."

"There are rare clinical situations, including pulmonary hypertension or hypoplasia, that have been inadequately studied in which INO may have benefit in infants of <34 weeks' gestation. In such situations, clinicians should communicate with families regarding the current evidence on its risks and benefits as well as remaining uncertainties."

The National Institutes for Health guidelines for COVID-19 treatment recommended against the routine use of INO in pediatric or adult patients who are mechanically ventilated; however, they suggest that INO may be used after other options have failed.

Pediatric Academic Society
In April 2019, the Pediatric Academic Society convened a workshop regarding the role of INO in infants born preterm. The controversy surrounding its use in this patient population was reviewed by established experts in the field. The experts at the workshop concluded that the "rate of INO use in the infant born preterm is not declining, despite the publication of RCTs and related consensus statements that discourage its routine use due to lack of evidence for bronchopulmonary dysplasia prevention." These experts stated that "none of these studies or recommendations are based on its role in the management of persistent primary hypertension of the newborn in infants born preterm." In this setting, "extensive case series, guidelines, and others recommend the selective use of INO in infants born preterm with documented persistent primary hypertension of the newborn physiology as a contributing cause of hypoxemia, as best confirmed by echocardiography."

Pediatric Pulmonary Hypertension Network
In 2016, the Pediatric Pulmonary Hypertension Network (a network of clinicians, researchers, and centers) published recommendations on the use of INO in premature infants with severe pulmonary hypertension. Key recommendations included:

(1) "iNO therapy should not be used in premature infants for the prevention of BPD, as multicenter studies data have failed to consistently demonstrate efficacy for this purpose.

(2) iNO therapy can be beneficial for preterm infants with severe hypoxemia that is primarily due to PPHN physiology rather than parenchymal lung disease, particularly if associated with prolonged rupture of membranes and oligohydramnios.

(3) iNO is preferred over other pulmonary vasodilators in preterm infants based on a strong safety signal from short- and long-term follow-up of large numbers of patients from multicenter randomized clinical trials for BPD prevention..."

U.S. Preventive Services Task Force Recommendations
Use of inhaled nitric oxide is not a preventive service.

KEY WORDS:
Inhaled Nitric Oxide, Treatment of Respiratory Failure, Nitric Oxide, Inhaled, Respiratory Failure, INOmax™, INO

APPROVED BY GOVERNING BODIES:
In 1999, INOmax™ (Ikaria®, Clinton, NJ) was approved by the FDA through the 510(k) process for the following indication: "INOmax, 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." In 2015, Mallinckrodt (Dublin, Ireland) acquired Ikaria.

In 2014, Advanced Inhalation Therapies received orphan drug designation for its proprietary formulation of nitric oxide as an adjunctive treatment of cystic fibrosis.

In 2019, Genosyl® (nitric oxide for inhalation; Vero Biotech, LLC) received FDA approval 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 April 2021, the GENOSYL DS Nitric Oxide Delivery System was recalled due to a software issue that leads to errors in the delivery of nitric oxide. For impacted devices, the issue was corrected with the release of Software 2.2.4.

In 2020, the FDA granted emergency expanded access for INOpulse (Bellerophon Therapeutics) inhaled nitric oxide delivery system for treating COVID-19.

BENEFIT APPLICATION:
Coverage is subject to member's specific benefits. Group-specific policy will supersede this policy when applicable.

CURRENT CODING:
CPT Codes:
There is not a specific CPT code.

This service is usually billed on the hospital bill with revenue code 412 for inhalation services. The physician component is included in critical care services.

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POLICY HISTORY:

Adopted for Blue Advantage, July 2010
Available for comment July 30-September 13, 2010
Medical Policy Group, August 2011
Available for comment September 22 through November 7, 2011
Medical Policy Group, December 2013
Medical Policy Group, October 2014
Medical Policy Group, May 2016
Medical Policy Group, May 2017
Medical Policy Group, June 2018
Medical Policy Group, June 2019
Medical Policy Group, June 2020
Medical Policy Group, June 2021
Medical Policy Group, May 2022
Medical Policy Group, May 2023
UM Committee, December 2023: Policy approved by UM Committee for use for Blue Advantage business.
Medical Policy Group, May 2024
UM Committee, May 2024: Annual review of policy approved by UM Committee for use for Blue Advantage business.
