AUSTRALIAN PRODUCT INFORMATION
INOmax® (nitric oxide) Medicinal Gas for Inhalation Cylinder

1. NAME OF THE MEDICINE

Nitric oxide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

INOmax® (nitric oxide) is a drug administered by inhalation. Nitric oxide, the active substance in INOmax®, is a pulmonary vasodilator. INOmax® is a gaseous blend of nitric oxide and nitrogen (0.08% and 99.92%, respectively for 800 ppm). INOmax 4,880® is a gaseous blend of nitric oxide (0.488%) and nitrogen (99.512%). INOmax® is supplied in aluminium cylinders as a compressed gas under high pressure (13, 789.51 kPa gauge). INOmax 4,880 ppm is supplied in aluminium cylinders as a compressed gas under high pressure (20,684.2 kPa gauge).

3. PHARMACEUTICAL FORM

Medicinal Gas for Inhalation Cylinder

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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, to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation.
- to selectively decrease pulmonary arterial pressure in patients with perioperative pulmonary hypertension in conjunction with heart surgery.

4.2 DOSE AND METHOD OF ADMINISTRATION

Persistent Pulmonary Hypertension in the Newborn (PPHN)

Prescription of nitric oxide should be supervised by a physician experienced in neonatal intensive care. Prescription should be limited to those neonatal units that have received adequate training in the use of a nitric oxide delivery system. INOmax® should only be delivered according to a neonatologist's prescription.

INOmax® should be used in ventilated infants expected to require support > 24 hours. INOmax® should be used only after respiratory support has been optimised. This includes optimising tidal volume/pressure and lung recruitment (surfactant, high frequency ventilation, and positive end expiratory pressure).

Dosage
INOmax® should only be used after respiratory support is optimised including the use of surfactant. The maximum recommended dose of INOmax® is 20 ppm and this dose should not be exceeded, as the risk of methaemoglobinaemia and increased NO_2 increases significantly at doses > 20 ppm. In the key clinical trials, the starting dose was 20 ppm. Starting as soon as possible and within 4-24 hours of therapy, the dose

should be weaned to 5 ppm provided that arterial oxygenation is adequate at this lower dose. Inhaled nitric oxide therapy should be maintained at 5 ppm until there is improvement in the neonate's oxygenation such that the FiO_2 (fraction of inspired oxygen) < 0.60.

Treatment can be maintained up to 96 hours or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from INOmax® therapy. The duration of therapy is variable, but typically less than four days. In cases of failure to respond to inhaled nitric oxide refer to Section 4.4 Special Warnings and Precautions for Use.

Weaning
Attempts to wean INOmax® should be made after the ventilator support is substantially decreased or after 96 hours of therapy (see Section 4.4 Special Warnings and Precautions for Use). When the decision is made to discontinue inhaled nitric oxide therapy, the dose should be reduced to 1 ppm for 30 minutes to one hour. If there is no change in oxygenation during administration of INOmax® at 1 ppm the FiO_2 should be increased by 10%, the INOmax® is discontinued, and the neonates monitored closely for signs of hypoxaemia. If oxygenation falls >20%, INOmax® therapy should be resumed at 5 ppm and discontinuation of INOmax® therapy should be reconsidered after 12 to 24 hours. Infants who cannot be weaned off INOmax® by 4 days should undergo careful diagnostic work-up for other diseases.

Pulmonary Hypertension associated with Cardiac Surgery

Prescription of nitric oxide should be supervised by a physician experienced in cardiothoracic anaesthesia and intensive care. Prescription should be limited to those anaesthetic and intensive care units that have received adequate training in the use of a nitric oxide delivery system. INOmax® should only be delivered according to a specialist's prescription.

INOmax® should be used only after conservative support has been optimized. In clinical trials INOmax® has been given in addition to other standard treatment regimens in the cardiac surgery setting, including inotropic and vasoactive medicinal products. INOmax® should be administered under close monitoring of haemodynamics and oxygenation.

Dosage
Paediatric use (ages 0-17 years)
The starting dose of inhaled nitric oxide is 10 ppm of inhaled gas. The dose may be increased up to 20 ppm if the lower dose has not provided sufficient clinical effects.

Clinical data supporting the suggested dose in the age range of 12-17 years is limited.

Adults (over 17 years)
The dose range for adult patients with pulmonary hypertension in the context of cardiac surgery is 10 – 20 ppm of inhaled nitric oxide.

The lowest effective dose should be administered, and the dose should be weaned down to 5 ppm provided that the clinical effect remains adequate at this lower dose.

Inhaled nitric oxide has a rapid onset of action; decrease in pulmonary artery pressure and improved oxygenation is seen within 5-20 minutes. In case of insufficient response the dose may be titrated after a minimum of 10 minutes.

Consideration should be given to discontinuation of treatment if no beneficial physiological effects are apparent after a 30-minute trial of therapy.

Treatment may be initiated at any time point in the peri-operative course to lower pulmonary pressure. In clinical studies treatment was often initiated before separation from Cardiopulmonary Bypass. Inhaled NO has been given for time periods up to 7 days in the peri- and post-operative setting, but common treatment duration is 24 - 48 hours.

Weaning
Attempts to wean INOmax® should be commenced as soon as the haemodynamics have stabilised in conjunction to weaning from ventilator and inotropic support. The withdrawal of inhaled nitric oxide therapy should be performed in a stepwise manner. The dose should be incrementally reduced to 1 ppm for 30 minutes with close observation of systemic and central pressure and then turned off. Weaning should be attempted at least every 12 hours when the patient is stable on a low dose of INOmax®.

INOmax® must not be stopped abruptly. Too rapid weaning from inhaled nitric oxide therapy carries the risk of a rebound increase in pulmonary artery pressure with subsequent circulatory instability.

Administration

Method
Do not use INOmax® undiluted. INOmax® is delivered to the patient via mechanical ventilation after dilution with an oxygen/air mixture using an approved nitric oxide gas delivery system provided by the sponsor that meets the criteria specified below. The controlled flow of 800 ppm INOmax® is delivered to the ventilator circuit via the injector tube where it is diluted by the ventilator gas flow to the concentration set by the operator. This concentration must not exceed 20 ppm. The delivery system must provide a constant inhaled nitric oxide concentration irrespective of the ventilator. INOmax® should be administered with monitoring for PaO_2, methaemoglobin and NO_2.

The delivery system must provide a constant inhaled INOmax® concentration irrespective of the ventilator. With a continuous flow neonatal ventilator, this may be achieved by infusing a low flow of INOmax® into the inspiratory limb of the ventilator circuit. Intermittent flow neonatal ventilation may be associated with spikes in nitric oxide concentration. The nitric oxide delivery system for intermittent flow ventilation should be adequate to avoid spikes in nitric oxide concentration.

The inspired INOmax® concentration must be measured continuously in the inspiratory limb of the circuit near the patient. The nitrogen dioxide (NO_2) concentration and FiO_2 must also be measured at the site using calibrated and approved monitoring equipment. For patient safety, appropriate alarms must be set for INOmax® (± 2 ppm of the prescribed dose), NO_2 (0.5 ppm) and FiO_2 (± 0.05). The INOmax® gas cylinder pressure must be displayed to allow timely gas cylinder replacement without inadvertent loss of therapy and backup gas cylinders must be available to provide timely replacement. INOmax® therapy must be available for manual ventilation such as suctioning, patient transport, and resuscitation.

In the event of a primary system failure or a wall-outlet power failure, in order to reduce the risk of rebound pulmonary hypertension, a system for nitric oxide administration must comprise backup battery power supply and two back-up systems – an integrated back-up system incorporated into the primary delivery system that allows back-up nitric oxide delivery while the patient remains mechanically ventilated, and an independent back-up system that can deliver nitric oxide while the patient is manually ventilated. Each

back-up system must be able to deliver nitric oxide pneumatically in the event of primary system failure. The power supply for the monitoring equipment should be independent of the delivery device function.

The upper limit of exposure (mean exposure) to nitric oxide for personnel (as defined by worker's legislation in most countries including Australia) is 25 ppm for 8 hours (30 mg/M^3) and the corresponding limit for NO_2 is 2-3 ppm (4-6 mg/M^3).

Training
The sponsor provides training to relevant hospital personnel, and ongoing 24-hour, 7 days a week technical support service, on the proper use of INOmax® in conjunction with the nitric oxide gas delivery system provided by the sponsor.

The key elements that need to be covered in training hospital personnel are as follows:

Correct set-up and connection
- Connections to the gas cylinder and to the ventilator patient breathing circuit.

Operation
- Pre-use check list procedure (a series of steps required immediately prior to each patient initiation to ensure that the system is working properly, and the system is purged of NO_2)
- Setting the device for the correct concentration of nitric oxide to be administered
- Setting the NO, NO_2, and O_2 monitors for high and low alarm limits.
- Using the manual backup delivery system
- Procedures for correctly switching gas cylinders and purging system.
- Troubleshooting alarms
- NO, NO_2, and O_2 monitor calibration.
- Monthly system performance check-up procedures

Monitoring for Methaemoglobin
Neonates are known to have diminished MetHb reductase activity compared to adults. Methaemoglobin level should be measured within one hour after initiation of INOmax® therapy, using an analyser which can reliably distinguish between foetal haemoglobin and methaemoglobin. If it is > 2.5% the INOmax® dose should be decreased and the administration of reducing agents may be considered. Although it is unusual for methaemoglobin level to increase significantly if the first level is low, it is prudent to repeat methaemoglobin measurement every one to two days.

Monitoring formation of Nitrogen Dioxide
Immediately prior to each patient initiation, proper procedure must be applied to purge the system of NO_2. The NO_2 concentration should be maintained as low as possible and always < 0.5 ppm. If the NO_2 is > 0.5 ppm, the delivery system should be assessed for malfunction, the NO_2 analyser should be recalibrated and the INOmax® and/or FiO_2 should be reduced if possible. If there is an unexpected change in INOmax® concentration, the delivery system should be assessed for malfunction and the analyser should be recalibrated.

The sponsor provides ongoing 24-hour, 7 days a week technical support service for INOmax® and the approved delivery system provided by the sponsor.

4.3 CONTRAINDICATIONS

Neonates known to be dependent on right-to-left or significant left-to-right shunting of blood. Hypersensitivity to the active substance or any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Do not use INOmax® undiluted. INOmax® is delivered to the patient via mechanical ventilation after dilution with an oxygen/air mixture using an approved nitric oxide gas delivery system provided by the sponsor that meets the criteria specified in Section 4.2 Dose and Method of Administration. The controlled flow of 800 ppm INOmax® is delivered to the ventilator circuit via the injector tube where it is diluted by the ventilator gas flow to the concentration set by the operator. This concentration must not exceed 20 ppm. The delivery system must provide a constant inhaled nitric oxide concentration irrespective of the ventilator. INOmax® should be administered with monitoring for PaO_2, methaemoglobin and NO_2. The sponsor provides training to relevant hospital personnel, and ongoing 24-hour, 7 days a week technical support service, on the proper use of INOmax® in conjunction with the nitric oxide gas delivery system provided by the sponsor.

If it is judged that clinical response is inadequate at 4-6 hours after starting INOmax®, the following should be considered:

- For patients who are referred to another hospital, to prevent worsening of their condition on acute discontinuation of INOmax®, the availability of nitric oxide during transport should be assured.

- Rescue, such as ECMO where available should be considered based on continued deterioration or failure to improve defined by criteria based on local circumstances.

Rebound pulmonary hypertension syndrome following abrupt discontinuation.
The INOmax® dose should not be discontinued abruptly as it may result in an increase in pulmonary artery pressure (PAP) and/or worsening of blood oxygenation (PaO_2), i.e. rebound pulmonary hypertension syndrome. Signs and symptoms of rebound pulmonary hypertension syndrome include hypoxaemia, systemic hypotension, bradycardia and decreased cardiac output. If rebound pulmonary hypertension syndrome occurs, reinstate therapy immediately. Deterioration in oxygenation and elevation in PAP may also occur in neonates with no apparent response to INOmax®. Weaning from inhaled nitric oxide should be performed with caution. For patients transported to other facilities for additional treatment, who need to continue with inhaled nitric oxide, arrangements should be made to ensure the continuous supply of inhaled nitric oxide during transportation. The physician should have access at the bedside to a reserve nitric oxide delivery system.

Methaemoglobinaemia
A large portion of nitric oxide for inhalation is absorbed systemically. The end products of nitric oxide that enter the systemic circulation are predominantly methaemoglobin and nitrate. The concentrations of methaemoglobin in the blood should be measured (see Section 4.2 Dose and Method of Administration) within one hour after initiation of INOmax® therapy, using an analyser which can reliably distinguish between foetal haemoglobin and methaemoglobin. If it is > 2.5% the INOmax® dose should be decreased and the administration of reducing agents may be considered. Although it is unusual for methaemoglobin level to increase significantly if the first level is low, it is prudent to repeat methaemoglobin measurement every one to two days.

Methaemoglobinaemia increases with the dose of nitric oxide. In the clinical trials, maximum methaemoglobin levels usually were reached approximately 8 hours after initiation of inhalation, although methaemoglobin levels have peaked as late as 40 hours following initiation of INOmax® therapy.

Elevated NO_2 Levels
NO_2 rapidly forms in gas mixtures containing nitric oxide and O_2, and nitric oxide may in this way cause airway inflammation and damage. The dose of nitric oxide should be reduced if the concentration of nitrogen dioxide exceeds 0.5 ppm (see Section 4.2 Dose and Method of Administration).

Left Ventricular Dysfunction
In a diagnostic study of pulmonary vasoreactivity in children, all patients received inhaled nitric oxide and oxygen. Some patients who had pre-existing left ventricular dysfunction (as indicated by elevated baseline pulmonary capillary wedge pressure), treated with nitric oxide, even for short durations, experienced an increased rate of serious adverse events including: increased pulmonary capillary wedge pressure, pulmonary oedema (30% (3 of 10 subjects); compared to 6.5% (8 of 124 subjects) for the entire cohort), worsening of left ventricular dysfunction, systemic hypotension, bradycardia and cardiac arrest. During the course of the study, the protocol was amended to exclude patients with a pulmonary capillary wedge pressure > 20 mmHg. The benefit/risk of using inhaled nitric oxide in patients with clinically significant left ventricular dysfunction should be evaluated on a case-by-case basis. Consider reducing left ventricular afterload to minimize the occurrence of pulmonary oedema. Alternatively, discontinue INOmax® while providing symptomatic care. INOmax® has not been approved by the TGA for diagnostic use and its safety and efficacy in this setting has not been established.

Cardiac insufficiency
Treatment with inhaled nitric oxide might aggravate cardiac insufficiency in a situation with left-to-right shunting. This is due to unwanted pulmonary vasodilation caused by inhaled nitric oxide, resulting in a

further increase of already existing pulmonary hyperperfusion. It, therefore, is recommended that prior to the administration of nitric oxide, pulmonary artery catheterisation or echocardiographic examination of central haemodynamics be performed.

Bleeding time
Animal models have shown that nitric oxide may interact with haemostasis, resulting in an increased bleeding time. Nitric oxide may modulate platelet function via the guanylate cyclase signalling pathway. Data in adult humans are conflicting, and there has been no increase in bleeding complications in randomised controlled trials in term and near-term neonates with hypoxic respiratory failure.

Congenital diaphragmatic hernia
In clinical trials, no efficacy has been demonstrated with the use of inhaled nitric oxide in patients with congenital diaphragmatic hernia.

Pulmonary veno-occlusive disease
Cases of pulmonary oedema have been reported with vasodilators, including nitric oxide, when used in patients with pulmonary veno-occlusive disease. Consequently, if signs of pulmonary oedema occur when INOmax is administered in patients with pulmonary arterial hypertension, the possibility of pulmonary veno-occlusive disease should be considered. If confirmed, the treatment is to be discontinued.

Long term effects
Long-term effects, particularly with regard to pulmonary and neurodevelopmental outcomes associated with INOmax®, have not been established beyond 18-24 months. The 18-24 months follow-up study of NINOS subjects was based on a relatively small number of patients treated with placebo (n=84) and inhaled nitric oxide (n=88), and the one-year follow-up data of CINRGI subjects was based on 71 patients in the placebo and 74 patients in the inhaled nitric oxide groups. In view of the potential long-term sequelae associated with the underlying condition, persistent pulmonary hypertension of the newborn, and the unknown long-term effects of INOmax®, it is recommended that these babies be monitored long-term regarding pulmonary, neurodevelopmental, growth and auditory outcomes.

Paediatric Use
Persistent Pulmonary Hypertension in the Newborn (PPHN)
Nitric oxide for inhalation has been studied in a neonatal population (up to 14 days of age). The safety and efficacy of INOmax® in premature infants less than 34 weeks of gestation has not yet been established.

Pulmonary Hypertension associated with Cardiac Surgery
Published literature reports in randomised, controlled studies provide additional information regarding the efficacy of inhaled nitric oxide in cardiac surgery patients aged 0 – 17 years. Clinical data supporting the suggested dose in the age range of 12-17 years is limited.

Use in the Elderly
No specific studies have been carried out in elderly patients.

Effect on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No drug-interaction studies have been performed. A clinically significant interaction with other medications used in the treatment of hypoxic respiratory failure cannot be excluded based on the available data. There may be an additive effect with INOmax® on the risk of developing methaemoglobinaemia with nitric oxide donor compounds, including sodium nitroprusside and nitroglycerine. INOmax® has been administered with tolazoline, dopamine, dobutamine, steroids, surfactant, and high-frequency ventilation. Experimental studies have suggested that nitric oxide and also nitrogen dioxide may react chemically with surfactant and/or surfactant proteins.

There is an increased risk of methaemoglobin formation if substances with a known tendency to increase methaemoglobin concentrations or are known to produce oxidative damage to the erythrocytes, are administered concomitantly with nitric oxide (e.g. prilocaine, alkyl nitrates and sulphonamides). The effects of these agents with INOmax® on methaemoglobin formation can be expected to be at least additive. Substances known to cause increased methaemoglobin levels, or that are known to produce oxidative damage to the erythrocytes, should be used with caution during therapy with inhaled nitric oxide. Appropriate pharmaceutical guidance should be sought before such agents are used concurrently with INOmax®.

The combined use with other vasodilators (e.g. sildenafil) is not extensively studied. Available data suggest additive effects on central circulation, pulmonary artery pressure and right ventricular performance. Inhaled nitric oxide combination with other vasodilators acting by the cGMP or cAMP systems should be done with caution.

In the presence of oxygen, nitric oxide is rapidly oxidised to derivatives which are toxic to the bronchial epithelium and alveolo-capillary membrane. Nitrogen dioxide (NO_2) is the main compound formed, and during treatment with nitric oxide, the NO_2 concentration should be < 0.5 ppm in the nitric oxide dose range < 20 ppm. If at any time the NO_2 concentration exceeds 1 ppm, the nitric oxide dose should immediately be reduced (see Section 4.2 Dose and Method of Administration).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
There are no animal or human studies to evaluate nitric oxide for effects on fertility.

Use in Pregnancy: Category B2
Animal reproduction studies have not been conducted with nitric oxide. It is not known if nitric oxide can cause foetal harm when administered to pregnant women or can affect reproductive capacity.

Use in Lactation
It is not known whether nitric oxide is excreted in human milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Persistent Pulmonary Hypertension of the Newborn (PPHN)

Controlled studies in the PPHN indication have included 325 patients on INOmax® doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOmax®, a result adequate to exclude INOmax® mortality being more than 40% worse than placebo.

In both the NINOS and CINRGI studies, the duration of hospitalisation was similar in INOmax® and placebo-treated groups.

Formation of methaemoglobin >5% has been observed despite administration of INOmax® at appropriate concentrations. Neonates have diminished MetHb reductase activity and could, therefore be at risk of developing methaemoglobinaemia.

Rapid rebound reactions such as intensified pulmonary vasoconstriction and hypoxaemia after sudden withdrawal of inhaled nitric oxide therapy have been described, precipitating cardiopulmonary collapse. The patient should be treated with increased FiO_2 and/or by reinstalment of therapy with inhaled nitric oxide. When possible, inhaled nitric oxide should be continued until the underlying disease has resolved.

NO_2 rapidly forms in gas mixtures containing nitric oxide and O_2, and NO_2 may in this way cause airway inflammation and damage. There are also animal data suggesting an increased susceptibility to airway infection upon exposure to low levels of NO_2.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOmax® and 212 patients who received placebo. Among these patients, there was no evidence of an adverse effect of treatment on the need for rehospitalisation, special medical services, pulmonary disease, or neurological sequelae.

In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial haemorrhage, Grade IV haemorrhage, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary haemorrhage, or gastrointestinal haemorrhage.

The incidence of periventricular leukomalacia was 5% with INOmax® and 2.6% in the placebo group.

Table 1 below shows adverse effects with an incidence of at least 5% on INOmax® in the CINRGI study, and that were more common on INOmax® than on placebo.

Table 1: Adverse Effects in the CINRGI Trial

Adverse Effect	Placebo (n=89)	Inhaled NO (n=97)
Hypotension	9 (10%)	13 (13%)
Bacteraemia and/or Local Infection	5 (6%)	13 (13%)
Rebound Hypoxaemia on Withdrawal	9 (10%)	12 (12%)
Atelectasis	8 (9%)	9 (9%)
Haematuria	5 (6%)	8 (8%)
Hyperglycaemia	6 (7%)	8 (8%)
Stridor	3 (3%)	5 (5%)
Cellulitis	0 (0%)	5 (5%)

The following adverse reactions were also reported in >5% of patients in the CINRGI trial: Thrombocytopenia (very common - > 1/10), hypokalaemia (common, >1/100, <1/10) and hyper-bilirubinaemia (common).

Long-term safety

Follow-up exams were performed at 18-24 months for infants enrolled in the NINOS study. In those available for follow-up, there were no statistically significant differences between the two treatment groups with respect to mental, motor, audiological, visual, or neurological evaluations. Mental development of the infants, as assessed by the Bayley scale of mental developmental index (MDI) was similar between the treatment groups. However, post-hoc analysis of adverse events for the actual-gas-received population showed some numerical differences between treatment groups (see Table 2 below).

Table 2: Adverse Events at 18-24 months of follow-up in NINOS subjects actual-gas-received population.

Adverse Events	Placebo	INO (all doses) *
Gait Disturbance (gait functional, gait device required, and no independent walking)	15/84 (17.9%)	22/88 (25.0%)
Cerebral Palsy Present	8/84 (9.5%)	11/88 (12.5%)
At Least One Seizure Since Discharge	12/85 (14.1%)	5/88 (5.7%)
Sensorineural Loss	6/75 (8.0%)	8/73 (11.0%)
Mean Bayley PDI ± STD	94.4 ± 17.9	85.0 ± 21.3
PDI < 50	3/76 (3.9%)	11/83 (13.3%)

*Patients received maximum 20 ppm or 80 ppm iNO as per the study protocol.

Long-term effects of INOmax®, particularly with regard to pulmonary and neurodevelopmental outcomes, have not been established beyond 18-24 months.

Data from the one-year follow-up of CINRGI study subjects (85% follow-up rate) showed that patients in the inhaled nitric oxide group had a higher hearing loss (4%) than those in the placebo group (0%). Additionally, patients treated with inhaled nitric oxide had a higher incidence of cerebral palsy (4%) than placebo (1%).

From the one-year follow-up of 145 patients of the original 155 infants in the study INO-01/02, 23% of patients in the inhaled nitric oxide group and 14% in placebo group had severe impairment of overall

assessment of neurological status. Patients in this study were treated with 5 ppm, 20 ppm or 80 ppm inhaled nitric oxide. However, there was no clear dose–response relationship between the adverse event and the nitric oxide dose.

The overall 5-year follow-up rate of NINOS and CINRGI study subjects was only 25%. These data were based on 43 patients in the placebo group and 55 patients in the inhaled nitric oxide group. Patients treated with nitric oxide had a significantly higher incidence of gait disturbance at 5-years (16% in inhaled nitric oxide group, 2% in placebo group, p=0.04). Additionally, the percentage of vision problems and recurrent non-febrile seizures was higher among inhaled nitric oxide patients. Due to the low follow-up rate, valid conclusions cannot be made.

Pulmonary Hypertension associated with Cardiac Surgery

Published clinical studies in the paediatric cardiac surgery population do not indicate any adverse events additional to those previously identified in controlled clinical studies in the PPHN indication. Whilst systematic monitoring of adverse events was either not included or incompletely reported in these published studies, such monitoring has been included in the post-marketing surveillance program. Published data from adult studies in cardiac surgery, transplantation or left ventricular assist device placement, support the known safety profile for inhaled nitric oxide. (see Section 4.4 Special Warnings and Precautions for Use; SECTION 4.8 Adverse Effects (Undesirable Effects)).

Post-Marketing Experience

The following adverse effects have been reported as part of the post-marketing surveillance. These events have not been reported above. Given the nature of spontaneously reported post-marketing surveillance data, it is impossible to determine the actual incidence of the events or definitively establish their causal relationship to the drug. The listing is alphabetical: dose errors associated with the delivery system; headaches associated with environmental exposure of INOmax® in hospital staff; bradycardia, hypotension and hypoxaemia associated with acute withdrawal of the drug; pulmonary oedema in patients with CREST syndrome.

Accidental exposure

Based upon post-marketing experience, accidental exposure of hospital staff to nitric oxide for inhalation has been associated with chest discomfort, dizziness, dry throat, dyspnoea, and headache.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Overdosage with INOmax® will be manifest by elevations in methaemoglobin and NO_2. Elevated NO_2 may cause acute lung injury. Elevations in methaemoglobinaemia reduce the oxygen delivery capacity of the circulation. In clinical studies, NO_2 levels >3 ppm or methaemoglobin levels >7% were treated by reducing the dose of, or discontinuing, INOmax®.

Methaemoglobinaemia that does not resolve after reduction or discontinuation of therapy can be treated with intravenous vitamin C, or blood transfusion, based upon the clinical situation.

For information on the management of overdosage, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic class: Pulmonary vasodilator

Mechanism of action
Nitric oxide is a compound produced by many cells of the body. It relaxes vascular smooth muscle by binding to the haem moiety of cytosolic guanylate cyclase, activating guanylate cyclase and increasing intracellular levels of cyclic guanosine 3',5'-monophosphate, which then leads to vasodilation. When inhaled, nitric oxide produces selective pulmonary vasodilation.

Pharmacodynamics
Effects on Pulmonary Vascular Tone in PPHN: Persistent pulmonary hypertension of the newborn (PPHN) occurs as a primary developmental defect or as a condition secondary to other diseases such as meconium aspiration syndrome (MAS), pneumonia, sepsis, hyaline membrane disease, congenital diaphragmatic hernia (CDH), and pulmonary hypoplasia. In these states, pulmonary vascular resistance (PVR) is high, which results in hypoxaemia secondary to right-to-left shunting of blood through the patent ductus arteriosus and foramen ovale. In neonates with PPHN, INOmax® improves oxygenation (as indicated by significant increases in PaO_2).

INOmax® appears to increase the partial pressure of arterial oxygen (PaO_2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from lung regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios.

Clinical Trials

Persistent Pulmonary Hypertension of the Newborn (PPHN)

The efficacy of INOmax® has been investigated in term and near-term newborns with hypoxic respiratory failure resulting from a variety of aetiologies. Inhalation of INOmax® reduces the oxygenation index (OI= mean airway pressure in cm H_2O x fraction of inspired oxygen concentration [F_iO_2] x 100 divided by systemic arterial concentration in mm Hg [P_aO_2]) and increases PaO_2 (see Pharmacodynamic Properties).
NINOS study: The Neonatal Inhaled Nitric Oxide Study (NINOS) group conducted a double-blind, randomised, placebo-controlled, multi-centre trial in 235 neonates with hypoxic respiratory failure. The objective of the study 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 PaO_2 of 46 mm Hg and a mean oxygenation index (OI) of 43 cm H_2O / mm Hg were initially randomised to receive 100% O_2 with (n=114) or without (n=121) 20 ppm nitric oxide for up to 14 days with a median duration of exposure of 40 hours. Response to study drug was defined as a change from baseline in PaO_2 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. The primary results from the NINOS study are presented in Table 3.

Table 3
Summary of Clinical Results from NINOS Study

	Control (n=121)	NO (n=114)	P value
Death or ECMO[a,b]	77 (64%)	52 (46%)	0.006
Death	20 (17%)	16 (14%)	0.60
ECMO	66 (55%)	44 (39%)	0.014

[a] Extracorporeal membrane oxygenation

[b] Death or need for ECMO was the study's primary end point

Although 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 PaO_2 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 effects collected in the NINOS trial occurred at similar incidence rates in both treatment groups (see Section 4.8 Adverse Effects (Undesirable Effects). 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, audiology, or neurological evaluations.

CINRGI study: This study was a double-blind, randomised, placebo-controlled, multicentre 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 PaO_2 of 54 mm Hg and a mean OI of 44 cm H_2O / 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 PaO_2 >60 mm Hg and a pH < 7.55 were weaned to 5 ppm INOmax® or placebo in 4 to 24 hours with a median duration of exposure of 44 hours. The primary results from the CINRGI study are presented in Table 4.

Table 4
Summary of Clinical Results from CINRGI Study

	Placebo	INOmax®	P value
ECMO[a,b]	51/89 (57%)	30/97 (31%)	< 0.001
Death	5/89 (6%)	3/97 (3%)	0.48

[a] Extracorporeal membrane oxygenation

[b] ECMO was the primary end point of this study.

Significantly fewer neonates in the INOmax® group required ECMO compared to the control group (31% vs. 57%, p<0.001). While 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 PaO_2, 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 methaemoglobin levels >4%. The frequency and number of adverse effects reported were similar in the two study groups (see Section 4.8 Adverse Effects (Undesirable Effects).

In clinical trials, no efficacy has been demonstrated with the use of INOmax® in patients with congenital diaphragmatic hernia.

Pulmonary Hypertension associated with Cardiac Surgery in children (0-17 years)

In patients undergoing cardiac surgery, an increase in pulmonary artery pressure due to pulmonary Vaso-constriction is frequently seen. Inhaled nitric oxide has been shown to selectively reduce pulmonary vascular resistance and reduce the increased pulmonary artery pressure. This may increase the right ventricular ejection fraction. These effects in turn lead to improved haemodynamics in the pulmonary circulation and oxygenation. Published literature has been used as the basis for approval of this indication.

In children, nine randomised controlled trials (RCT) involving a total of 321 children undergoing cardiac surgery (mostly for congenital heart disease) were assessed as published study reports for the indication of peri- and postoperative pulmonary hypertension in paediatric cardiac surgery. Four of the nine studies were defined as key studies, two of which (Miller *et al*, 2000; Russell *et al*, 1998) were placebo-controlled, double blind studies, while the other two (Day *et al*, 2000; Morris *et al*, 2000) were controlled against conventional therapy.

The largest RCT by **Miller *et al*** (2000) randomised 124 children (age range 1 to 5 months) to treatment with inhaled NO 10 ppm (n=63) or placebo nitrogen (n=61) after surgery (after chest radiography and measurement of arterial blood gas and cardiac index) until just before extubation. Routine care post-surgery in both treatment groups included hyperventilation and vasodilators and an additional iNO 10 ppm could be used as rescue therapy. The median number of pulmonary hypertensive crises (PHTC) (per patient) was 4 and 7 crises respectively in the two groups (relative risk, unadjusted 0·66, p<0·001, adjusted for dispersion 0·65, p=0·045).

Miller *et al* (2000) also documented favourable outcomes for inhaled nitric oxide (iNO) patients on other secondary clinical endpoints such as shorter time until criteria for extubation were met (80 h [38-121] vs. 112 h [63-164], p=0.019) and shorter total time on study gas by 30 h for the nitric oxide group (87 h [43-125] vs. 117 h [67-168], p=0.023). Other secondary endpoints, such as length of stay in ICU were in favour of iNO treatment, but not statistically significant.

Russell *et al* (1998) randomised 40 children (age range 2 days to 6.5 years) with preoperative pulmonary hypertension (mean pulmonary arterial pressure (mPAP) >50% of mean systemic arterial pressure (mSAP)) to inhaled NO at a dose of 80 ppm or placebo for 20 minutes in the period immediately following cardiopulmonary bypass (CBP). In patients who emerged from CPB with pulmonary hypertension (PH) (13 in total; 5 received inhaled NO, 8 received placebo nitrogen), iNO reduced mPAP by 19% vs. an increase of 9% in the placebo group. No effect on mPAP was observed in patients emerging from CPB without pulmonary hypertension (n=23). All patients who emerged from CPB with PH and received iNO had a response to treatment (i.e. all experienced a decline in mPAP ranging from 8% to 35%

at 20 minutes); there were no non-responders in the iNO group. This study shows that only patients with pulmonary hypertension after surgery responded with a lowering of pulmonary pressures.

The RCT by **Day *et al*** (2000) assessed the effects of iNO on the incidence of PHTC in patients after corrective operation or heart transplantation due to congenital heart disease. Patients were randomised to either conventional therapy, (n=19; age range 1 day to 3 years) or to treatment with iNO 20 ppm (n=19; age range 1 day to 20 years). There were no differences in acute haemodynamic and blood gas measurements between the two groups 1 hours after treatment. In addition, the iNO and control groups showed no significant difference in the incidence of PHTC (3 vs. 4 patients, respectively), although the study was underpowered to detect such differences.

In a prospective, randomised, crossover study, **Morris *et al*** (2000) investigated the haemodynamic effects of iNO against control therapy involving mild alkalosis (pH 7.5) induced by hyperventilation (HV), in a group of 12 children (age range 0.1 – 17.7 years) with postoperative PH (mPAP >25 mmHg) after surgical repair of congenital heart disease. Inhaled NO and HV were both effective at lowering PAP and pulmonary vascular resistance (PVR), producing significant changes compared to baseline, but there were no significant differences between the two treatments. HV produced a significant increase in mean systemic vascular resistance index (SVRI) and a significant reduction in cardiac index (CI), relative to baseline, but iNO did not have significant effects on systemic haemodynamics. The differences between the two treatments for SVRI and CI were not statistically significant, but the selective action of iNO on the pulmonary circulation offered advantages over HV because a decrease in cardiac output and an increase in systemic vascular resistance (SVR) are undesirable in the postoperative period.

Pulmonary Hypertension associated with Cardiac Surgery in adults.

The selective pulmonary anti-hypertensive effect of iNO in this population has been demonstrated in randomised studies comparing iNO with placebo, conventional therapy, prostaglandin, nitroprusside/nitroglycerin, prostacyclin, and milrinone. The main efficacy results are seen in PAP and PVR.

A total of 15 prospective randomised controlled trials involving 512 adult patients (296 treated with iNO) were assessed as published study reports for the indication of perioperative PHT in conjunction with cardiac surgery. Four of these were controlled studies: Argenziano *et al* (1998) was a placebo-controlled double-blind study and Knothe *et al* (1996), Fernandes *et al* (2011) and Rajek *et al* (2000) were controlled against conventional therapy. Their designs and results are detailed below.

Argenziano *et al* (1998) was a placebo-controlled, double blind randomised study investigating the effects of iNO (20ppm) versus placebo (N_2) in 11 patients (mean age: 55±3 years) with PHT (mPAP>25 mmHg) implanted with a left ventricular assist device (LVAD) for advanced heart failure. Patients randomised to placebo were to be crossed over to receive iNO if no clinical response was obtained after 15minutes. In the iNO group, PAP decreased rapidly from 35±6 mmHg to 24±4 mmHg (p=0.02) and the LVAD flow index increased from 1.9±0.2 L/min/m^2 to 2.7±0.3 L/min/m^2 (p=0.02). In the placebo group, no significant change was seen in PAP or LVAD flow index.

Knothe *et al* (1996) was a randomised open study investigating the effect of iNO (30 ppm) versus conventional therapy in 20 patients (age range 46 to 80 years) with PHT (PAP>25 mmHg) before valve replacement surgery. It did not demonstrate a significant difference between iNO and conventional therapy. In the iNO group, PAP and PVR were significantly reduced compared to baseline ($p<0.05$) and returned to their baseline value after iNO was stopped. In the control group, changes in PAP and PVR were observed,

and the changes for PAP were significant relative to baseline. Treatment with iNO was associated with significantly increased SVR, relative to baseline, and SVR remained elevated after iNO was stopped.

Fernandes *et al* (2011) was an open randomised study investigating the effect of iNO (10 ppm) versus O_2 in 29 patients (mean age 46±2 years) with severe PHT (systolic PAP>60 mmHg) undergoing mitral valve stenosis surgery. The decrease in PVR was significantly greater (p=0.005) in the iNO group than in the O_2 group, but only at 48 hours. Cardiac index was increased in both groups, but the differences between groups were not significant. Changes in cardiac index relative to baseline were significant for iNO. Pulmonary capillary wedge pressure and systolic PAP were not significantly reduced in either group, and the differences between groups were not significant. The changes in systolic PAP at 24 and 48 hours were almost identical in the two groups.

Rajek *et al* (2000) was a double-blind randomised study investigating the efficacy of iNO (34 patients, mean age: 54±11 years) versus intravenous prostaglandin E1 (PGE1) (34 patients, mean age: 55±9 years) in patients with PHT (mean PVR >250 dyn/sec/cm^5, PAP >30 mmHg) undergoing heart transplantation. Patients were switched to the alternative study drug when PAP was consistently elevated and when weaning from cardiopulmonary bypass was difficult because of right heart failure. Pulmonary arterial pressure was decreased by approximately 30% with iNO ($p<0.0001$ compared to baseline), but only by approximately 16% with PGE1. PVR was nearly halved in the iNO group ($p<0.0001$ compared to baseline) but reduced by only 10% in the PGE1 group. Comparisons between groups were statistically significant ($p<0.05$) and in favour of iNO for PVR, mPAP, PVR/SVR and several other haemodynamic parameters. Weaning from cardiopulmonary bypass was successful in all patients in the iNO group and failed in six patients in the PGE1 group.

In summary, iNO was effective in reducing PAP (expressed either directly as PAP or indirectly by PVR measurement) in adults with PHT in conjunction with cardiac surgery. In the studies that reported changes in PAP, the reduction of PAP was approximately from 15% to 40%. In the studies that reported changes in vascular resistance, iNO reduced the PVR by approximately 35% to 65% and had no significant effect on SVR (where reported). In the majority of studies, iNO treatment maintained or improved cardiac function. It should be noted that the adult studies have some methodological limitations such as the relatively low total number of patients included in the trials and the heterogeneity of the trials.

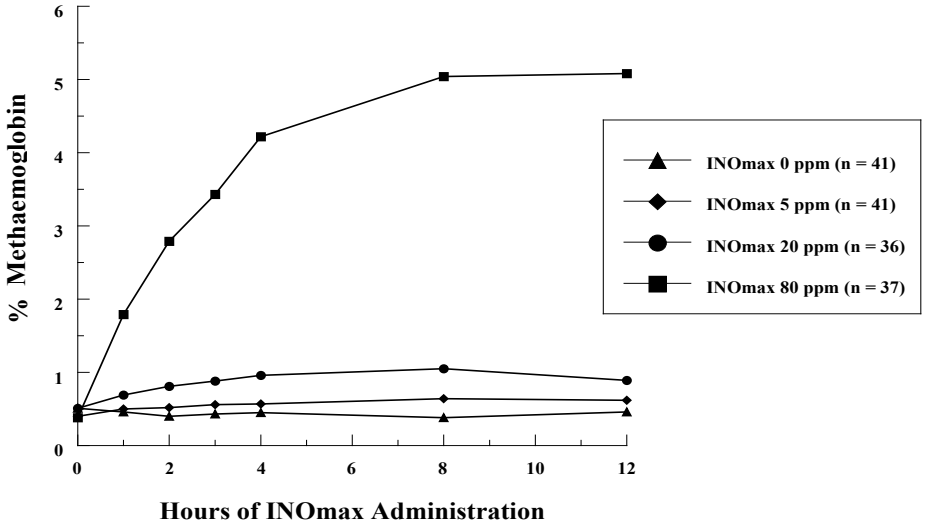
5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of nitric oxide has been studied in adults.

Nitric oxide is absorbed systemically after inhalation. Most of it traverses the pulmonary capillary bed where it combines with haemoglobin that is 60% to 100% oxygensaturated. At this level of oxygen saturation, nitric oxide combines predominantly with oxyhaemoglobin to produce methaemoglobin and nitrate. At low oxygen saturation, nitric oxide can combine with de-oxyhaemoglobin to transiently form nitrosyl-haemoglobin, which is converted to nitrogen oxides and methaemoglobin upon exposure to oxygen. Within the pulmonary airways, nitric oxide can combine with oxygen and water to produce nitrogen dioxide and nitrite, respectively, which interact with oxyhaemoglobin to produce methaemoglobin and nitrate.

Methaemoglobin disposition has been investigated as a function of time and nitric oxide exposure concentration in neonates with respiratory failure. The methaemoglobin (MetHb) concentration–time profiles during the first 12 hours of exposure to 0, 5, 20, and 80 ppm INOmax® is shown in Figure 1.

Figure 1
Methaemoglobin Concentration- Time Profiles
Neonates Inhaling 0, 5, 20 or 80 ppm INOmax®



Methaemoglobin concentrations increased during the first 8 hours of nitric oxide exposure. The mean methaemoglobin level remained below 1% in the placebo group and in the 5 ppm and 20 ppm INOmax® groups but reached approximately 5% in the 80 ppm INOmax® group. Methaemoglobin levels >7% were attained only in patients receiving 80 ppm, where they comprised 35% of the group. The average time to reach peak methaemoglobin was 10 ± 9 (SD) hours (median, 8 hours) in these 13 patients; but one patient did not exceed 7% until 40 hours.

Nitrate has been identified as the predominant nitric oxide metabolite excreted in the urine, accounting for >70% of the nitric oxide dose inhaled. Nitrate is cleared from the plasma by the kidney at rates approaching the rate of glomerular filtration.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Nitric oxide is genotoxic. Nitric oxide induced gene mutation or DNA damage in bacteria and in mammalian cells (mouse lymphoma cells, Chinese hamster lung cells and human lymphoblastoid cells) *in vitro,* chromosome aberrations in Chinese hamster ovary cells, *in vitro,* and gene mutations in rat lung cells *in vivo*.

Carcinogenicity
A carcinogenicity study in rats exposed to 20 ppm NO daily, 20 h/day for 2 years from 6 weeks of age showed no evidence of carcinogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Nitrogen

6.2 INCOMPATIBILITIES

Use nitric oxide for inhalation with registered nitric oxide delivery systems to assure compatibility of materials with nitric oxide.

6.3 SHELF LIFE

3 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 25°C, avoid temperature excursions below 5°C.
All regulations concerning handling of pressure vessels must be followed.

Store gas cylinders indoors in well-ventilated rooms or outdoors in ventilated sheds where they are protected from rain and direct sunlight.

Protect the gas cylinders from shocks, falls, oxidising and flammable materials, moisture and sources of heat or ignition.

The installation of a nitric oxide pipeline system with supply station of gas cylinders, fixed network and terminal units is forbidden.

The gas cylinders should be transported with appropriate material to protect them from shocks and falls.

During inter- or within-hospital transfers of patients treated with INOmax®, the gas cylinders should be securely stowed to hold the gas cylinders vertically and to avoid the risk of fall or changes in output. Particular attention should also be made to fastening of the pressure regulator to avoid the risk of accidental failure.

6.5 NATURE AND CONTENTS OF CONTAINER

INOmax® (nitric oxide) is available in the following sizes:

Size MD 15	Portable aluminium cylinders containing 353 litres at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 344 litres). Water capacity 2.818 litres
Size 88	Aluminium cylinders containing 1963 litres at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 1918 litres). Water capacity 15.731 litres.
0.4 litre	Portable aluminium cylinders containing 78 litres at STP of nitric oxide gas in 4,880 ppm concentration in nitrogen (delivered volume 70 litres) Water capacity 0.4 litres.

The cylinder valve is a CGA (Compressed Gas Association) 626 stainless steel valve made in accordance with CGA Standard V -1 and CGA Pamphlet S1.1. The outer thread is 1.030 inches – 14 NGO. It contains a backed unitised safety device with fuse metal -23166 kPa. A tamper evident plastic film overwrap is

placed on the valve. If cylinder is received with the tamper evident seal broken or missing, do not use, return the cylinder.

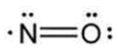
Not all presentations may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements. Do not discard empty or damaged cylinders. These must be returned to the distributor.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure:



Molecular formula:
NO

Chemical Abstracts Service (CAS) registry number:
[10102-43-9]

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4

8. SPONSOR

Ikaria Australia Pty Ltd
Ground Floor, 17 Cotham Road,
Kew, Victoria 3101
Phone 1300 198 565: 24/7 Customer Care and Technical Support
www.ikariaaust.com

9. DATE OF FIRST APPROVAL

22 November 2007

10. DATE OF REVISION

15 April 2026

Summary Table of Changes

Section Changed	Summary of new Information
Complete document	Format updated as per TGA Nov 2017 Guidance
4.1 Therapeutic Indications	New indication of adult cardiac surgery
4.2 Dose and method of Administration	Updated sections with information specific to the indication of cardiac surgery in adults
4.8 Adverse effects (Undesirable effects)	
5.1 Pharmacodynamic properties (Clinical Trials)	
2 Qualitative and Quantitative Composition	Added INOmax 4,880®-cylinder information
6.5 Nature and Contents of Container	
4.4 Special Warnings and Precautions for Use	Added warning re pulmonary veno-occlusive disease (PVOD)

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AUST R 128136 INOmax 800 ppm
AUST R 513545 INOmax 4880 ppm