Qualified Health Plans offered in North Carolina by CareSource North Carolina Co., d/b/a CareSource

MEDICAL POLICY STATEMENT
North Carolina Marketplace

Policy Name & Number	Date Effective
Inhaled Nitric Oxide-NC MP-MM-1420	05/01/2024
Policy Type	
MEDICAL	

Medical Policy Statement prepared by CareSource and its affiliates are derived from literature based on and supported by clinical guidelines, nationally recognized utilization and technology assessment guidelines, other medical management industry standards, and published MCO clinical policy guidelines. Medically necessary services include, but are not limited to, those health care services or supplies that are proper and necessary for the diagnosis or treatment of disease, illness, or injury and without which the patient can be expected to suffer prolonged, increased or new morbidity, impairment of function, dysfunction of a body organ or part, or significant pain and discomfort. These services meet the standards of good medical practice in the local area, are the lowest cost alternative, and are not provided mainly for the convenience of the member or provider. Medically necessary services also include those services defined in any Evidence of Coverage documents, Medical Policy Statements, Provider Manuals, Member Handbooks, and/or other policies and procedures.

Medical Policy Statements prepared by CareSource and its affiliates do not ensure an authorization or payment of services. Please refer to the plan contract (often referred to as the Evidence of Coverage) for the service(s) referenced in the Medical Policy Statement. If there is a conflict between the Medical Policy Statement and the plan contract (i.e., Evidence of Coverage), then the plan contract (i.e., Evidence of Coverage) will be the controlling document used to make the determination. According to the rules of Mental Health Parity Addiction Equity Act (MHPAEA), coverage for the diagnosis and treatment of a behavioral health disorder will not be subject to any limitations that are less favorable than the limitations that apply to medical conditions as covered under this policy.

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A. Subject

Inhaled Nitric Oxide (iNO)

B. Background

Inhaled nitric oxide (iNO) is a lipophilic gas that is naturally produced in numerous cells in the body and is readily absorbed across pulmonary membranes in the ventilated lung after inhalation. In the body, nitric oxide is involved in oxygen transport to the tissues, the transmission of nerve impulses, and other physiological activities. When administered via inhalation, it is a potent endogenous vasodilator that induces relaxation of vascular and bronchial smooth muscle, vasodilation of blood vessels, and can increase the partial pressure of arterial oxygen. iNO was initially approved by the U.S. Food and Drug Administration (FDA) in 1999. A complete nitric oxide delivery system is comprised of a nitric oxide administration apparatus, a nitric oxide gas analyzer, and a nitrogen dioxide gas analyzer. Additional warnings and precautions were added in 2013, including rebound hypertension following abrupt discontinuation, hypoxia from methemoglobinemia, and airway injury from nitrous dioxide.

Dilation of pulmonary vessels in well-ventilated lung areas redistributes blood flow away from lung areas where ventilation/perfusion ratios are poor. iNO has been used in conjunction with ventilator support as a treatment of hypoxic respiratory failure associated with persistent pulmonary hypertension of the newborn (PPHN), in infants who are at term or near-term (greater than 34 weeks gestation) to improve oxygenation, and decrease the need for extracorporeal membrane oxygenation (ECMO).

Respiratory failure is a clinical state defined either by the inability to rid the body of carbon dioxide or establish an adequate blood oxygen level. Acute respiratory failure is the most common clinical problem seen in term, near-term (born at 34 or more weeks of gestation), and pre-term (less than 34 weeks of gestation) infants admitted to neonatal intensive care units. Acute respiratory failure is frequently associated with meconium aspiration syndrome, sepsis, pulmonary hypoplasia, and/or primary pulmonary hypertension of the newborn.

Management of infants with respiratory failure includes administration of high

does not lead to reduced ECMO use, and Putnam,

treated with iNO compared to controls, but no reduction in death or BPD alone. They stated that further studies are needed to explore subgroups of infants and to assess long-term outcomes including function in childhood. There is currently no evidence to support the use of iNO in preterm infants with respiratory failure outside the context of rigorously conducted RCTs.

To provide health care professionals, families, and the general public with a responsible assessment of currently available data regarding the benefits and risks of iNO in premature infants, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Heart, Lung, and Blood Institute, and the Office of Medical Applications of Research of the National Institutes of Health (Cole, et al, 2011) convened a consensus-development conference. Findings from a substantial body of experimental work in developing animals and other model systems suggest that iNO may enhance lung growth and reduce lung inflammation independently of its effects on blood vessel resistance. Although this work demonstrates biological plausibility and the results of RCTs in term and near-term infants were positive, combined evidence from the 14 RCTs of iNO treatment in premature infants of gestation of 34 weeks or less shows equivocal effects on pulmonary outcomes, survival, and neurodevelopmental outcomes.

A National Institutes of Health Consensus Development Conference for inhaled nitric oxygen in premature infants (Cole, et al, 2010) recommended the following:

1. Taken as a whole, the available evidence does not support use of iNO in early routine, early rescue, or later rescue regimens in the care of premature infants <34 weeks gestation who require respiratory support.
2. There are rare clinical situations, including pulmonary hypertension or hypoplasia, that have been inadequately studied in which iNO may have benefit in infants <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.
3. Basic research and animal studies have contributed to important understandings of iNO benefits on lung development and function in infants at high risk of bronchopulmonary dysplasia. These promising results have only partly been realized in clinical trials of iNO treatment in premature infants. Future research should seek to understand this gap.
4. Predefined subgroup and post hoc analyses of previous trials showing potential benefit of iNO have generated hypotheses for future research for clinical trials. Prior strategies shown to be ineffective are discouraged unless new evidence emerges. The positive results of one multicenter trial, which was characterized by later timing, higher dose, and longer duration of treatment, require confirmation. Future trials should attempt to quantify the individual effects of each of these treatment-related(e)13(m)-3(p)13(t)

An American Academy of Pediatrics clinical report on the use of iNO in preterm infants (Kumar, et al, 2014) concluded the following:

1. The results of randomized controlled trials, traditional meta-analyses, and an individualized patient data meta-analysis study indicate that neither rescue nor routine use of iNO improves survival in preterm infants with respiratory failure (Evidence quality, A; Grade of recommendation, strong).
2. 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 (Evidence quality, A; Grade of recommendation, strong).
3. The incidence of cerebral palsy, neurodevelopmental impairment, or cognitive impairment in preterm infants treated with iNO is similar to that of control infants (Evidence quality, A).
4. The results of 1 multicenter, randomized controlled trial suggest that treatment with a high dose of iNO (20 ppm) beginning in the second postnatal week may provide a small reduction in the rate of BPD. However, these results need to be confirmed by other trials.
5. An individual-patient data meta-analysis that included 96% of preterm infants enrolled in all published iNO trials found no statistically significant differences in iNO effect according to any of the patient-level characteristics, including gestational age, race, oxygenation index, postnatal age at enrollment, evidence of pulmonary hypertension, and mode of ventilation.
6. There are limited data and inconsistent results regarding the effects of iNO treatment on pulmonary outcomes of preterm infants in early childhood.

Following surgical intervention, children and adults can experience life-threatening reactive or persistent elevated pulmonary arterial pressure, or pulmonary hypertension. Due to its specificity for the pulmonary vascular bed, iNO acts directly on pulmonary vascular smooth muscle. Because of its ability to decrease pulmonary vascular resistance (PVR) and intrapulmonary shunting, and increase oxygenation, iNO is an established treatment option for pulmonary hypertension following surgical repair of congenital heart disease.

Randomized controlled trials, non-randomized comparative studies and case series reported that iNO effectively lowered pulmonary vascular resistance and pulmonary artery pressure in children and adults with pulmonary hypertension after open heart surgery. However, it did not appear to increase the survival rate in those with severe pulmonary hypertension. Studies have shown that in children with pulmonary hypertension crises (PHC)/acute right ventricular (RV) failure, iNO may be used as the initial therapy for pulmonary hypertensive crisis (PHCs) and failure of the right side of the heart. iNO is commonly used to treat postoperative PH in CHD patients. A retrospective review suggested that iNO may reduce mortality following repair of atrioventricular septal defects.

Studies have shown that the effectiveness of iNO in the post-operative management of infants and children with congenital heart disease. iNO versus placebo and/or

The MEDICAL Policy Statement detailed above has received due c

II. CareSource considers the use of iNO therapy medically appropriate in **ANY** of the following clinical conditions:
   A. post-operative management of neonates ≥ 34 weeks corrected gestational age after repair of congenital heart disease with evidence of pulmonary hypertension.
   B. postoperative management following pediatric heart or lung surgery with evidence of pulmonary hypertension.
   C. management of pulmonary hypertension during a heart catheterization to determine pulmonary vasoreactivity.

III. iNO therapy is subject to medical necessity review with medical record documentation to support initial and continued use.

IV. CareSource considers the use of iNO not medically necessary for the following indications:
   A. congenital diaphragmatic hernia
   B. acute bronchiolitis
   C. bronchopulmonary dysplasia
   D. pulmonary embolism, acute
   E. acute respiratory distress syndrome
   F. acute lung injury
   G. lung transplantation
   H. liver transplantation
   I. pulmonary fibrosis
   J. hemorrhagic shock
   K. pneumonectomy post trauma
   L. cystic fibrosis
   M. malaria

E. Conditions of Coverage
NA

F. Related Policies/Rules
NA

G. Review/Revision History

	DATE	ACTION
Date Issued	03/15/2023	New policy
Date Revised	01/31/2023	Annual review. No changes to content. Updated references. Approved at Committee.
Date Effective	05/01/2024	
Date Archived		

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The MEDICAL Policy Statement detailed above has received due consideration as defined in the MEDICAL Policy Statement Policy and is approved.

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