Subject: Inhaled Nitric Oxide (iNO) for Neonatal Hypoxic Respiratory Failure		Original Effective Date: 10/4/12
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Medical Coverage Guidance Approval Date: 10/30/13		

PREFACE

This Medical Guidance is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusions or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the following website: http://www.cms.hhs.gov/center/coverage.asp.

FDA INDICATIONS

The U.S. FDA approved iNOmax (iNO or inhaled Nitric Oxide) in 1999 for use in intubated full term and late preterm infants with hypoxemic respiratory failure. Current labeling of iNOmax is for use in respiratory failure in term and near term infants (> 34 weeks gestation). iNOmax is a vasodilator used in conjunction with ventilatory support and other appropriate agents and 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. [1 2]

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina medical coverage guidance (MCG) document and provide the directive for all Medicare members. The directives from this MCG document may be followed if there are no available NCD or LCD documents available and outlined below.

CMS does not have a NCD or LCD for the use of inhaled Nitric Oxide in newborns. [3]

INITIAL COVERAGE CRITERIA

1. iNOmax or inhaled nitric oxide (iNO) is indicated for the treatment of term and near-term (>34 weeks gestation) and < 14 days chronological age neonates who have persistent primary pulmonary hypertension (PPHN) and all of the following [1 2 4 11 13 14 15]: [ALL]

    - ❑ Severe hypoxemic respiratory failure [11]: oxygenation index OI ≥25 despite maximum medical therapy that includes all of the following: [ALL]
        - high concentrations of oxygen (100%)
        - correction of acidosis [22]
        - neuromuscular blockade and sedation
        - maximum respiratory support using conventional mechanical ventilation; OR
        - high frequency oscillatory ventilation (HFOV)

    - ❑ Echocardiogram findings: [ALL]
        - diagnosis of PPHN [11]
        - absence of congential heart disease with right to left shunting:
            - *patent ductus arteriosus (PDA)*-dependent heart lesions [2 16]

    - ❑ Absence of a congenital diaphragmatic hernia [11]

    - ❑ Facility must have the availability of extracorporal membrane oxygenation (ECMO), OR an established mechanism for timely transfer of infants to an ECMO center [4 11]

    - ❑ Facility must have personnel trained in the administration of iNOmax [4 11]

2. The recommended dose of INOmax is 20 ppm. Treatment should be maintained up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from INOmax therapy. [1 2 13 14]

Note: *iNO should be administered using FDA-approved devices capable of administering iNO in constant concentration ranges in parts per million or less throughout the respiratory cycle.*[4]

CONTINUATION OF THERAPY

iNOmax treatment should be maintained up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from iNOmax therapy. [1 2 13]

COVERAGE EXCLUSIONS

1. iNOmax is contraindicated in the treatment of neonates with congential heart disease dependent on right-to-left shunting of blood (i.e., *patent ductus arteriosus (PDA)*-dependent heart lesions)[2 16]

2. The following indications are considered investigational and not covered:
    - ❑ Neonates born <34 weeks gestation [1 11]
    - ❑ Neonates with congenital diaphragmatic hernia [11]

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

iNOmax (Inhaled Nitric Oxide)

iNOmax is a vasodilator used in conjunction with ventilatory support and other appropriate agents and 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. The initial recommended starting dose for these infants is 20 ppm with continued use for 14 days or until improvement in the underlying disease process results in normal oxygen saturations. The dose is weaned incrementally with improving oxygen saturations beginning as soon as four hours after the initiation of therapy, to 5 ppm before discontinuation.[5] Doses above 20 ppm should not be used because of the risk of methemoglobinemia and elevated nitrogen dioxide (NO2), a toxic metabolite. [23]

GENERAL INFORMATION

Summary of Medical Evidence

The Neonatal Inhaled Nitric Oxide Study (NINOS) group conducted a double-blind, randomized, placebo-controlled, multicenter trial in 235 neonates with hypoxic respiratory failure. The objective 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 PaO2 of 46 mm Hg and a mean oxygenation index (OI) of 43 cm H2O / mm Hg were initially randomized to receive 100% O2 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 PaO2 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. While 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 PaO2 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. 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. [10]

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 INOmax 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 PaO2 of 54 mm Hg and a mean OI of 44 cm H2O / mm Hg were randomly assigned to receive either 20 ppm INOmax (n=97) or nitrogen gas (placebo; n=89) in addition to their ventilatory support. Patients who exhibited a PaO2 >60 mm Hg and a pH < 7.55 were weaned to 5 ppm INOmax or placebo. Significantly fewer neonates in the INOmax group required ECMO compared to the control group (31% vs. 57%, p<0.001). Although the number of deaths were similar in both groups (INOmax, 3%; placebo, 6%), the combined incidence of death and/or receipt of ECMO was decreased in the INOmax group (33% vs. 58%, p<0.001). In addition, the INOmax group had significantly improved oxygenation as measured by PaO2, OI, and alveolar-arterial gradient (p<0.001 for all parameters). Of the 97 patients treated with INOmax, 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. [2 13]

ARDS Study: In a randomized, double-blind, parallel, multicenter study, 385 patients with adult respiratory distress syndrome (ARDS) who had a PaO_2/FiO_2 less than 250 mmHg despite optimal oxygenation and ventilation, received either placebo (n = 193) or nitric oxide (n = 192), 5 ppm, for 4 hours to 28 days or until weaned off due to improvements in oxygenation. This study found that 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). Nitric oxide is not indicated for use in ARDS. [2 13]

A double-blind study done at 36 centers in nine countries in the European Union by Mercier et al. [12] of 800 preterm infants with a gestational age at birth of between 24 weeks and 28 weeks plus 6 days (inclusive), weighing at least 500 g, requiring surfactant or continuous positive airway pressure for respiratory distress syndrome within 24 h of birth were randomly assigned in a one-to-one ratio to inhaled nitric oxide (5 parts per million) or placebo gas (nitrogen gas) for a minimum of 7 days and a maximum of 21 days. Care providers and investigators were masked to the computer-generated treatment assignment. The primary outcome was survival without development of bronchopulmonary dysplasia at postmenstrual age 36 weeks. Analysis was by intention to treat. Infants were assigned to inhaled nitric oxide, and 401 to placebo; 395 and 400, respectively, were analyzed. Treatment with inhaled nitric oxide and placebo did not result in significant differences in survival of infants without development of bronchopulmonary dysplasia (258 [65%] of 395 versus 262 [66%] of 400, respectively; relative risk 1.05, 95% CI 0.78-1.43); in survival at 36 weeks' postmenstrual age (343 [86%] of 399 versus 359 [90%] of 401, respectively); and in development of bronchopulmonary dysplasia (81 [24%] of 339 versus 96 [27%] of 358, respectively). The authors concluded that early use of low-dose inhaled nitric

oxide in very premature babies did not improve survival without bronchopulmonary dysplasia or brain injury, suggesting that such a preventive treatment strategy is unsuccessful.

A systematic review the evidence on the use of iNO in infants born at_34 weeks gestation who receive respiratory support was conducted by Donahue and colleagues in 2011. [19] The review focused on mortality, bronchopulmonary dysplasia (BPD), the composite outcome of death or BPD, and neurodevelopmental impairment (NDI). Fourteen randomized controlled trials, 7 follow-up studies, and 1 observational study were eligible for inclusion. Mortality rates in the NICU did not differ for infants treated with iNO compared with controls. BPD at 36 weeks for iNO and control groups also did not differ for survivors A small difference was found in favor of iNO in the composite outcome of death or BPD. There was no evidence to suggest a difference in the incidence of cerebral palsy neurodevelopmental impairment or cognitive impairment. The authors concluded that there was no benefit or increased risk to preterm infants born at < 34 weeks' gestational age treated with iNO compared with control infants for mortality, BPD at 36 weeks post menstrual age, short-term risks (patent ductus arteriosus, sepsis, necrotizing enterocolitis, treated retinopathy of prematurity, pulmonary hemorrhage, air leak, brain injury), or NDI. There was a 7% reduction in the risk of the composite outcome of death or BPD at 36 weeks for infants treated with iNO compared with controls but no reduction in death alone or BPD.

Hayes, Cochrane, UpToDate, MD Consult etc.

Hayes: There is Directory report called Inhaled Nitric Oxide for the Treatment of Persistent Pulmonary Hypertension in Term and Near Term Newborns. [8] The report summarizes that iNO therapy has been investigated for the treatment of term and near-term newborns with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, with the goal of improving blood oxygenation, reducing the need for extracorporeal membrane oxygenation (ECMO), and increasing survival. In a number of the randomized controlled trials, nitric oxide inhalation (iNO) therapy improved oxygenation in term and near-term newborns with persistent pulmonary hypertension of the newborn (PPHN). However, a significant clinical benefit of the therapy, such as a drop in extracorporeal membrane oxygenation (ECMO) rates, was only seen in a few trials. Moreover, iNO therapy had no effect on mortality rates. iNO therapy appeared to be most promising in patients with a gestational age of more than 34 weeks, suffering from severe PPHN, and without congenital diaphragmatic hernia (CDH). In general, response to treatment occurred within 2 days after treatment initiation, with 20 parts per million (ppm) nitric oxide (NO) as the most effective and safest iNO dosage. Since iNO therapy did not improve oxygenation in all newborns with PPHN, the identification of risk factors of treatment failure and a better understanding of the PPHN etiology are important aspects of future research. Inhaled NO therapy was safe with only few adverse effects, although gradual weaning from NO was essential to prevent a rebound increase in arterial pressure and insufficient oxygenation of pulmonary tissue. Inhaled NO treatment is contraindicated in newborns known to be dependent on right-to-left shunting of blood.

iNO therapy has a potential benefit in term and near-term newborns with PPHN and without CDH, when administered at the recommended dosage of 20 ppm in conjunction with ventilatory support and other appropriate agents, and when monitored according to institutionally derived protocols designed to avoid the

potential toxic effects associated with iNO administration, at centers with expertise and experience to provide multiple modes of ventilatory support and rescue therapies, or offer transfer in a timely manner to such an institution. iNO is not recommended for newborns with congenital diaphragmatic hernia or who are not dependent on right-to-left shunting of blood.

There is a Hayes Directory Report called Inhaled Nitric Oxide for the Treatment of Respiratory Failure in Preterm Infants. [9] Nitric oxide inhalation (iNO) therapy is a minimally invasive treatment that involves inhalation of gaseous nitric oxide in conjunction with ventilatory support. iNO therapy is used to treat preterm newborns with hypoxic respiratory failure to reduce mortality, and prevent early lung injury leading to chronic lung (CLD). There is not sufficient evidence to support nitric oxide inhalation (iNO) therapy in the overall population of preterm newborns with respiratory failure. There is some evidence that the early routine use of iNO in ventilated preterm newborns prevents early lung injury and reduces severe brain injury; however, iNO therapy has no effect on survival in this population. Clear patient selection criteria are lacking for this population, and longer follow-up trials are needed to exclude treatment-induced pulmonary or neurodevelopmental problems. In very sick preterm newborns who meet the criteria for poor oxygenation, rescue therapy with iNO does not improve survival, prevent the development of chronic lung disease (CLD), or reduce the incidence of brain injury, despite a transient improvement of oxygenation in some newborns. There is insufficient evidence of late use of iNO in preterm newborns at risk of developing CLD. iNO therapy has potential but unproven benefit for treatment in preterm newborns (gestational age < 32 weeks) with respiratory failure when administered at a dosage of 5 to 20 parts per million (ppm) in conjunction with ventilatory support and other appropriate agents, and when monitored according to institutionally derived protocols designed to avoid the potential toxic effects associated with iNO administration. There is potential but unproven benefit for preterm newborns routinely treated with iNO after intubation and for preterm newborns treated with iNO in the first 3 days of life due to defects in oxygenation. There is no proven benefit for iNO therapy in preterm newborns treated at a later age (after 3 days) due to an elevated risk for early lung injury.

UpToDate:

In a report called Persistent Pulmonary Hypertension of the Newborn (PPHN) [11] that authors summarize that iNO therapy is recommended in term or late preterm infants (gestational age ≥34 weeks) with severe hypoxemic respiratory failure, defined as an oxygenation index OI ≥25 with maximum respiratory support using conventional mechanical ventilation or high frequency oscillatory ventilation (HFOV). Prior to initiating treatment, echocardiography is done to confirm the diagnosis of persistent pulmonary hypertension (PPHN) and exclude congenital heart disease. The initial dose of iNO is 20 ppm. In infants who respond, an improvement of approximately 20 percent in PaO2 or SaO2 typically occurs within 15 to 20 minutes. The iNO concentration is decreased slowly as oxygenation improves. Patients who respond to iNO typically require treatment for three to four days, although some require longer courses. Monitoring for potential toxic effects by measuring the serum methemoglobin concentration, levels of nitrogen dioxide at the airway opening, and ambient air contamination should be performed.

Treatment recommendations for PPHN include:

- Supplemental oxygen should be administered in a concentration of 100 percent to infants with PPHN in an attempt to reverse pulmonary vasoconstriction. PaO2 should be maintained in the range of 50 to 90 mmHg (oxygen saturation >90 percent).
- Mechanical ventilation to initially maintain PaCO2 between 35 to 40 mmHg, as hypercarbia and acidosis increase PVR
- Maintenance of adequate circulatory by providing sufficient vascular volume and the use of inotropic agents
- Use of oxygenation index (OI) to assess the severity of hypoxia
- Inhaled nitric oxide (iNO) used to initially treat term or late preterm infants on maximum ventilatory support with an OI ≥25 except those with congenital diaphragmatic hernias.
- Use of extracorporeal membrane oxygenation in patients who have an OI ≥40 despite the use of iNO and maximum ventilatory support

Cochrane:

A Cochrane review was published in 2010 to determine the effect of treatment with iNO on death, bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH),and neurodevelopmental disability in preterm newborn infants with respiratory disease. The search included the years from 1985 to 2010. Fourteen randomized controlled trials of inhaled nitric oxide therapy in preterm infants were reviewed. The trials were grouped into three categories depending on entry criteria: entry in the first three days of life based on oxygenation criteria, routine use in preterm babies with pulmonary disease, and later enrolment based on an increased risk of BPD. No overall analyses were performed. Nine trials of early rescue treatment of infants based on oxygenation criteria demonstrated no significant effect of iNO on mortality or BPD. Three studies with routine use of iNO in infants with pulmonary disease also demonstrated no significant reduction in death or BPD [typical RR 0.93 (95% CI 0.86 to 1.01)] although this small effect approached significance. Later treatment with iNO based on the risk of BPD (two trials) demonstrated no significant benefit for this outcome in analyses which are possible using summary data. There is no clear effect of iNO on the frequency of all grades of IVH or of severe IVH. Early rescue treatment was associated with a non-significant 20% increase in severe IVH. No effect on the incidence of neurodevelopmental impairment was found. The authors concluded that iNO as rescue therapy for the very ill preterm infant does not appear to be effective. Early routine use of iNO in preterm infants with respiratory disease does not affect serious brain injury or improve survival without BPD. Later use of iNO to prevent BPD might be effective, but requires further study. [18]

Professional Organizations

American Academy of Pediatrics (AAP): The AAP recommendations for iNO therapy include all of the following: [4]

- Infants with progressive hypoxic respiratory failure should be cared for in centers with the expertise and experience to provide multiple modes of ventilatory support and rescue therapies or be transferred in a timely manner to such an institution.
- iNO therapy should be given using the indications, dosing, administration, and monitoring guidelines outlined on the product label. An echocardiogram to rule out congenital heart disease is recommended.

Center-specific criteria for treatment failure should be developed to facilitate timely consideration of alternative therapies.

- iNO therapy should be directed by physicians qualified by education and experience in its use and offered only at centers that are qualified to provide multisystem support, generally including on-site ECMO capability.
- Generally, iNO should be initiated in centers with ECMO capability. If iNO is offered by a center without ECMO capability, for geographic or other compelling reasons, mutually acceptable treatment failure criteria and mechanisms for timely transfer of infants to a collaborating ECMO center should be established prospectively. Transfer must be accomplished without interruption of iNO therapy.
- Centers that provide iNO therapy should provide comprehensive long-term medical and neurodevelopmental follow-up.
- Centers that provide iNO therapy should establish prospective data collection for treatment time course, toxic effects, treatment failure, use of alternative therapies, and outcomes.
- Administration of iNO for indications other than those approved by the FDA or in other neonatal populations, including compassionate use, remains experimental. As such, iNO should be administered according to a formal protocol that has been approved by the FDA and the institutional review board and with informed parental consent.

European Medicines Agency (EMEA): In August 2001, INO Therapeutics received centralized approval for the distribution of INOmax in Europe through the EMEA. The EMEA stated that INOmax, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of newborns ≥ 34 weeks of gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation. [6]

National Institutes of Health (NIH) [17]**:** In a consensus statement called Inhaled Nitric Oxide Therapy for Premature Infants (2010) the outlined summary indicates the following:

- The available evidence does not support use of inhaled nitric oxide in early routine, early rescue, or later rescue regimens in the care of premature infants <34 weeks gestation who require respiratory support.
- There are rare clinical situations, including pulmonary hypertension or hypoplasia, that have been inadequately studied in which inhaled nitric oxide 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.
- Basic research and animal studies have contributed to important understandings of inhaled nitric oxide 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 inhaled nitric oxide treatment in premature infants. Future research should seek to understand this gap.
- Predefined subgroup and post hoc analyses of previous trials showing potential benefit of inhaled nitric oxide 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 variables (timing, dose, and duration), ideally by randomizing them separately.
- Based on assessment of currently available data, hospitals, clinicians, and the pharmaceutical industry should avoid marketing inhaled nitric oxide for premature infants <34 weeks gestation

Occupational Safety and Health Administration (OSHA): The exposure limit set by OSHA for NO is 25 ppm, and the limit is 5 ppm for NO_2. Several European countries have regulated maximal occupational exposure to 2 ppm NO_2.[7]

CODING INFORMATION

CPT	Description
94799	Unlisted pulmonary service or procedure

ICD-9	Description
	Procedure Code
00.12	Administration of inhaled nitric oxide
	Diagnosis Codes
416.0	Primary pulmonary hypertension
747.83	Persistent fetal circulation (primary pulmonary hypertension of newborn)
765.27	Weeks of gestation; 33-34 completed weeks of gestation
765.28	Weeks of gestation; 35-36 completed weeks of gestation
765.29	Weeks of gestation; 37 or more completed weeks of gestation

ICD-10	Description
I27.0	Primary pulmonary hypertension
P07.37-P07.39	Preterm newborn 34-36 complete weeks

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