Subject: Inhaled Nitric Oxide (iNO) for Neonatal Hypoxic Respiratory Failure		Original Effective Date: 10/4/12
Policy Number: MCP-121	**Revision Date(s):** 10/30/13, 12/16/15, 7/21/16, 9/18/19	
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DISCLAIMER

This Molina Clinical Policy (MCP) 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 exclusion(s) 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 CMS website. 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 Clinical Policy (MCP) document and provide the directive for all Medicare members.[1]

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL [2 3 14]

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. According to the FDA package labeling, 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. Doses above 20 ppm should not be used because of the risk of methemoglobinemia and elevated nitrogen dioxide (NO2), a toxic metabolite. [2-3]

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. [2 3]

INITIAL COVERAGE CRITERIA [2 3 6 8 10 15]

Criteria for initiation of treatment. Initial approval for 72 hours:

1. iNOmax or inhaled nitric oxide (iNO) is indicated for the treatment of term and near-term (≥34 weeks gestational age at birth who have severe documented hypoxic respiratory failure secondary to persistent primary pulmonary hypertension (PPHN) and all of the following: [ALL]

    - ❑ Oxygenation index (OI) recorded x 2 measurements taken 15 min apart that are >25 despite maximum medical therapy that includes all of the following: [ALL]
        - o FiO2 concentration of 100%
        - o Failure to respond to additional optimal medical treatment which must include high frequency oscillatory ventilation (HFOV), cardiovascular support and attempts to correct the blood pH; and

    - ❑ Echocardiogram findings suggestive of PPHN ; and

    - o Absence of a congenital diaphragmatic hernia (CDH) except when used to repair a congenital diaphragmatic hernia and limited to patients with all of the following: [10] [ALL]
        - o suprasystemic PVR with right-to-left shunting across the oval foramen causing critical preductal hypoxemia and;
        - o after optimal lung inflation and;
        - o adequate LV performance are established; and

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

    - ❑ Facility must have personnel trained in the administration of iNOmax

2. iNOmax or inhaled nitric oxide (iNO) is indicated for the postoperative management in infants ≥34 weeks gestational age at birth and children who have one of the following indications: [10]
    - ❑ Congenital heart defect and any of the following:
        - o iNO therapy for vasodilation is used in response to cardiac bypass surgery to repair a congenital heart defect that is causing PAH; or
        - o Postoperative stabilization and management of hypoxia; or
    - ❑ Pulmonary hypertensive crisis associated with heart or lung surgery (including immediately pre-operatively for congenital diaphragmatic hernia); and

2. The recommended dose of INOmax is 20 ppm. Treatment should be maintained until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from INOmax therapy. [15]

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.*[8]

CONTINUATION OF THERAPY [2 3 11 15]

1. Initial signs of improvement as documented by at least two of the following: [TWO]
   - ❑ Repeat cardiac ECHO demonstrating significantly lower pulmonary artery pressures; or
   - ❑ Lower O2 requirements; or
   - ❑ Lower ventilator settings; or
   - ❑ Improved blood gases; and
2. Re-evaluation every 48 hours; and
3. Weaning: Following improvement in oxygenation and after a 4 h to 6 h period of stability, during which the inspired oxygen concentration is decreased to 60% to 80%, or the OI falls to ≤10, the dose of iNO should be weaned. [11]
4. Infants who cannot be weaned from iNO after seven days should be carefully evaluated for other forms of lung pathology and cardiac disease. Continuation of iNO beyond 7 days must be reviewed by a medical director. [11]

COVERAGE EXCLUSIONS [2 3 6-11 27-31 34 39 40 44 46 47]

1. iNO therapy is contraindicated in the treatment of neonates with cardiac anomalies dependent on right-to-left shunts, (i.e., patent ductus arteriosus (PDA)-dependent heart lesions), congestive heart failure, and those with lethal congenital anomalies.

2. iNO therapy is not medically necessary for any other indications such as preterm infants < 34 weeks gestation at birth, acute bronchiolitis, bronchopulmonary dysplasia (BPD), congenital diaphragmatic hernia (CDH) (except as noted above), adult respiratory distress syndrome or acute lung injury, treatment in adults with positive vaso-reactivity testing, post-op cardiac surgery in adults, and vaso-occlusive crises in members with sickle cell disease because safety and effectiveness have not been established in the peer reviewed literature.

3. iNO therapy is not recommended for life threatening conditions deemed by the neonatologist/ medical team as likely to result in death or significant neurological impairment (certain genetic syndromes or other conditions with a poor prognosis).

SUMMARY OF MEDICAL EVIDENCE [18-47]

Systematic reviews, meta-analysis, and randomized controlled trials have reported that INO improved systematic oxygenation and that fewer term and near-term infants' birth age greater than 34 weeks gestation required ECMO and/or developed chronic lung disease. A summary of the most relevant studies are outlined below.

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. [19]

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. [15 21]

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. [15]

A double-blind study done at 36 centers in nine countries in the European Union by Mercier et al. (2010) 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. [20]

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. 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. [22]

Cochrane:

A 2010 (updated 2017) Cochrane review determined the effect of treatment with iNO on death, bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH),and neurodevelopmental disability in preterm newborn infants with respiratory disease. 17 randomised controlled trials of iNO therapy in preterm infants were reviewed. We grouped these trials post hoc into three categories on the basis of entry criteria: treatment during the first three days of life for impaired oxygenation, routine use in preterm babies along with

respiratory support and later treatment for infants at increased risk for bronchopulmonary dysplasia (BPD). We performed no overall analyses. Eight trials providing early rescue treatment for infants on the basis of oxygenation criteria demonstrated no significant effect of iNO on mortality or BPD (typical risk ratio (RR) 0.94, 95% confidence interval (CI) 0.87 to 1.01; 958 infants). Four studies examining routine use of iNO in infants with pulmonary disease reported no significant reduction in death or BPD (typical RR 0.94, 95% CI 0.87to 1.02; 1924 infants), although this small effect approached significance. Later treatment with iNO based on risk of BPD (three trials)revealed no significant benefit for this outcome in analyses of summary data (typical RR 0.92, 95% CI 0.85 to 1.01; 1075 infants).Investigators found no clear effect of iNO on the frequency of all grades of IVH nor severe IVH. Early rescue treatment was associated with a non-significant 20% increase in severe IVH. We found no effect on the incidence of neurodevelopmental impairment. The authors concluded that iNO does not appear to be effective as rescue therapy for the very ill preterm infant. Early routine use of iNO in preterm infants with respiratory disease does not prevent serious brain injury or improve survival without BPD. Later use of iNO to prevent BPD could be effective, but current 95% confidence intervals include no effect; the effect size is likely small (RR 0.92) and requires further study [42]

A 2014 Cochrane review compared the effects of postoperative administration of iNO versus placebo or conventional management, or both, on infants and children with CHD and pulmonary hypertension. The primary outcome was mortality. Secondary outcomes included length of hospital stay; neurodevelopmental disability; number of pulmonary hypertensive crises (PHTC); changes in mean pulmonary arterial pressure (MPAP), mean arterial pressure (MAP), and heart rate (HR); changes in oxygenation measured as the ratio of arterial oxygen tension (PaO2) to fraction of inspired oxygen (FiO2); and measurement of maximum methaemoglobin level as a marker of toxicity. In total four randomized trials involving 210 participants were included in this review. We observed no differences in mortality (OR 1.67, 95% CI 0.38 to 7.30; P = 0.50); PHTC (OR 0.80, 95% CI 0.15 to 4.18; P = 0.79); changes in MPAP (treatment effect -2.94 mm Hg, 95% CI -9.28 to 3.40; P = 0.36), MAP (treatment effect -3.55 mm Hg, 95% CI -11.86 to 4.76; P = 0.40), HR (treatment effect 0.02 bpm, 95% CI -8.13 to 8.18; P = 1.00), or PaO2:FiO2 (mean difference 17.18, 95% CI -28.21 to 62.57; P = 0.46). There was a significant increase in the methaemoglobin level (mean difference 0.30%, 95% CI 0.24 to 0.36; P < 0.00001) in patients treated with iNO, although levels did not reach toxicity levels. Data from long-term mortality, neurodevelopmental disability, and length of stay were not available. Two trials had a low risk of bias. Very low quality of the evidence was observed considering grading of the outcomes. No differences with the use of iNO in the outcomes reviewed. No data were available for several clinical outcomes including long-term mortality and neurodevelopmental outcome. We found it difficult to draw valid conclusions given concerns regarding methodologic quality, sample size, and heterogeneity. [45]

In an updated 2016 Cochrane database review, the evidence was insufficient to support iNO in any category of critically ill adults and children with acute respiratory distress syndrome. Although iNO results in a transient improvement in oxygenation, it does not reduce mortality and may be harmful, as it seems to increase renal impairment. [47]

Professional Organizations [6-10]

American Academy of Pediatrics (AAP): The 2014 published AAP recommendations for iNO therapy include all of the following: [6]

- 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
- 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
- The incidence of cerebral palsy, neurodevelopmental impairment, or cognitive impairment in preterm infants treated with iNO is similar to that of control infants
- 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.
- 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.
- There are limited data and inconsistent results regarding the effects of iNO treatment on pulmonary outcomes of preterm infants in early childhood.

American Association for Respiratory Care (AACR): The 2010 clinical practice guidelines on INO for neonates with acute hypoxic respiratory failure include the following recommendations: [8]

- A trial of INO is recommended in newborns (≥ 34 wk gestation, < 14 d [days] of age) with PaO2 < 100 mm Hg [millimeters of mercury] on FIO2 1.0 and/or an oxygenation index (OI) > 25
- INO therapy be instituted early in the disease course, which potentially reduces the length of mechanical ventilation, oxygen requirement, and stay within the intensive care unit
- INO should not be used routinely in newborns with congenital diaphragmatic hernia
- The recommended starting dose for INO is 20 ppm [parts per million]
- FDA-approved INO delivery systems should be used to assure consistent and safe gas delivery during therapy.
- INO therapy should not be used routinely in newborns with cardiac anomalies dependent on right-to-left shunts, congestive heart failure, and those with lethal congenital anomalies
- INO therapy should not be used routinely in postoperative management of hypoxic term or near-term infants with congenital heart disease

American Heart Association and American Thoracic Society (AHA/ATS): The 2015 Pulmonary Hypertension (PH) Guidelines include the following recommendations for persistent PH of the newborn: [10]

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

(PPHN) or hypoxemic respiratory failure who have an oxygenation index that exceeds 25 (Class I, level A recommendation).

- iNO is indicated in postoperative pulmonary hypertensive crises. The guidelines state that iNO is an established therapy for postoperative pulmonary hypertension due to its selective pulmonary vasodilator properties, rapid effect onset, and ease of administration. (class 1, level B recommendation)

CODING INFORMATION: THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
93463	Pharmacologic agent administration (eg, inhaled nitric oxide, intravenous infusion of nitroprusside, dobutamine, milrinone, or other agent) including assessing hemodynamic measurements before, during, after and repeat pharmacologic agent administration, when performed (List separately in addition to code for primary procedure)
94002	Ventilation assist and management, initiation of pressure or volume preset ventilators for assisted or controlled breathing; hospital inpatient/observation, initial day
94003	Ventilation assist and management, initiation of pressure or volume preset ventilators for assisted or controlled breathing; hospital inpatient/observation, each subsequent day

ICD-10	Description: ***Diagnosis Codes*** **[For dates of service on or after 10/01/2015]**
I27.0	Primary pulmonary hypertension
P07.37-P07.39	Preterm newborn 34-36 complete weeks
ICD-10	***Procedure Codes***
3E0F3SD	Introduction of Nitric Oxide Gas into Respiratory Tract, Percutaneous Approach
3E0F7SD	Introduction of Nitric Oxide Gas into Respiratory Tract, Via Natural or Artificial Opening
3E0F8SD	Introduction of Nitric Oxide Gas into Respiratory Tract, Via Natural or Artificial Opening Endoscopic

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Revision/Review History:
10/4/12: New Policy
10/30/13: Policy reviewed, no changes to criteria.
12/15: Policy reviewed by staff from the NICU program and neonatologists Dr. Karotkin and Dr. Dubose. No changes to criteria.
7/21/16: Policy was reviewed and updated with changes to the initiation of treatment criteria that include OI index measured x2 15 min apart and failure to respond to optimal medical management. The initial approval will be granted for 72 hours with re-evaluation criteria required every 72 hours. Bronchopulmonary dysplasia was added as an exclusion. Changes recommended by staff from the NICU program and neonatologists Dr. Karotkin and Dr. Dubose.
6/22/17, 3/8/18: Policy reviewed, clinical criteria has not changed.
9/18/19: Policy reviewed, clinical criteria has been updated based on new literature and guidelines. Added new criteria for congenital heart defects causing PAH and pulmonary hypertensive crisis associated with heart or lung surgery. Updated the continuation of therapy section based on new guidelines and coverage exclusions. Updated professional society guidelines and reference sections.