**Inhaled Nitric Oxide**

**Policy Statement**

Inhaled nitric oxide (INO) may be considered **medically necessary** as a component of treatment of hypoxic respiratory failure in neonates born at more than 34 weeks of gestation.

**Note:** Use of inhaled NO therapy for more than 4 days is subject to further medical necessity review by a Blue Shield Medical Director.

Other indications for inhaled nitric oxide are considered **investigational**, including, but not limited to:

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

**Policy Guidelines**

Inhaled nitric oxide (INO) appears to be of greatest benefit to individuals for whom primary or secondary pulmonary hypertension is a component of hypoxic respiratory failure.

The benefit of INO appears limited in term or near-term infants whose hypoxic respiratory failure is due to diaphragmatic hernia.

**Hypoxic Respiratory Failure**

The following criterion for hypoxic respiratory failure has been reported:

- An oxygenation index (OI) of at least 25 on 2 measurements made at least 15 minutes apart

(The OI is calculated as the mean airway pressure times the fraction of inspired oxygen divided by the partial pressure of arterial oxygen times 100. An OI of 25 is associated with a 50% risk of requiring extracorporeal membrane oxygenation [ECMO] or dying. An OI of 40 or more is often used as a criterion to initiate ECMO therapy.)

**Prolonged Use of Inhaled Nitric Oxide**

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

- Prolonged use (greater than 1 to 2 weeks) of INO has not been shown to improve outcomes. Use of INO beyond 2 weeks of treatment is therefore not recommended
- If ECMO is initiated in near-term neonates, INO should be discontinued because there is no benefit to combined treatment

**U.S. Food and Drug Administration Approval for INOmax™**

INOmax™ (Ikaria®, Clinton, NJ) is a commercially available inhaled nitric oxide product approved by the U.S. Food and Drug Administration (FDA) for the following indication: INOmax, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (greater than 34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension.
**Description**

Inhaled nitric oxide (INO) is a natural vasodilator and has been studied for a variety of types of respiratory failure. Most commonly, it is used as an initial treatment for neonates with hypoxic respiratory failure to improve oxygenation and reduce the need for invasive extracorporeal membrane oxygenation. It is also proposed as a treatment for premature infants, critically ill children and adults with respiratory failure, as well as in the postoperative management of children undergoing repair of congenital heart disease and patients after lung transplantation to prevent or reduce reperfusion injury.

**Related Policies**

- N/A

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

**Regulatory Status**

In 1999, INOmax™ (Ikaria) was cleared for marketing by the U.S. Food and Drug Administration 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 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.

**Rationale**

**Background**

**Hypoxic Respiratory Failure**

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

**Treatment**

Treatment typically includes oxygen support, mechanical ventilation, induction of alkalosis, neuromuscular blockade, or sedation.

Extracorporeal membrane oxygenation 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.

**Literature Review**

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

**Hypoxic Respiratory Failure in Term or Late Preterm Neonates**

A number of RCTs and a Cochrane review of RCT data on inhaled nitric oxide (INO) in infants with hypoxia born at or late preterm (>34 weeks of gestation) have been published. The Cochrane review, last updated by Barrington et al (2017), identified 17 trials. Ten trials compared INO with a control (placebo or standard neonatal intensive care without INO) in infants who had moderately severe illness scores. One trial permitted backup treatment with INO and 2 enrolled only infants with a diaphragmatic hernia. Another 6 trials included infants with moderately severe disease and compared immediate INO with INO only when infants’ conditions deteriorated to a more severe illness. The remaining trial compared INO with high-frequency ventilation. In all trials, hypoxic respiratory failure was required for study entry, and most also required echocardiographic evidence of persistent pulmonary hypertension. The main findings of the meta-analysis are provided in Table 1. Only findings of trials that did not allow backup INO or were not limited to patients with a diaphragmatic hernia are presented; there were too few studies on other subgroups to permit meaningful meta-analysis.

<table>
<thead>
<tr>
<th>No. of Trials</th>
<th>N</th>
<th>Outcomes</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>p</th>
<th>I²</th>
<th>QOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>860</td>
<td>Death before hospital discharge</td>
<td>0.89</td>
<td>0.60 to 1.31</td>
<td>0.55</td>
<td>0%</td>
<td>High</td>
</tr>
<tr>
<td>7</td>
<td>815</td>
<td>ECMO before hospital discharge</td>
<td>0.60</td>
<td>0.50 to 0.71</td>
<td>&lt;0.001</td>
<td>0%</td>
<td>High</td>
</tr>
<tr>
<td>8</td>
<td>859</td>
<td>ECMO before hospital discharge</td>
<td>0.66</td>
<td>0.57 to 0.77</td>
<td>&lt;0.001</td>
<td>0%</td>
<td>High</td>
</tr>
</tbody>
</table>


Reviewers found that INO in hypoxic infants significantly reduced the incidence of the combined end point of death or the need for extracorporeal membrane oxygenation (ECMO).
compared with controls, in studies that did not allow INO backup in controls. INO did not have a statistically significant effect on mortality when analyzed as the sole outcome measure; however, there was a significant effect of INO on the need for ECMO only. The analysis of mortality alone may have been underpowered.

Section Summary: Hypoxic Respiratory Failure in Term or Late Preterm Neonates
Evidence from RCTs and a meta-analysis of RCTs has supported the use of INO in term or late preterm infants to improve the net health outcome. Pooled analyses of RCT data have found that INO leads to a significant reduction in the combined outcome of ECMO or death and a significant reduction of ECMO use before hospital discharge.

Hypoxic Respiratory Failure in Premature Neonates
In late preterm neonates, INO primarily functions as a vasodilator to treat pulmonary hypertension, often due to meconium aspiration or bacterial pneumonia. However, in earlier preterm neonates with respiratory failure, pulmonary hypertension with shunting is less of a risk. Therefore, these 2 groups of neonates represent distinct clinical issues, and the results of INO in late preterm neonates cannot be extrapolated to preterm neonates. Also, the risk of intraventricular hemorrhage associated with INO is higher in premature infants.

Systematic Reviews
Numerous several systematic reviews and RCTs on INO for treating hypoxic respiratory failure in preterm neonates have been published. Most recently, another Cochrane review by Barrington et al (2017) identified 17 RCTs on the efficacy of INO for treating premature infants (i.e., <35 weeks of gestation) with respiratory disease. The main findings of the meta-analysis are provided in Table 2. Results are reported separately for studies with entry before 3 days based on oxygenation, studies with entry after 3 days based on oxygenation and bronchopulmonary dysplasia (BPD) risk, and studies of routine use of INO in premature infants on respiratory support. Pooled analyses of 3 or more studies are shown.

Table 2. Main Cochrane Findings on INO in Preterm Infants

<table>
<thead>
<tr>
<th>No. of Trials</th>
<th>N</th>
<th>Outcomes</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>p</th>
<th>I²</th>
<th>QOE(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death before hospital discharge</td>
<td>10</td>
<td>1066 Studies with entry before 3 d</td>
<td>1.02</td>
<td>0.89 to 1.18</td>
<td>0.75</td>
<td>3%</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1075 Studies with entry after 3 d</td>
<td>1.18</td>
<td>0.81 to 1.71</td>
<td>0.39</td>
<td>0%</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1924 Studies of routine use</td>
<td>0.90</td>
<td>0.74 to 1.10</td>
<td>0.32</td>
<td>50%</td>
<td>Moderate</td>
</tr>
<tr>
<td>BPD at 36 weeks of gestation</td>
<td>8</td>
<td>681 Studies with entry before 3 d</td>
<td>0.89</td>
<td>0.76 to 1.04</td>
<td>0.13</td>
<td>29%</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>990 Studies with entry after 3 d</td>
<td>0.91</td>
<td>0.83 to 1.01</td>
<td>0.068</td>
<td>11%</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1782 Studies of routine use</td>
<td>0.95</td>
<td>0.85 to 1.05</td>
<td>0.32</td>
<td>10%</td>
<td>NR</td>
</tr>
<tr>
<td>BPD or death at 36 weeks of gestation</td>
<td>8</td>
<td>957 Studies with entry before 3 d</td>
<td>0.94</td>
<td>0.87 to 1.01</td>
<td>0.084</td>
<td>26%</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1075 Studies with entry after 3 d</td>
<td>0.92</td>
<td>0.85 to 1.01</td>
<td>0.079</td>
<td>51%</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1924 Studies of routine use</td>
<td>0.94</td>
<td>0.87 to 1.02</td>
<td>0.12</td>
<td>11%</td>
<td>High</td>
</tr>
</tbody>
</table>

Adapted from Barrington et al (2017).\(^2\)
BPD: bronchopulmonary dysplasia; CI: confidence interval; INO: inhaled nitric oxide; NR: not reported; QOE: quality of evidence.
\(^a\) QOE assessed using the GRADE tool.

Reviewers found that use of INO in premature infants with respiratory failure did not significantly improve on the outcomes (e.g., death before hospital discharge, BPD at 36 weeks of postmenstrual age) or the combined outcome (BPD or death at 36 weeks of postmenstrual age). Findings were not statistically significant in subgroups of studies that enrolled patients before 3 days old, enrolled patients after 3 days, and that used INO routinely. A fourth primary outcome (intraventricular hemorrhage) was only pooled in studies with entry before 3 days, and again did not find a significant benefit of INO vs control (relative risk [RR], 0.94; 95% confidence interval [CI], 0.69 to 1.28)
A meta-analysis by Yang et al (2016) identified 22 trials comparing INO with a control intervention in preterm infants. Reviewers did not define “preterm” as used to identify studies, beyond use of the keyword in literature searches. A pooled analysis of all 22 studies did not find a significant difference between groups in mortality (RR=1.00; 95% CI, 0.92 to 1.09). There was also no significant difference between INO and control in the rate of severe intracranial hemorrhage in a pooled analysis of 17 studies (RR=0.99; 95% CI, 0.83 to 1.16). However, a pooled analysis of 20 studies did find a significantly lower rate of BPD in the INO groups than in the control groups (RR=0.88; 95% CI, 0.82 to 0.95). Reviewers noted that their findings on BPD differed from those in other meta-analyses and suggested that the difference might have been due to their inclusion of Chinese-language studies.

Previously, an Agency for Healthcare Research and Quality–sponsored systematic review by Donohue et al (2011) of randomized trials on INO for premature infants (<35 weeks of gestation) was published. Thirty-one articles were initially selected; they included 14 unique RCTs. Regardless of how mortality was reported or defined (e.g., death ≤7 days or ≤28 days, or death in the neonatal intensive care unit), there were no statistically significant differences between the INO group and the control group in any of the 14 RCTs or pooled analyses of these RCTs. For example, in a pooled analysis of 11 trials that reported death by 36 weeks of postmenstrual age or in the neonatal intensive care unit, the RR was 0.97 (95% CI, 0.82 to 1.15). Twelve trials reported data on BPD at 36 weeks of postmenstrual age, and despite variations in reporting of BPD, there was no significant benefit of INO treatment in any trial. A pooled analysis of data from 8 trials reporting BPD at 36 weeks of postmenstrual age among survivors found a RR of 0.93 (95% CI, 0.86 to 1.00).

**Randomized Trials**

The largest trial to date was published by Mercier et al (2010). This multicenter industry-sponsored study, known as the European Union Nitric Oxide (EUNO) trial, evaluated low-dose INO therapy. The trial included 800 preterm infants (gestational age at birth between 24 weeks and 28 weeks 6 days) who weighed at least 500 grams and required surfactant or continuous positive airway pressure for respiratory distress syndrome within 24 hours of birth. Patients were randomized to treatment with INO 5 ppm (n=399) or placebo-equivalent nitrogen gas (n=401). Therapy was given for 7 to 21 days (mean duration, 16 days). Of 800 patients, 792 (99%) received their assigned treatment, and all 800 were included in the intention-to-treat analysis.

Primary outcomes were survival without BPD at 36 weeks of postmenstrual age, overall survival at 36 weeks of postmenstrual age, and BPD at 36 weeks of postmenstrual age. Survival without BPD at 36 weeks of postmenstrual age was attained by 258 (65%) of patients in the INO group and by 262 (66%) in the placebo group; this difference was not statistically significant (RR=1.05; 95% CI, 0.78 to 1.43; p=0.73). Overall survival at 36 weeks of postmenstrual age was attained by 343 (86%) in the INO group and by 359 (90%) in the control group (RR=0.74; 95% CI, 0.48 to 1.15; p=0.21). The number of patients with BPD at 36 weeks of postmenstrual age was 81 (24%) in the INO group and 96 (27%) in the control group (RR=0.83; 95% CI, 0.58 to 1.17; p=0.29). The secondary end point (survival without brain injury at gestational age 36 weeks) also did not differ significantly between groups (RR=0.78; 95% CI, 0.53 to 1.17; p=0.23). This end point was attained by 181 (69%) patients in the INO group and 188 (76%) patients in the placebo group.

Serious adverse events (i.e., intraventricular hemorrhage, periventricular leukomalacia, patient ductus arteriosus, pneumothorax, pulmonary hemorrhage, necrotizing enterocolitis, sepsis) were reported in 158 (40%) of 395 patients in the INO group and 164 (41%) of 397 patients in the control group (p=0.72). The most common adverse event was intracranial hemorrhage, which affected 114 (29%) in the INO group and 91 (23%) in the control group (p value not reported).

Durmeyer et al (2013) published 2-year outcomes of the EUNO trial. Of the original 800 patients, 737 (92%) were evaluable at this time point. A total of 244 (67%) of 363 evaluable children at 2 years in the INO group survived without severe or moderate disability compared with 270 (72%) of 374 evaluable children in the placebo group. The difference in disability rates was not
statistically significant (p=0.09). There were also no statistically significant differences between groups in other outcomes (e.g., hospitalization rates, use of respiratory medications, growth).

Section Summary: Hypoxic Respiratory Failure in Premature Neonates
A large number of RCTs have evaluated INO for premature neonates, and most trials have reported no significant differences in primary end points such as mortality and BPD. Meta-analyses of these RCTs have not found better survival rates in patients who receive INO compared with a control intervention. Most meta-analyses also did not find other outcomes (e.g., BPD, intracranial hemorrhage) were improved by INO.

Acute Hypoxemic Respiratory Failure in Adults and Children
Systematic Reviews
Several meta-analyses and RCTs have evaluated the efficacy of INO for treating acute respiratory distress syndrome (ARDS) and acute lung injury (together known as acute hypoxic respiratory failure). Most recently, a Cochrane review by Gebistorf et al (2016) identified 14 RCTs comparing INO with control interventions in adults and children with ARDS.7 The primary objective of the review was to evaluate the effects of INO on mortality, which was measured in several ways. The main findings of the meta-analysis are provided in Table 3.

Table 3. Main Cochrane Findings on INO in Patients with ARDS

<table>
<thead>
<tr>
<th>No. of Trials</th>
<th>N</th>
<th>Outcomes</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>p</th>
<th>P</th>
<th>QOEa</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>1243</td>
<td>Overall mortality</td>
<td>1.04</td>
<td>0.90 to 1.19</td>
<td>0.63</td>
<td>0%</td>
<td>Moderate</td>
</tr>
<tr>
<td>9</td>
<td>1105</td>
<td>Mortality at 28-30 d</td>
<td>1.08</td>
<td>0.92 to 1.27</td>
<td>0.36</td>
<td>0%</td>
<td>Moderate</td>
</tr>
<tr>
<td>Overall mortality stratified by age group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>185</td>
<td>Pediatric</td>
<td>0.78</td>
<td>0.51 to 1.18</td>
<td>0.24</td>
<td>22%</td>
<td>Moderate</td>
</tr>
<tr>
<td>10</td>
<td>1085</td>
<td>Adult</td>
<td>1.09</td>
<td>0.93 to 1.25</td>
<td>0.32</td>
<td>0%</td>
<td>NR</td>
</tr>
</tbody>
</table>

Adapted from Gebistorf et al (2016).7
ARDS: acute respiratory distress syndrome; CI: confidence interval; INO: inhaled nitric oxide; NR: not reported; QOE: quality of evidence.

a QOE assessed using the GRADE tool.

INO was not found to significantly improve mortality when used to treat ARDS. Other outcomes (e.g., mean number of ventilator days, duration of mechanical ventilation) also did not differ significantly between groups. Regarding potential harms associated with INO use in this population, a pooled analysis of 4 trials found a significantly higher rate of renal impairment in groups treated with INO than with a control intervention (RR=1.59; 95% CI, 1.17 to 2.16).

Other systematic reviews and meta-analyses have reported similar findings on mortality.8,9 For example, a systematic review by Adhikari et al (2014) identified 9 RCTs conducted with adults or children (other than neonates) in which at least 80% of patients, or a separately reported subgroup, had ARDS.8 The trials selected compared INO with placebo or no gas, used INO as a treatment of ARDS (i.e., not a preventive measure), and had less than 50% crossover between groups. Findings were not stratified by adult and pediatric populations. A pooled analysis of data from the 9 trials (total N=1142 patients) found no statistically significant benefit of INO on mortality (RR=1.10; 95% CI, 0.94 to 1.29; p=0.24). In a preplanned subgroup analysis, INO did not reduce mortality in patients with severe ARDS (baseline partial pressure of oxygen, arterial [Pao2]/fraction of expired oxygen [Fio2] ≤100 mm Hg) or patients with mild-to-moderate ARDS (baseline Pao2/Fio2 >100 mm Hg).

Adverse Events
A cohort study by Ruan et al (2016) evaluated the risk of renal dysfunction in patients with ARDS treated using INO.10 Using electronic medical record data from a teaching hospital, 547 patients with ARDS were identified. Among these patients, 216 had been treated with and 331 without INO. The 30-day incidence of renal replacement therapy was 34% in the INO group and 23% in the non-INO group. In the final propensity-matched analysis, there was a significantly higher risk of need for renal replacement therapy in the INO group than in the non-INO group (hazard ratio, 1.59; 95% CI, 1.08 to 2.34; p=0.02).
Section Summary: Acute Hypoxemic Respiratory Failure in Adults and Children

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. Moreover, subgroup analysis by age group in a 2016 Cochrane review did not find a significant benefit of INO on mortality in either pediatric or adult studies. There is evidence from a meta-analysis of 4 RCTs included in the Cochrane review and from a cohort study that INO increases the risk of renal impairment in patients with ARDS.

Adults and Children with Congenital Heart Disease Who Have had Heart Surgery

Adults

A trial by Potapov et al (2011) evaluated the prophylactic use of INO in adults undergoing left ventricular assist device implantation for congestive heart failure.11 This double-blind trial was conducted at 8 centers in the United States and Germany. Patients were randomized to INO 40 ppm (n=73) or placebo (n=77) beginning at least 5 minutes before the first weaning attempt from mechanical ventilation. The primary trial outcome was right ventricular dysfunction (RVD). Patients continued use of INO or placebo until they were extubated, reached the study criteria for RVD, or were treated for 48 hours, whichever came first. Patients were permitted to crossover to open-label INO if they failed to wean from mechanical ventilation, still required pulmonary vasodilator support at 48 hours, or met criteria for RVD. Thirteen (9%) of 150 randomized patients did not receive the trial treatment. Also, crossover to open-label INO occurred in 15 (21%) of 73 patients in the INO group and 20 (26%) of 77 in the placebo group. In an intention-to-treat analysis, RVD criteria were met by 7 (9.6%) of 73 patients in the INO group and 12 (15.6%) of 77 patients in the placebo group; this difference between groups was not statistically significant (p=0.33). Other outcomes also did not differ significantly between groups; e.g., mean number of days on mechanical ventilation (5.4 days for INO vs 11.1 days for placebo; p=0.77) and mean number of days in the hospital (41 in each group).

Children

A Cochrane review by Bizzarro et al (2014) identified 4 RCTs (total N=210 patients) comparing postoperative INO with placebo or usual care in the management of children who had congenital heart disease.12 All trials included participants identified as having pulmonary hypertension in the preoperative or postoperative period. Three trials were parallel group, and one was a crossover. Mortality was the primary outcome of the meta-analysis. Two trials (n=162 patients) reported mortality before discharge. A pooled analysis of findings from these 2 trials did not find a significant difference in mortality between the INO group and the control group (OR=1.67; 95% CI, 0.38 to 7.30). Among secondary outcomes, a pooled analysis of 2 studies did not find a significant between-group difference in mean pulmonary arterial hypertension (pooled treatment effect, -2.94 mm Hg; 95% CI, -9.28 to 3.40 mm Hg), and likewise a pooled analysis of 3 studies did not find a significant difference between groups in mean arterial pressure (pooled treatment effect, -3.55 mm Hg; 95% CI, -11.86 to 4.76 mm Hg). Insufficient data were available for pooling other outcomes. Reviewers noted a lack of data on long-term mortality, length of stay in an intensive care unit or hospital, and neurodevelopmental disability, and concerns about the methodologic quality of studies, sample sizes, and heterogeneity between studies. These results did not support a benefit for INO treatment for this patient group. Wide CIs around the pooled treatment effects reflect the relative paucity of available data for each outcome.

The RCT assessing the largest sample was published by Miller et al (2000).13 This trial out of Australia included 124 infants (median age, 3 months) who were candidates for corrective heart surgery. Eligibility requirements included the presence of congenital heart lesions, high pulmonary flow pressure, or both, and objective evidence of pulmonary hypertension in the immediate preoperative period. Participants were randomized to INO gas 10 ppm (n=63) or placebo nitrogen gas (n=61) after surgery until just before extubation. Randomization was stratified by the presence (45/124 [36%]) or absence (79/124 [64%]) of Down syndrome. The
primary outcome was a reduction of pulmonary hypertensive crisis episodes, defined as a pulmonary/systemic artery pressure ratio greater than 0.75. Episodes were classified as major if there was a fall in systemic artery pressure of at least 20% and/or a fall in transcutaneous oxygen saturation to less than 90%. Episodes were classified as minor if the systemic artery pressure and transcutaneous oxygen saturation remained stable. The trial found that infants who received INO after surgery had significantly fewer pulmonary hypertensive crisis episodes (median, 4) than those who received placebo (median, 7; unadjusted RR=0.66; 95% CI, 0.59 to 0.74; p<0.001).

Among secondary outcomes, the median time to eligibility for extubation was significantly shorter in the INO group (80 hours) than in the placebo group (112 hours; p=0.019). There were 5 deaths in the INO group and 3 deaths in the placebo group; this difference was not statistically significant (p=0.49). Similarly, there was no significant between-group difference in median time to discharge from intensive care (138 hours for INO vs 162 hours for placebo; p>0.05). Although this trial reported a reduction in pulmonary hypertensive crisis episodes, changes in this physiologic outcome did not result in improvements in survival or other clinical outcomes. The trial was likely underpowered to detect differences in these more clinically relevant secondary outcomes.

Section Summary: Adults and Children with Congenital Heart Disease Who Have Had Heart Surgery

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 the use of INO for adults with congenital heart disease. One RCT did not find a significant effect of INO treatment on the improvement of postoperative outcomes in adults with congestive heart failure who had left ventricular assist device surgery.

Lung Transplantation

Tavare and Tsakok (2011) reviewed the literature to assess whether the use of prophylactic INO in patients undergoing a lung transplant reduces morbidity and mortality.14 They identified 6 studies, 2 RCTs (Meade et al [2003],15 Perrin et al [2006]16) and 4 uncontrolled cohort studies. They also identified a third RCT (Botha et al [2007]17), which they excluded from their review based on the utility of that trial’s clinical outcomes. Reviewers noted the paucity of controlled studies and the small sample sizes of all available studies. Moreover, they found that none of the RCTs showed INO reduced mortality or morbidity (e.g., time to extubation, length of hospital stay). Thus they concluded that “it is difficult to currently recommend the routine use of prophylactic inhaled NO [nitric oxide] in lung transplant surgery.” Published RCTs are summarized in Table 4.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Interventions</th>
<th>Primary End Points</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meade et al (2003)15</td>
<td>84</td>
<td>INO 20 ppm 10 min after reperfusion vs placebo gas mixture</td>
<td>Duration of mechanical ventilation from admission to ICU to first successful extubation</td>
<td>• No statistically significant difference in time to successful extubation (mean, 25.7 h in INO group vs 27.3 h in control group; p=0.76)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• No statistically significant differences in secondary outcomes (e.g., severe reperfusion injury, time to hospital discharge, hospital mortality, 30-d mortality)</td>
</tr>
<tr>
<td>Perrin et al (2006)16</td>
<td>30</td>
<td>INO 20 ppm at reperfusion for 12 h vs no intervention</td>
<td>Not specified</td>
<td>No statistically significant differences between groups in outcomes (e.g., ICU length of stay, duration of ventilation, fluid balance during 24 h after ICU admission)</td>
</tr>
<tr>
<td>Botha et al (2007)17</td>
<td>20</td>
<td>Prophylactic INO 20 ppm vs standard gas mixture for 30 min of reperfusion</td>
<td>Not specified</td>
<td>No statistically significant differences between groups in development of grade II-III primary graft dysfunction or gas exchange</td>
</tr>
</tbody>
</table>

ICU: intensive care unit; INO: Inhaled nitric oxide; RCT: randomized controlled trial.
Section Summary: Lung Transplantation

Three small RCTs have evaluated INO after lung transplantation, and none found statistically significant improvements in health outcomes. A systematic review of RCTs and observational studies concluded that available evidence did not support the routine use of INO after lung transplant.

Summary of Evidence

For individuals who are neonates, are term or late preterm at birth, and have hypoxic respiratory failure who receive INO, the evidence includes RCTs and a systematic review. Relevant outcomes are overall survival, 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 and the combined outcome of extracorporeal membrane oxygenation or death. The evidence is sufficient to determine that the technology results in a meaningful 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 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 for primary end points such as mortality and bronchopulmonary dysplasia. 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 (e.g., bronchopulmonary dysplasia, intracranial hemorrhage). The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are adults and children in acute hypoxemic 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 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 and a cohort study has suggested that INO may be associated with an increased risk of renal impairment in patients with acute respiratory distress syndrome. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are adults and children with congenital heart disease who have had heart surgery who receive INO, the evidence includes RCTs and a systematic review. 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 the effects of the technology on health outcomes.

For individuals who have lung transplant who receive INO, the evidence includes 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; 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 the effects of the technology on health outcomes.
Supplemental Information

Clinical Input from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2012 Input

Input was received from 2 physician specialty societies and 9 academic medical centers in 2012. There was a consensus that inhaled nitric oxide (INO) may be considered medically necessary as a component of treatment of hypoxic respiratory failure in neonates born at more than 34 weeks of gestation. There was general agreement with the criterion in the Policy Guidelines section for hypoxic respiratory failure—an oxygenation index of at least 25 on 2 measurements made at least 15 minutes apart. Also, input was mixed on whether other indications for INO should be considered investigational. Several reviewers stated that INO is clinically useful for the postoperative treatment of select patients with congenital heart disease.

Also, clinician reviewers generally agreed that INO should be discontinued when extracorporeal membrane oxygenation is initiated. There was near-consensus agreement that prolonged use of INO (e.g., >1-2 weeks in near-term neonates) does not improve outcomes (i.e., beyond a transient improvement in oxygenation). However, there was a wide range of responses to the question on how long INO should be continued once initiated; most reviewers who responded cited an upper limit of not more than 2 weeks.

2010 Input

Input was received from 4 physician specialty societies and 5 academic medical centers in 2010. Input was consistent in its agreement with the policy statements on the treatment of hypoxic respiratory failure in neonates born at 34 or more weeks of gestation and adults with acute respiratory distress syndrome; it was mixed for the statement on premature neonates born at less than 34 weeks of gestation. There was no consensus among reviewers on potential additional medically necessary indications for INO therapy.

Practice Guidelines and Position Statements

Pediatric Pulmonary Hypertension Network

The Pediatric Pulmonary Hypertension Network (2016; a network of clinicians, researchers, and centers) published recommendations on the use of inhaled nitric oxide (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 (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.”

**American Academy of Pediatrics**

In 2000 (reaffirmed in 2009), the American Academy of Pediatrics (AAP) issued recommendations on the use of INO in pediatric patients. The recommendations stated that “Inhaled nitric oxide therapy should be given using the indications, dosing, administration and monitoring guidelines outlined on the product label.” Also, AAP recommended the following:

4. “…INO should be initiated in centers with ECMO [extracorporeal membrane oxygenation] capability…”
5. Centers that provide INO therapy should provide comprehensive long-term medical and neurodevelopmental follow-up.
6. Centers that provide INO therapy should establish prospective data collection for treatment time course, toxic effects, treatment failure, and use of alternative therapies, and outcomes.
7. Administration of INO for indications other than those approved by the FDA [Food and Drug Administration] or in other neonatal populations, including compassionate use, remains experimental…”

AAP provided the following recommendations on the use of INO in premature infants (see Table 5).

**Table 5. Guidelines on Use of INO for Premature Infants**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>QOE</th>
<th>GOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Neither rescue nor routine use of INO improves survival in preterm infants with respiratory failure.”</td>
<td>A</td>
<td>Strong</td>
</tr>
<tr>
<td>“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.”</td>
<td>A</td>
<td>Strong</td>
</tr>
<tr>
<td>“The incidence of cerebral palsy, neurodevelopmental impairment, or cognitive impairment in preterm infants treated with INO is similar to that of control infants.”</td>
<td>A</td>
<td>NR</td>
</tr>
</tbody>
</table>

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**

Not applicable.

**Medicare National Coverage**

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 6.

**Table 6. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCTNo.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NC00515281</td>
<td>Inhaled Nitric Oxide and Neuroprotection in Premature Infants</td>
<td>484</td>
<td>Jan 2017 (ongoing)</td>
</tr>
<tr>
<td>NC1891500a</td>
<td>Early INO for Oxidative Stress, Vascular Tone and Inflammation in Babies With Hypoxic Respiratory Failure</td>
<td>68</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NC1939301</td>
<td>Randomized Trial of Inhaled Nitric Oxide to Treat Acute Pulmonary Embolism</td>
<td>78</td>
<td>Jun 2018</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.
References


### Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
  - Previous treatment(s) and response(s)
  - MD progress notes and orders (specific to inhaled nitric oxide therapy)
  - Inhalation/respiratory therapy notes (specific to inhaled nitric oxide therapy)
    - Arterial blood gases (ABGs)
    - Nitric oxide administration
    - Oxygenation indices
    - Pulse oximetry records

### Post Service

- Discharge summary (if available)

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### Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>HCPCS</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>ICD-10</td>
<td>3E0F7SD</td>
<td>Introduction of Nitric Oxide Gas into Respiratory Tract, Via Natural or</td>
</tr>
<tr>
<td>Procedure</td>
<td></td>
<td>Artificial Opening</td>
</tr>
</tbody>
</table>

### Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>03/30/2012</td>
<td>New Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>01/11/2013</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>04/16/2014</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>06/30/2015</td>
<td>Coding update</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>07/01/2016</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>
**Definitions of Decision Determinations**

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member’s health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member’s eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.