BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Inhaled Nitric Oxide

Policy #: 440
Category: Therapy

Latest Review Date: June 2020
Policy Grade: B

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:

Effective for dates of service on or after November 8, 2011:

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.

In addition, inhaled nitric oxide is proposed for management of 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 post-operative pulmonary hypertension, which can prevent weaning from ventilation and is associated with substantial morbidity and mortality. Another potential surgical application is use of INO in lung transplantation to prevent or reduce reperfusion injury.

Clinical input from academic medical centers and specialty societies obtained by the Blue Cross and Blue Shield Association in 2012 indicated that:

- Prolonged use of INO [inhaled NO] beyond one to two weeks has not been shown to improve outcomes. Use of INO beyond two weeks of treatment is therefore not recommended.
- If ECMO is initiated in near-term neonates, INO should be discontinued as there is no benefit to combined treatment.

KEY POINTS:

This policy includes literature found via MEDLINE search through April 8, 2019.

Summary of Evidence

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

For individuals who are neonates and are premature at birth and have hypoxic respiratory failure who receive INO, the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, 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 on primary end points such as mortality and bronchopulmonary dysplasia (BPD). Meta-analyses of these RCTs have not found better survival rates in patients who receive with INO compared with a control intervention. Most meta-analyses did not find other outcomes e.g., BPD and intracranial hemorrhage were improved by INO. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have acute hypoxemic respiratory failure (non-neonates) who receive INO, the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, 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 significant reduces mortality or shortens the duration of mechanical ventilation. There is some evidence from a meta-analysis of 4 RCTs and from a cohort study 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 the effects of the technology on health outcomes.

For individuals who have congenital heart disease who underwent heart surgery who receive INO, the evidence consists of RCTs and a systematic review. Relevant outcomes are overall survival, 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 of postoperative outcomes in adults with congestive heart failure. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have lung transplant who receive INO, the evidence consists of RCTs and a systematic review. Relevant outcomes are overall survival, hospitalizations, resource utilization, and treatment-related morbidity. Several small RCTs have evaluated INO after lung transplantation and have not found statistically significant improvement in health outcomes. A systematic review of RCTs and observational studies concluded that there is insufficient evidence to support routine use of INO after lung transplant. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

Pediatric Pulmonary Hypertension Network

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

> "(1) INO therapy should not be used in premature infants for the prevention of BPD [bronchopulmonary dysplasia], 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 [persistent pulmonary hypertension of the newborn] 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…."

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."

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American Academy of Pediatrics

In 2000 (reaffirmed in 2009), the American Academy of Pediatrics (AAP) issued recommendations regarding the use of inhaled nitric oxide in pediatric patients. The recommendations were reaffirmed on April 1, 2010. They stated that "Inhaled nitric oxide therapy should be given using the indications, dosing, administration and monitoring guidelines outlined on the product label." This recommendation is consistent with the policy statement. In addition, the AAP recommended the following:

- Inhaled nitric oxide should be initiated in centers with extracorporeal membrane oxygenation capability.
- Centers that provide inhaled nitric oxide therapy should provide comprehensive long-term medical and neurodevelopmental follow-up.
- Centers that provide inhaled nitric oxide therapy should establish prospective data collection for treatment time course, toxic effects, treatment failure, and use of alternative therapies and outcomes.
- Administration of INO for indications other than those approved by the U.S. Food and Drug Administration (FDA) or in other neonatal populations, including compassionate use, remains experimental.

The AAP policy statement does not address the use of INO in premature infants.

Table 13. 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.

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 2020, 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.

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:

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