Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Nitric oxide

Proprietary Product Name: INOmax

Sponsor: Ikaria Australia Pty Ltd

May 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
AE	Adverse Event
BP	Blood Pressure
cAMP	Cyclic Adenosine Monophosphate
cGMP	Cyclic Guanosine Monophosphate
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMI	Consumer Medicine Information
CO	Cardiac Output
CPB	Cardio Pulmonary Bypass
DB	Double Blind
ECG	Electrocardiogram
EF	Ejection Fraction
FiO_2	Fraction of Inspired Oxygen
GCP	Good Clinical Practice
GMP	Guanosine Monophosphate
HR	Heart Rate
HV	Hyperventilation (induced alkalosis)
iNO	inhaled Nitric Oxide
iPGI2	inhaled Prostacyclin (prostaglandin I2)
IPPV	intermittent positive pressure ventilation
IQR	Interquartile range
LVAD	Left Ventricular Assist Device
MAH	Marketing Authorisation Holder

Abbreviation	Meaning
metHb	Methahaemoglobin
mmHg	mm of Mercury
mPAP	Mean Pulmonary Artery Pressure
mSAP	Mean Systemic Arterial Pressure
N_2	Nitrogen
NO	Nitric Oxide
NO_2	Nitrogen Dioxide
NOAEL	No observed adverse effect level
NTG	Nitroglycerin
OD	Orphan Drug
PA	Pulmonary Artery
PAH	Pulmonary Artery Hypertension
PAP	Pulmonary Artery Pressure
PBO	Placebo
PCWP	Pulmonary Capillary Wedge Pressure
PD	pharmacodynamic
PGE1	Prostaglandin E1
PH	Pulmonary Hypertension
PHT	Pulmonary Hypertension
PHTC	Pulmonary Hypertensive Crisis
PI	Product Information
PK	pharmacokinetic
PPHN	Persistent Pulmonary Hypertension of the Newborn
ppm	part per million
PSUR	Periodic Safety Update Report
PVR	Pulmonary Vascular Resistance

Abbreviation	Meaning
PVRI	Pulmonary Vascular Resistance Index
RCT	Randomised Controlled Trial
RV	Right Ventricular
SAE	Serious Adverse Event
SAP	Systemic Arterial Pressure
SD	Standard Deviation
SPAP	Systolic Pulmonary Arterial Pressure
SPC	Summary of Product Characteristics
SSAP	Systolic Systemic Arterial Pressure
SVR	Systemic Vascular Resistance

I. Introduction to product submission

Submission details

Type of submission:	Major variation (new indication)
Decision:	Approved
Date of decision:	27 July 2015
Date of entry onto ARTG	30 July 2015
Active ingredient:	Nitric oxide
Product name:	INOmax
Sponsor's name and address:	Ikaria Australia Pty Ltd 17 Cotham Rd Kew VIC 3101
Dose form:	Medicinal gas
Strength:	800 ppm
Container:	Gas cylinder
Pack size(s):	Size 88 cylinder, size MD15 cylinder
Approved therapeutic use:	*INOmax, in conjunction with ventilatory support and other appropriate agents, is indicated* • *as part of the treatment of peri- and post-operative pulmonary hypertension in newborn infants, infants and toddlers, children and adolescents, ages 0-17 years in conjunction with heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation.*
Route(s) of administration:	inhalation
Dosage:	For instructions regarding dosage please see the Product Information
ARTG number:	128136

Product background

This AusPAR describes the application by Ikaria Australia Pty Ltd (the sponsor) to register INOmax nitric oxide 800 ppm (part per million) medicinal gas for inhalation for the following indication:

> *INOmax, in conjunction with ventilatory support and other appropriate agents, is indicated as part of the treatment of peri- and post-operative pulmonary hypertension in newborn infants, infants and toddlers, children and adolescents, ages*

0-17 years in conjunction with heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation.'

Nitric Oxide (NO) is an endogenous signalling molecule. It acts in vascular smooth muscle cells by activating guanylate cyclase, causing the formation of cyclic guanosine monophosphate (cGMP). Elevated levels of cGMP set off a phosphorylation cascade leading to smooth muscle relaxation and vasodilation. NO is inhaled and has relative selectivity for the pulmonary vasculature. NO is also an inhibitor of platelet activation and vascular smooth muscle cell proliferation.

Pulmonary hypertension is defined as a mean pulmonary artery pressure (mPAP) > 25 mmHg, a normal capillary wedge pressure (PCWP) and increased pulmonary vascular resistance (PVR). It has been argued that pulmonary hypertension is present if the ratio of mean pulmonary artery pressure (mPAP) to mean systemic arterial pressure (mSAP) is > 0.4, or > 0.5 for children with congenital cardiovascular disease undergoing surgical repair.[1] Pulmonary hypertensive crises (PHTCs) are life threatening events characterised by a rapid increase in PVR to the point where pulmonary artery pressure (PAP) exceeds the systemic blood pressure (SBP). The resulting right heart failure leads to a decrease in pulmonary blood flow, decreased cardiac output, hypoxia and biventricular failure. Without treatment these crises result in rapid cardiovascular collapse and death.

Pulmonary hypertension in the context of paediatric cardiac surgery has a number of contributing factors. Among these is the effect of cardiopulmonary bypass on the lung resulting in impaired endothelial function in the pulmonary vasculature and pulmonary vasoconstriction. Children undergoing cardiac surgery are also at risk of pulmonary hypertension on the basis of their underlying cardiac abnormality (for example shunting, cardiac failure). This is important in the peri-and post-operative setting.

Nitric oxide has been described in this literature for use in pulmonary hypertension for approximately two decades.

INOmax was first registered in the USA in 1999 and in the EU in 2001 for the treatment of neonates (> 34 weeks gestation) with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 22 November 2007 for the 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 order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation.*

At the time the TGA considered this application, a similar application had been approved in European Union: March 2011, Argentina: April 2012, Chile: June 2012, Columbia: October 2013, Mexico: March 2012 and Uruguay: July 2013. An application submitted to Switzerland in 2011 was withdrawn (for business reasons). The sponsor at the time had no intention to submit the application in the USA, Canada, New Zealand or Singapore.

[1] Barst RJ, et al Pulmonary arterial hypertension: a comparison between children and adults *Eur Respi R.* 2011; 37:665-677

Orphan drug designation
The proposed indication was granted Orphan Drug Designation (ODD) by the TGA on 12 September 2013.

Product information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

Nonclinical summary and conclusions

The sponsor submitted the following study reports and information:

- A 6 month intermittent, repeat dose, pulse inhalation study in sheep.
- Newly proposed chronic exposure margin calculations for INOmax based on local pulmonary exposure.
- A re-assessment of uterine lesion findings in the previously submitted 2 year rat carcinogenicity study.
- Various published papers on nitric oxide, nitrate and nitrite pharmacology/toxicology.
  - No overt treatment related effects were observed in the repeat dose inhalation study in sheep. However, non-dose related increases in methaemoglobin levels were generally present in all nitric oxide exposed groups, with the worst case (approximately 12%) producing signs of cyanosis but no other physiologically adverse effects in normal animals. No other signs of oxidative damage to the erythron were observed.
  - The sponsor's new relative exposure calculations for the rat and sheep repeat dose studies were incorrectly based on lung burdens and pulmonary region surface areas. As the key site/mode of adverse effect is methaemoglobin formation within erythrocytes, the calculations have been adjusted accordingly, yielding relative exposure margins at the no observed adverse effect level (NOAEL) of ≥ 1.0 for the 6 month sheep study and ≥ 0.8 for the 2 year rat study.
  - The published literature shows variable effects of nitric oxide on the coagulation system in different species; however, no overt coagulopathies or bleeding tendencies were noted in any of the repeat dose toxicity studies in rats and sheep.
  - The nonclinical evaluator concurs with the sponsor that the uterine lesions in the 2 year rat carcinogenicity study are not treatment related. Substantial (up to approximately 30% relative to the controls) hepatomegaly (most likely due to diffuse hepatocyte hyperplasia) was present in this study, which has implications for drug metabolism and drug interactions if there is particularly extended usage.

Comments on the safety specification of the risk management plan

Results and conclusions drawn from the nonclinical program for INOmax detailed in the sponsor's draft Risk Management Plan (RMP) (EU RMP, Part II, Nonclinical part of the safety specification) are generally concordant with those of the nonclinical evaluator although the following modifications are suggested:

> Table 5, located in section 3.1 (page 28)[of the RMP].

Given that the key adverse effect for NO is methaemoglobinaemia, the target tissue is actually the blood (specifically the erythrocytes that is technically distal to the pulmonary region of the lung). Therefore, an extra column should be added to the relative exposure table for systemic (SYS) effects as follows in Table 1.

Table 1 recommended format changes to Table 5 of the RMP

Species (Study Nos.)	Duration, dose	Lung burden (mg iNO/gram lung/day)a	Exposure Margin (Lung burden)b	Exposure Margin (Systemic)c
Rat (NOO5243)	2 years, 20 ppm (NOAEL)	3.4	5.5	0.8
Sheep (ABRAB1)	6 months, 0.23 mg/kg/h (NOAEL)	0.43	0.70	1.0

NOAEL = no observed adverse effect level a: Part per million concentration in the rat toxicity study was converted to lung burden based on a respiratory rate of 290 L per day (ICH Q3C(R2)) and the mean lung weight obtained at terminal necropsy b: Lung burden at 20 ppm inhaled nitric oxide (iNO) for a preterm infant calculated as 0.617 mg/g/day based on an average birth weight of 0.790 kg (studies INOT25, INOT27, BALLR1), a respiratory rate using Bide, RW 2000[2] (RMV (L) = 0.499 x $W^{0.809}$), and a lung weight of 3% of the birth weight based on preterm infant data.[3] C: Calculated systemic (SYS) exposure using EPA "Advances in Inhalation Gas Dosimetry for Derivation of a Reference Concentration (RfC) and Use in Risk Assessment". NO as a Category 3 gas (water soluble, perfusion limited), respiratory parameters for sheep; 40 breaths/min, tidal volume 238 to 380 mL.

Conclusions and recommendations

Methaemoglobinaemia was the primary adverse effect of inhaled nitric oxide noted in the sheep repeat dose toxicity study. The highest levels achieved in this study (approximately 12%) could be expected to produce some skin discoloration but would not be physiologically adverse in normal circumstances. However, this may not be the case in individuals with compromised oxygenation and/or reduced blood oxygen carrying capacity. Such individuals are likely to be more sensitive to the adverse effects of INOmax such as methaemoglobinemia and oxidative damage to the erythrocytes: careful assessment and monitoring is suggested as outlined in the proposed RMP.

There are no objections on nonclinical grounds to the extension of indications for INOmax.

[2] Bide RW, et al. Allometric respiration/body mass data for animals to be used for estimates of inhalation toxicity to young adult humans. *J Appl Toxicol*. 2000; 20: 273-290

[3] De Paepe ME, et al. Post-mortem lung weight/body weight standards for term and preterm infants. *Pediatr Pulmonol*. 2005; 40: 445-448.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Nitric oxide (NO) is an endogenous signalling molecule originally known as endothelial derived relaxing factor, but later shown to be identical to the simple gaseous molecule, nitric oxide. It is unique in its class.

INOmax is an inhaled vasodilator that diffuses into vascular smooth muscle cells where it activates guanylate cyclase, causing the formation of cGMP. Elevated levels of cGMP set off a phosphorylation cascade leading to smooth muscle relaxation and vasodilatation. Because it is inhaled, it has relative selectivity for the pulmonary vasculature.

Clinical rationale

Cardiopulmonary bypass (CPB) causes complex changes in the lung that have the end result of impairing endothelial function in the pulmonary vasculature and producing pulmonary vasoconstriction. Impaired endogenous production of NO appears to be a major contributor to this problem. Even without these CPB effects, many subjects undergoing cardiac surgery have pre-existing pulmonary hypertension because of impaired cardiac function, shunting, or other causes. The combination of these problems puts cardiac surgical patients at high risk of post-operative pulmonary hypertension, with subsequent right heart strain or right heart failure. Subjects are also at risk of pulmonary hypertensive crises (PHTCs), in which severe pulmonary hypertension compromises cardiac output and impairs oxygenation, leading to circulatory collapse and a high mortality rate unless the pulmonary hypertension is reversed.

Systemically administered vasodilators (such as sodium nitroprusside, nitroglycerin or milrinone) may lower pulmonary blood pressure, but they lack specificity for the pulmonary circulation, so their use is often complicated by systemic hypotension. Inhaled vasodilators, such as inhaled nitric oxide (iNO), offer the prospect of treating pulmonary hypertension without compromising systemic blood pressure. Furthermore, to the extent that post-operative pulmonary hypertension is caused by impaired production of endogenous NO, inhaled NO potentially restores normal NO levels.

Another proposed advantage of iNO is that it has better access to parts of the lung that are well ventilated, so it potentially improves ventilation-perfusion matching by preferentially dilating pulmonary vessels in well-ventilated parts of the lung.

Because of these theoretical advantages of iNO over intravenous pulmonary vasodilators, it has shown increasing off-label use for the treatment of pulmonary hypertension (PH) in the cardiac surgical setting, and over the last 20 years it has become the first-line agent for the treatment and prevention of PHTC. Even though it was not formally approved for this indication, iNO has been recommended for this indication for many years, by a number of specialist bodies.

The sponsor now seeks to officially register iNO for this indication.

Guidance

The EU guidelines adopted by the TGA that are of relevance for this submission are:

- EMEA/CHMP/EWP/356954/2008: Guideline on the Clinical Investigations of Medicinal Products for the Treatment of Pulmonary Arterial Hypertension.

- EMEA/CHMP/EWP/147013/2004: Clinical Investigation of Medicinal Products in the Paediatric Population.
- EMEA/536810/2008: Guideline on the Investigation of Medicinal Products in the Term and Preterm Neonate.
- CHMP/EWP/83561/2005: Guideline on Clinical Trials in Small Populations.
- EMEA/CHMP/EWP/147013/2044 Corr: Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population.

Contents of the clinical dossier

The current submission is primarily a literature based submission, with all pivotal studies and most supportive studies consisting of published, peer reviewed papers that were identified through a literature search, using a search strategy approved by the TGA. In the updated literature searches conducted prior to the Australian submission, two new published clinical studies were retrieved that were not available at the time of preparation of the EU submission (Kirbas et al., 2012, and Loukanov et al., 2011)[4], [5] but in other respects the submitted data is essentially the same. The Australian submission retains the studies done in adults, but these are considered supportive.

The submission contained the following clinical information:

- 12 clinical pharmacology studies in children, none of which provided pharmacokinetic data, 11 of which provided interventional pharmacodynamic data and one of which was an observational study recording endogenous NO levels. One of the interventional pharmacodynamic (PD) studies (INOT22) was a sponsor led study; the other 10 were investigator led studies identified through a literature search.
- No population pharmacokinetic analyses.
- 4 pivotal efficacy studies, in which iNO was compared to placebo or standard care in the target population of paediatric cardiac surgery patients. All of these were investigator led studies, and safety monitoring and reporting was suboptimal.
- 5 supportive efficacy studies in the target population, where iNO was compared to an active control. All of these were investigator led studies. In no case was the active control an approved agent for the treatment of pulmonary hypertension in the cardiac surgical setting, which is why these studies can only be considered supportive.
- 13 supportive efficacy studies in adults, which have only indirect relevance to the proposed indication in children, but have been retained after the EU application and remain of substantial interest for both efficacy and safety assessments. One of these studies (INOT41) was a sponsor led study with comprehensive safety assessments; the others were investigator led studies with variable and generally suboptimal safety reporting.
- A Cochrane meta-analysis of the efficacy of iNO for the treatment of pulmonary hypertension in the cardiac surgery setting; this was actually of minimal value given that it only accepted a small number of underpowered studies with clinical endpoints.
- Clinical Overview, Summary of Clinical Pharmacology, Summary of Clinical Efficacy, Summary of Clinical Safety.

[4] Kirbas, A. et al. Comparison of inhaled nitric oxide and aerosolized iloprost in pulmonary hypertension in children with congenital heart surgery. *Cardiol J.* 2012; 19: 387-394.
[5] Loukanov, T. et al. Comparison of inhaled nitric oxide with aerosolized iloprost for treatment of pulmonary hypertension in children after cardiopulmonary bypass surgery. *Clin Res Cardiol*, 2011; 100: 595-602.

- Literature references.
- Synopses of all 34 submitted studies.

The 34 submitted studies are listed in Table 2.

Table 2: Submitted studies[6]

Type of study	Study identifier
Pharmacodynamics	
Paediatric population	INOT22, 2008 Beghetti et al 1998 Girard et al 1992 Journois et al 1994 Lepore et al 2005 Lindberg et al 1994 Miller at al 1994 Roberts et al 1993 Turanlahti et al 1998 Turanlahti et al 2000 Wessel et al 1993 Winberg et al 1994
Efficacy	
Paediatric cardiac surgery	Cai et al 2008 Day et al 2000 Goldman et al 1995 Kirbas et al 2012 Loukanov et al 2011 Miller et al 2000 Morris et al 2000 Russell et al 1998 Stocker et al 2003
Adult cardiac surgery	Fattouch et al 2005 Fattouch et al 2006 Gianetti et al 2004 Schmid et al 1999 Solina et al 2000 Solina et al 2001 Winterhalter et al 2008
Adult cardiac assessment	Kieler-Jensen et al 1994 Radovancevic et al 2005
Adult LAVD	INOT41 2009 Argenziano et al 1998
Adult cardiac transplant	Rajek et al 2000 Ardehali et al 2001

[6] For the full citation of these references please see the list of references in Attachment 2.

Paediatric data

The proposed indication exclusively refers to paediatric use, though a similar application in the EU sought and gained approval for use of iNO in children and adults with PH in the setting of cardiac surgery. As outlined above, all 12 of the PD studies and 9 of the efficacy studies were performed in the paediatric population. An additional 13 supportive efficacy studies were performed in adults, and these are only indirectly relevant to the proposed indication.

Good clinical practice

Both of the sponsor led studies (INOT22 and INOT41) were performed according to Good Clinical Practice (GCP) guidelines. The remaining studies, which include all four pivotal studies, did not contain a formal declaration of compliance with GCP, and in most cases clearly failed to comply with GCP. For instance, most investigator led studies did not formally declare a single prospective primary endpoint, many of them performed multiple statistical comparisons without correcting for this in reporting p-values, only a few studies performed power calculations, and most studies failed to collect or report on adverse events.

Overall, the quality of the investigator led studies was well below the standard normally expected of sponsor led studies, and the two GCP compliant studies performed by the sponsor were not pivotal; one was a PD study using a crossover design, without an untreated control group, and the other was performed in adults. This means that no single, well designed, adequately powered, GCP compliant pivotal study has been submitted in support of the proposed indication. On the other hand, iNO is already widely recognised as effective for the proposed indication, it is widely used off-label for this indication, and its use is recommended by all of the major authorities and guidelines. The proposed target population represents a relatively small population with very specific needs in whom, it could be argued, placebo controlled studies would no longer be ethical. Furthermore, no competing agent is registered for the same indication, so a non-inferiority study against an active agent would not allow clear efficacy inferences to be made.

Despite their lack of GCP compliance, one distinct advantage of the investigator led studies is that in most cases, the authors have no particular incentive to exaggerate the efficacy or safety of iNO. (In fact, in a couple of the submitted papers, the authors were primarily arguing that they preferred some new agent to iNO, so they potentially had some incentive to highlight problems with iNO.) Furthermore, the large number of different investigative teams, different hospitals and different treatment protocols involved in the submitted studies means that are likely to have good external validity.

Thus, despite the lack of GCP compliant studies in the submission, it remains reasonably appropriate to assess the efficacy and safety of iNO on the basis of the studies found in the literature.

Pharmacokinetics

Studies providing pharmacokinetic data

No new pharmacokinetic (PK) data was submitted for evaluation, and understanding of the PK of iNO has not changed since it was originally approved for treatment of persistent pulmonary hypertension of the newborn (PPHN). The proposed use of iNO in the post-surgical paediatric population does not raise any significant new issues, particularly in view of the fact that PD studies did not show a dose response across a wide range of doses.

The main importance of iNO levels relates to potential toxicity with methahaemoglobin (metHb) and nitrogen dioxide (NO_2), so iNO should be used at the lowest effective dose to reduce exposure. This is discussed in more detail in the safety section.

Evaluator's conclusions on pharmacokinetics

The proposed extension of indications does not raise specific concerns based on the PK of iNO. The PK of iNO in the new proposed target population is expected to be very similar to the PK in neonates.

Pharmacodynamics

Studies providing pharmacodynamic data

Summaries of the 12 individual pharmacodynamic (PD) studies are presented in this report. One of the studies, INOT22, was a sponsor driven PD study of the effects of iNO and oxygen in patients undergoing pulmonary vasoreactivity testing; the other 11 were published investigator led studies uncovered by a literature search.

Many of the PD studies involved post-operative care of patients and iNO was used therapeutically, not merely as an investigational agent, so the line between PD studies and efficacy studies is somewhat blurred. Many of the studies submitted as efficacy studies could also be considered to be PD studies, because they merely assessed the short-term haemodynamic response to iNO, with the main distinction being that all studies submitted as "efficacy" studies employed a control group (placebo or active comparator). By contrast, the studies designated as PD studies required a comparison to baseline haemodynamic status to infer the effects of iNO. Where the studies were based on pre-operative vasoreactivity testing, the comparison to baseline provided a reasonably robust measure of the haemodynamics of iNO. Where the setting was post-operative treatment of pulmonary hypertension, it was sometimes not possible to determine to what extent the observed changes were due to recovery from the surgery.

Most of the submitted PD studies (11 of 12) directly assessed the primary PD effect of iNO on the pulmonary vasculature, as reflected in pulmonary vascular resistance (PVR) and mPAP, and in all studies where these parameters were assessed, iNO produced significant and clinically meaningful reductions.

None of the submitted PD studies specifically addressed differences in responsiveness to iNO based on age or gender, but results were broadly similar in adults and children. Many of the studies assessed the effect of baseline PVR on subsequent sensitivity to iNO, showing that iNO produced relatively little haemodynamic change in subjects without elevated PVR, and the efficacy of iNO was correlated with baseline PVR.

Two studies sought to clarify the proposed mechanism of action of iNO, assessing the role of post-cardio pulmonary bypass (CPB) endothelial dysfunction as a contributor to post-operative pulmonary hypertension. One of these compared the effects of acetylcholine (ACH), an endothelium-dependent vasodilator, with iNO, which is an endothelium independent vasodilator (normally NO is produced by the endothelium, but exogenous iNO bypasses this step).[7] The other study was an observational study, measuring levels of exhaled endogenous NO to infer endothelial dysfunction after CPB.[8] Both of these studies were consistent with the proposed mechanism of action and the hypothesis that CPB

[7] Wessel, D. et al. Use of inhaled nitric oxide and acetylcholine in the evaluation of pulmonary hypertension and endothelial function after cardiopulmonary bypass. *Circulation* 1993; 88: 2128-2138
[8] Beghetti, M. et al. Decreased exhaled nitric oxide may be a marker of cardiopulmonary bypass-induced injury. *Ann Thorac Surg* 1998; 66: 532-534

induces endothelial dysfunction characterised by a deficiency of endogenous iNO (more detail is provided in the references cited).

One study assessed a pharmacodynamic interaction between iNO and dipyridamole,[9] while a couple of early studies assessed the effects of oxygen in comparison to iNO, as well as the combination of oxygen and iNO. All of these interaction studies showed an effect of iNO on mPAP and PVR that exceeded the effects of pure oxygen.

Table 3 below, shows the studies relating to each pharmacodynamic topic.

Table 3: Submitted pharmacodynamic studies[6]

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on PVR and mPAP	Girard et al, 1992 INOT22 Journois et al, 1994 Lindberg et al, 1994 Miller et al, 1994 Roberts et al, 1993 Turanlahti et al, 1998 Turanlahti et al, 2000 Wessel et al, 1993 Winberg et al, 1994 Lepore et al, 2005
Secondary Pharmacology	Effect on oxygenation	Girard et al, 1992 Journois et al, 1994 Lindberg et al, 1994
Gender other Genetic and Age Related Differences in PD Response		None provided
PD Interactions	Interaction with dipyridamole	Lepore et al, 2005
Population PD and PK-PD Analyses		None provided

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

For further details of the evaluation of the PD please see Attachment 2, extract of the clinical evaluation report.

[9] Lepore, J. et al., Combined administration of intravenous dipyridamole and inhaled nitric oxide to assess reversibility of pulmonary arterial hypertension in potential cardiac transplant recipients. *J Heart Lung Transplant* 2005; 24: 1950-1956

Evaluator's conclusions on pharmacodynamics

The PD of iNO was established with the original marketing authorisation application for treatment of persistent neonatal pulmonary hypertension, and the proposed indication is consistent with that original characterisation.

In the current submission, the sponsor has submitted studies specifically pertaining to the perioperative setting, including both pre-operative vasoreactivity studies and post CPB studies, in both children and adults. Many of these studies were small in scale and lacked clearly defined prospective endpoints, but the studies can be considered reasonably robust as a group because of the high reproducibility of the PD effects which were observed across a range of independent investigative teams, different hospital settings and different target populations.

Although the submitted PD studies lacked control groups, and therefore did not qualify as efficacy studies, the use of baseline comparisons and crossover designs allowed the various investigators to demonstrate the haemodynamic effects of iNO. The PD studies provided a consistent view of iNO as an agent that produces selective pulmonary vasodilation in most subjects with elevated PVR, and particularly in subjects who have undergone CPB and have impaired endothelial function. The effect was observed in both children and adults, and was clinically meaningful in magnitude.

Additional exploratory studies were consistent with the hypothesis that CPB induces a deficit in endogenous NO production, which iNO specifically and effectively targets.

Dosage selection for the pivotal studies

As discussed above, there was little evidence of a dose response relationship over a large range of doses from 2 ppm to 80 ppm, but occasional studies suggested that the effect of 40 ppm might be more pronounced than lower doses.

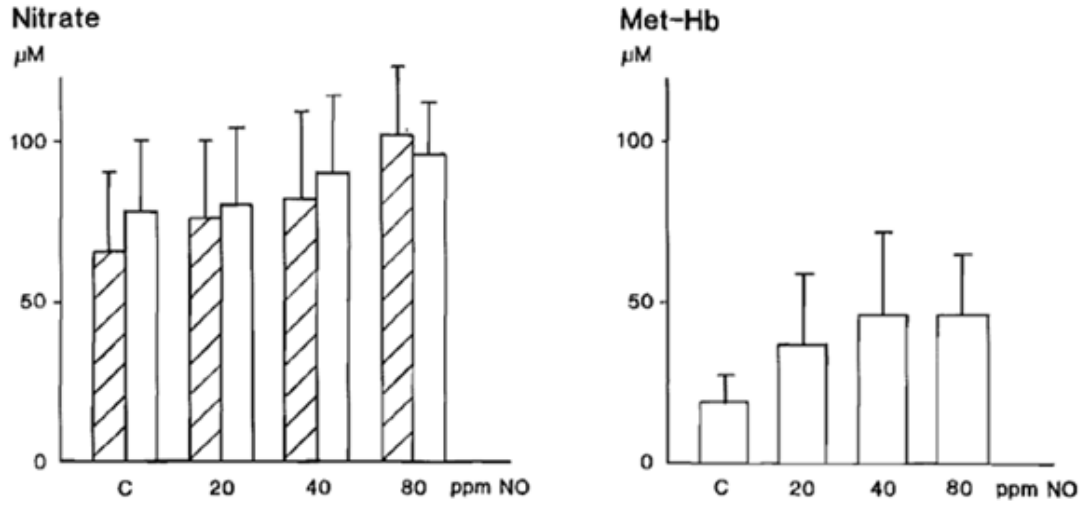
None of the pivotal efficacy studies was sponsor driven, and several different doses were used by the investigators, ranging from 5 ppm to 80 ppm, as shown in Table 4.

Table 4: Studies in paediatric patients post-surgery for congenital heart disease

Publication	Design	N	Age	Dose & duration iNO	Primary endpoints
Miller et al 2000	Randomised, placebo controlled, double blind	124	NO: 1-5 mths PBO: 1-4 mths	10 ppm for mean 87 hrs	Clinical: PHTC Frequency
Russell et al 1998	Randomised, placebo controlled, double blind	40	2 days – 6.5 yrs	80 ppm for 20 min	Haemodynamics: mPAP, mSAP, HR
Day et al 2000	Randomised, Conventional therapy control	40	NO: 1 day – 20 yrs Control: 1 day – 3 yrs	20 ppm until weaned from ventilation	Clinical: PHTC Frequency
Morris et al 2000	Randomised, conventional therapy control, cross-over	12	0.1 – 17.7 yrs	5 and 40 ppm for 15 min	Haemodynamics: mPAP, mSAP, HR

Increasing doses of iNO increase exposure to potentially toxic by-products, including metHb and nitrate. This is evident in Figure 1 below from one of the submitted efficacy studies.[10]

Figure1: Levels of nitrate and metHb in response to iNO



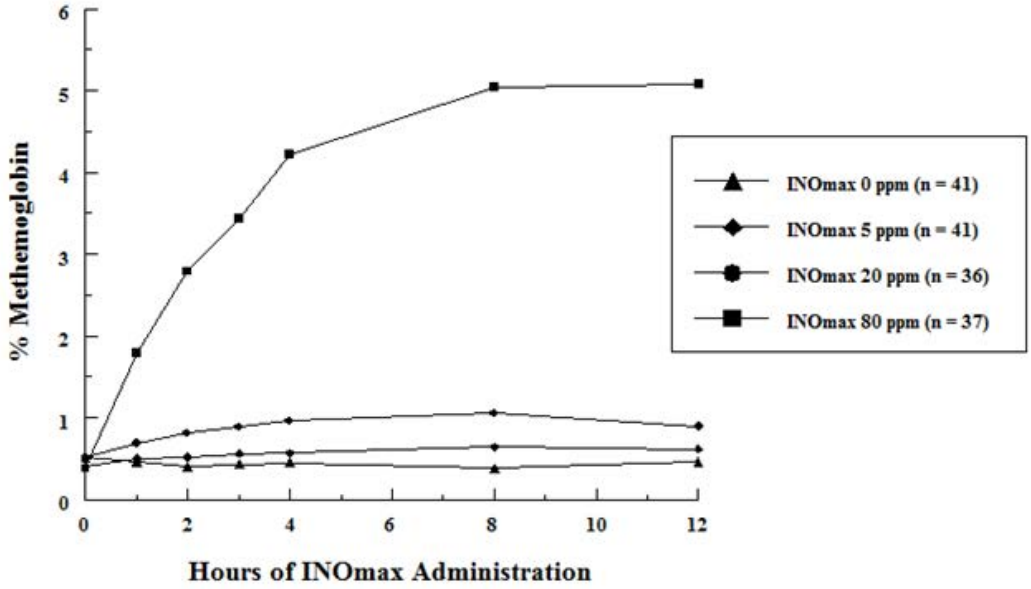
Plasma levels of nitrate *(left panel)* and methemoglobin *(Met-Hb) (right panel)* in basal state *(C)* and during inhalation of nitric oxide (NO, 20 to 80 ppm) in six patients. *Filled bars* represent pulmonary arterial blood; *open bars* represent systemic arterial blood. Data presented are mean ± standard error of the mean.

A similar relationship between administered dose and metHb was described in the approved PI, based on a study previously submitted as part of the original marketing application.

"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 2."

[10] Kieler-Jensen, N. et al. Inhaled nitric oxide in the evaluation of heart transplant candidates with elevated pulmonary vascular resistance. *J Heart Lung Transplant* 1994; 13: 366-375

Figure 2: MetHb Concentration- Time Profiles, Neonates, 0, 5, 20 or 80 ppm INOmax



Importantly, this figure suggests that accumulation of metHb is minimal for doses of 20 ppm and below, but becomes problematic for sustained doses of 80ppm.

In the proposed PI, the following recommendations are made in the section relating to "Pulmonary Hypertension associated with Cardiac Surgery in children (0 to 17 years)":

> *Dosage*
>
> *Newborn infants, infants and toddlers, children and adolescents, 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. The lowest effective dose should be administered and the dose should be weaned down to 5 ppm provided that the pulmonary artery pressure and systemic arterial oxygenation remain adequate at this lower dose.*
>
> *Clinical data supporting the suggested dose in the age range of 12-17 years is limited.*

These recommendations are somewhat more conservative than the approved dosing recommendations for Persistent Pulmonary Hypertension in the Newborn (PPHN), which propose a starting dose of 20 ppm instead of 10 ppm and read as follows:

> *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 pivotal clinical trials, the starting dose was 20 ppm. Starting as soon as possible and within 4 to 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.*

The proposed starting dose for the cardiac surgery indication is 10 ppm, which matches that used in the main pivotal study.[11]

Given the available studies on the treatment of pulmonary hypertension in the cardiac surgery setting, which show no major advantage of higher doses, and the safety

[11] Miller, O. et al. Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: a randomised double blind study. *Lancet* 2000; 356: 1464-1469

requirement to minimise accumulation of metHb and NO by-products, the proposed dosing recommendations for the new indication are appropriate.

Efficacy

Studies providing efficacy data

The three tables below (Tables 5, 6 and 7) provided by the sponsor, list the 22 efficacy studies that were submitted for review. These included 9 randomised controlled studies in children undergoing cardiac surgery, which constitute the primary evidence base on which the submission rests, as well as 13 supportive studies in adults, which are only indirectly relevant to the proposed paediatric indication. Many of the studies submitted as efficacy studies would ordinarily be considered pharmacodynamic studies, because they only involved brief treatment and haemodynamic endpoints; iNO was not used as a sustained intervention as it would be when used for the proposed indication.

The only study that used iNO in a sustained, double blind fashion in the target population was the study by Miller et al, which should be considered the pivotal study of the submission.

Table 5: Studies in children undergoing cardiac surgery for congenital heart disease

Authors	Study Design	No Pts	Primary Outcome
Pivotal studies, placebo controlled			
Miller et al 2000[11]	R, C, DB	124	Routine iNO post cardiac surgery can reduce the risk of pulmonary hypertensive crises with no adverse effects.
Russell et al 1998[12]	R, C, DB	40	iNO selectively reduced mPAP in those who had evidence of postoperative Pulmonary Artery Hypertension (PAH).
Pivotal studies, versus conventional therapy			
Day et al 2000[13]	R, C	40	No significant difference in incidence of PHTC compared with control (3 patients for iNO versus. 4 for control). Control patients who experienced PHTC were allowed to crossover and receive iNO after failing conventional; none of the control patients experienced a PHTC after being treated with iNO.
Morris et al 2000[14]	R, C, XO	12	iNO versus. hyperventilation. NO selective for pulmonary circulation and did not increase Systemic Vascular Resistance (SVR).

[12] Russell, I. et al. The effects of inhaled nitric oxide on post-operative pulmonary hypertension in infants and children undergoing surgical repair of congenital heart disease. *Anesth Analg* 1998; 87: 46-51
[13] Day, R. et al. Randomized controlled study of inhaled nitric oxide after operation for congenital heart disease. *Ann Thorac Surg* 2000; 69: 1907-1913
[14] Morris, K. et al. Comparison of hyperventilation and inhaled nitric oxide for pulmonary hypertension after repair of congenital heart disease. *Crit Care Med* 2000; 28: 2974-2978

Authors	Study Design	No Pts	Primary Outcome
Supportive studies, versus active controls			
Cai et al 2008[15]	R, C	46	Combined iNO and milrinone were more effective in lowering PVR, PAH compared to either drug alone. The combined group had significantly shorter time on mechanical ventilation ($p < 0.043$)
Goldman et al 1995[16]	R, C, XO	13	mPAP lower during iNO compared to prostacyclin.
Kirbas et al 2012[4]	R, C	16	Both iNO and aerosolized iloprost are effective to selectively reduce PAP following cardiac surgery; no difference was found between the groups in terms of these effects.
Loukanov et al 2011[5]	R, C	15	There was no difference between the groups treated with iNO or iloprost with regard to the frequency of PHTCs, mean PAP and duration of mechanical ventilation ($p > 0.05$).
Stocker at al 2003[17]	R, XO, C	15	Both drugs, iNO 20 ppm and intravenous sildenafil lowered pulmonary vascular resistance index. Sildenafil also lowered systemic blood pressure.

R = randomised, C = controlled, DB = Double blind, XO = cross-over

Table 6: Studies in adults undergoing cardiac surgery (excluding heart transplant and left ventricular assist device insertion)[18]

Authors	Study Design	No Pts	Primary Outcome
Fattouch et al 2005[19]	R, C, DB	58	iNO was as effective in treating PAH as inhaled prostacycline. Both inhaled treatments superior to nitroprusside.
Fattouch et al 2006[20]	R, C, DB	58	iNO was as effective in treating PAH as inhaled prostacycline. Both inhaled treatments superior toIV vasodilators. Inhaled treatments superior with

[15] Cai, J. et al. Nitric oxide and milrinone: combined effect on pulmonary circulation after Fontan-type procedure: a prospective, randomized study. *Ann Thorac Surg* 2008; 86: 882-888
[16] Goldman, A., et al. Nitric oxide is superior to prostacyclin for pulmonary hypertension after cardiac operations. *Ann Thorac Surg* 1995
[17] Stocker, C. et al. Intravenous sildenafil and inhaled nitric oxide: a randomised trial in infants after cardiac surgery. *Intensive Care Med* 2003; 29: 1996-2003
[18] Corrections to table made during the evaluation
[19] Fattouch, K. et al. Inhaled prostacyclin, nitric oxide, and nitroprusside in pulmonary hypertension after mitral valve replacement. *J Card Surg* 2005; 20: 171-176
[20] Fattouch, K. et al. Treatment of pulmonary hypertension in patients undergoing cardiac surgery with cardiopulmonary bypass: a randomized, prospective, double blind study. *J Cardiovasc Med (Hagerstown)* 2006; 7: 119-123

Authors	Study Design	No Pts	Primary Outcome
			regards to time to weaning, intubation time and Intensive Care Unit (ICU) stay ($p < 0.05$)
Gianetti et al 2004[21]	R, C	29	Low concentration iNO can blunt release of markers of myocardial injury and antagonise LV dysfunction after CPB.
Schmid et al 1999[22]	R, XO	14	iNO and prostacycline iv decreased PVR and increased cardiac index
Winterhalter et al 2008[23]	R, C	46	iNO and iloprost both reduced PAP and PVR immediately after weaning from CPB. Iloprost gave larger reductions in PVR and mPAP and greater increase in cardiac output (CO).
Solina et al 2000[24]	R, C	45	iNO lead to lower HR, higher Right Ventricular (RV) ejection fraction and lower vasopressor requirement compared to milrinone.
Solina et al 2001[25]	R, C	62	Doses of iNO > 10p pm showed no difference in PVR response.

Of note, the two Fattouch studies were described[26] as double blind but it is unclear if blinding was adequate. [Information redacted].

Table 7: Studies in adult patients undergoing heart transplant or left ventricular assist device insertion18

Authors	Study Design	No. Pts	Primary Outcome
Heart transplant patients			
Ardehali et al 2001[27]	Pr, C	16	Post-transplant iNO significantly reduced RV stroke work and PVR.

[21] Gianetti, J. et al. Supplemental nitric oxide and its effect on myocardial injury and function in patients undergoing cardiac surgery with extracorporeal circulation. *J Thorac Cardiovasc Surg* 2004;127: 44-50
[22] Schmid, E. et al. Inhaled nitric oxide versus intravenous vasodilators in severe pulmonary hypertension after cardiac surgery. *Anesth Analg* 1999; 89: 1108-1115
[23] Winterhalter, M. et al. Comparison of inhaled iloprost and nitric oxide in patients with pulmonary hypertension during weaning from cardiopulmonary bypass in cardiac surgery: a prospective randomized trial. *J Cardiothorac Vasc Anesth* 2008; 22: 406-413
[24] Solina, A. et al. A comparison of inhaled nitric oxide and milrinone for the treatment of pulmonary hypertension in adult cardiac surgery patients. *J Cardiothorac Vasc Anesth* 2000; 14: 12-17
[25] Solina, A. et al. Dose response to nitric oxide in adult cardiac surgery patients. *J Clin Anesth* 2001; 13: 281-286
[26] Clarification; the text should read "the two Fattouch studies were described by the authors' as double blind"

Authors	Study Design	No. Pts	Primary Outcome
Kieler-Jensen et al 1994[10]	Pr, C	12	Should read "INO significantly increased PCWP and decreased PVR (p<0.01) during 20ppm NO, with no further effects at 40 or 80ppm
Rajek at al 2000[28]	R, C	68	iNO commenced at 4 ppm but tritrated up as needed to 24 ppm cause selective reduction in PAP iNO aided weaning from CPB more successfully than PGE1.
Radovancevic et al 2005[29]	R, XO	19	iNO and PGE1 have comparable dilatory effects in PAH.
Left Ventricular Assist Device (LVAD) Placement			
Argenziano et al 1998[30]	R, C, DB	11	iNO at 20 ppm induced significant reductions in mPAP and increases in LVAD flowindex.
INOT41	R, C	150	LVAD. iNO reduced the incidence of right ventricular dysfunction, but not significantly. Time on mechanical ventilation reduced for iNO (p=0.077)

For the full details of the evaluation of efficacy please see Attachment 2, Extract of the Clinical Evaluation Report.

Evaluator's conclusions on efficacy

The efficacy data submitted by the sponsor was largely derived from investigator led studies found in a literature search (the two sponsor led studies, consisting of a PD study in children, and a negative efficacy study in adults, were merely supportive). After identifying potentially relevant investigator led studies of the use of iNO in relation to cardiac surgery, the sponsor subdivided the studies into 22 efficacy studies (9 in children, 13 in adults) and 11 PD studies according to whether they compared iNO to a randomised control therapy. This subdivision was somewhat artificial, and many of the studies classified as efficacy studies had designs more typical of PD studies. Also, many of the studies listed as efficacy studies were small, used iNO for only short periods to gauge the short-term haemodynamic response, or used a control therapy of unproven utility.

Four of 9 efficacy studies in children were designated as "pivotal"[31], because the control group received placebo or standard care in a randomised prospective design, but three of

[27] Ardehali, A. et al. Inhaled nitric oxide for pulmonary hypertension after heart transplantation. *Transplantation*, 2001; 72:, 638-641
[28] Rajek, A. et al. Inhaled nitric oxide reduces pulmonary vascular resistance more than prostaglandin E(1) during heart transplantation. *Anesth Analg* 2000; 90: 523-530
[29] Radovancevic, B. et al. Nitric oxide versus prostaglandin E1 for reduction of pulmonary hypertension in heart transplant candidates. *J Heart Lung Transplant* 2005; 24: 690-695
[30] Argenziano, M. et al. Randomized, double blind trial of inhaled nitric oxide in LVAD recipients with pulmonary hypertension. *Ann Thorac Surg* 1998; 65: 340-345

these lacked the core features expected of a Phase III pivotal study. For instance, both Day et al and Morris et al used an open label design.[13, 14] Of the four studies, only two were positive (Miller et al, 2000, and Russell et al, 1998) and one of these (Russell et al) was only positive in a small subgroup that was possibly identified post hoc.[11, 12]

The only truly pivotal study was the one by Miller et al, 2000 (n = 124). [11] Miller et al assessed the efficacy of iNO 10 ppm versus placebo in the target population of paediatric cardiac surgical patients using a prospective, randomised, double blind design, with a robust methodology and clearly defined clinical endpoints. The treatment benefits in this study could have been partially masked by the use of rescue therapy with open label iNO, but it demonstrated a statistically significant benefit anyway. The primary endpoint was the number of PHTCs in the treatment period, which lasted for up to 7 days. Infants who received iNO had significantly fewer PHTCs (median four [Interquartile range (IQR) 0 to 12]) than infants receiving nitrogen placebo (median seven PHTCs [IQR 1 to 19]; unadjusted relative risk 0·66 [95%CI 0·59 to 0·74] p < 0·001; adjusted for dispersion 0·65 [0·43 to 0·99], p = 0·045). They also reached extubation criteria significantly sooner, and spent less time overall on study gas. The PVRI during study-gas administration was also significantly lower in the iNO group (p < 0·001).

The studies by Russell et al and Morris et al were listed as pivotal but they used haemodynamic endpoints rather than clinical endpoints, and the iNO treatment duration (≤ 30 min) was more consistent with a brief pharmacodynamic assessment than with realistic clinical use.[11, 12]

The study by Russell et al (n = 40) showed a significant haemodynamic effect for iNO over 20 min compared to placebo, but it produced its positive results in a subset of the study population, consisting of 13 subjects with elevated pulmonary artery pressure, only 5 of whom received iNO. Russell et al demonstrated that mPAP in this subgroup was reduced by 19% with iNO (p = 0.008) versus an increase of 9% with placebo. The iNO dose used in Russell et al was well above that proposed for registration (80 ppm, instead of 10 to 20 ppm as recommended in the PI).[12]

Morris et al performed a small study (n = 12) with a randomised, controlled, open label crossover design to compare the haemodynamic effects of iNO (at 5 ppm and at 40 ppm for 15 min each) versus hyperventilation induced alkalosis (HV) in children recovering from biventricular repair and CPB. They showed no significant differences between the combination of iNO and HV and HV alone, so this study does not provide evidence that iNO adds significantly to the pulmonary vasodilatory effects of standard care with HV. Significant changes were observed in PVRI and mPAP with both treatments, relative to baseline, but this does not constitute clear positive evidence of a treatment effect because some improvement could be due to recovery from CPB.[14]

The open label study by Day et al (n = 40) compared the efficacy of iNO 20 ppm with conventional therapy (determined by the treating clinician) in children with post-operative pulmonary hypertension after cardiac surgery. It used a similar clinical endpoint as Miller et al (number of PHTCs), but it was clearly underpowered for this endpoint and for secondary haemodynamic endpoints. The primary endpoint, PHTC, occurred infrequently: PHTCs occurred in 4 control patients and in 3 iNO patients, a difference that was not statistically significant. It was also negative for all major secondary endpoints, but the trends were favourable. Systolic pulmonary arterial pressure (SPAP) in the control group started relatively low and increased after an hour, whereas SPAP in the iNO group started relatively high and decreased by approximately10%. The changes in ratio of systolic pulmonary and systemic arterial pressures were greater with iNO than with conventional therapy, and this comparison approached statistical significance (p = 0.066).

[31] Clarification: Sponsor use of term 'pivotal' was related to the fact that these were key studies in this orphan indication – not that they were comparative, randomised and controlled in design.

Given that the study was underpowered and open label, and that clinicians used variable agents as control therapies, this study cannot be considered pivotal.[13]

The remaining 5 efficacy studies in children compared iNO to active alternatives. None of the non-iNO therapies has been approved for the treatment of pulmonary hypertension in the setting of paediatric cardiac surgery, which is why none of these studies was considered pivotal. In general, the emphasis of these studies was in demonstrating that the non-iNO therapy was comparable in efficacy to iNO (which was used as a control therapy because the authors considered iNO to be the standard treatment of pulmonary hypertension in this setting). These studies were not specifically powered to demonstrate equivalence or non-inferiority of iNO compared to the active alternative, but in general the findings were favourable, as follows:

In Cai et al, 2008 (n = 46), iNO at a starting dose of 10 ppm and continued for at least 24 hours was compared to intravenous milrinone 0.5 μg kg^{-1} min^{-1} in children with pulmonary hypertension after a Fontan procedure. In a 3 group, open label design, each agent was compared to the other agent and to the combination of both agents. Inhaled NO was significantly superior to milrinone for the study's main measure of pulmonary vascular resistance, transpulmonary gradient (TPG). Given that milrinone is likely to be superior to placebo, this provides reasonably strong evidence of haemodynamic efficacy of iNO in this setting. The combination of iNO and milrinone was also significantly more effective at reducing TPG than milrinone alone.[15]

Goldman et al, 1995 (n = 13), was a small, brief, open label crossover study, which showed that iNO 20 ppm was significantly superior to intravenous prostacyclin 20 ng per kg per minute in the short-term (10 minute) treatment of severe pulmonary hypertension in paediatric subjects after cardiac surgery. mPAP was reduced by 33% during iNO treatment (95%CI, -24% to -51%), compared to a reduction of 15% during prostacyclin treatment (95%Cl, -4% to -38%; $p < 0.01$).[16]

Kirbas et al, 2012 (n = 16), was another small, open label study performed in paediatric cardiac surgery patients. It compared the efficacy of iNO 20 ppm and aerosolised iloprost in the treatment of pulmonary hypertension, and found no difference. Favourable reductions in PAP and in PAP/ systemic arterial pressure (SAP) ratio were observed, but these are difficult to interpret given the lack of an untreated or placebo treated control group.[4]

Loukanov et al, 2011 (n = 15), was a small, open label pilot study comparing iNO 10 ppm and aerosolised iloprost 0.5 μg/kg every 2 h. The study suggested that the two drugs might have similar efficacy when used to prevent PHTCs in the paediatric setting, but the study was not adequately powered to demonstrate equivalence. Trends in mPAP were weakly in favour of iNO, but there was no convincing reduction in mPAP relative to baseline.[5]

Stocker et al, 2003 (evaluable n = 15), compared iNO 20 ppm and intravenous sildenafil 0.35 mg/kg in a small, open label crossover study in paediatric cardiac surgery patients, showing that the two drugs were similar in their ability to lower mPAP and PVRI. In the iNO first group, mPAP had fallen after 20 min of therapy, reducing by 1.4 ± 0.4 mmHg (by 7.8 ± 2.1%; $p = 0.008$). The subsequent addition of sildenafil did not further lower pulmonary artery (PA) pressure. In the sildenafil-first group, mPAP had also fallen by 20 min; the reduction seen with sildenafil was numerically greater than that seen in the iNO first group when expressed as a percentage of baseline, but the fall was not statistically significant (reduction of 10 ± 4.1%; $p = 0.055$). The subsequent addition of iNO produced a further fall in mPAP. The authors noted that iNO had greater pulmonary selectivity.[17]

Thus, of the five supportive studies in children, two of them (Cai et al[15] and Goldman et al[16]) produced significant results strongly supportive of a short term

haemodynamic effect with iNO relative to an unproven active control. The other three showed broad equivalence of iNO and the active control.

The remaining 13 efficacy studies were performed in adults, and so they are not directly relevant to the proposed indication. Also, most of these studies were small, or used iNO for only a brief period, as indicated in Table 34 of Attachment 2.

Positive results

Positive results were obtained for the 3 studies below, which all showed superiority of iNO relative to the control therapy.

Ardehali, 2001,[27] was a study of heart transplant patients. Study subjects who received iNO 20 ppm (n = 16) were compared with historical control subjects (n = 16), and the incidence of right ventricular (RV) dysfunction was substantially lower with iNO ($p < 0.05$). Survival was 100% with iNO, compared to 13 out of 16 (81.25%) in historical controls.

In Argenzanio et al, 1998[30] (evaluable n = 11), iNO 20 ppm (n = 6) was compared to placebo (n = 5) in subjects receiving an LVAD. The period of randomised treatment was brief (15 min), after which rescue therapy was initiated. Subjects randomised to iNO showed a reduction in mPAP from 35 ± 6 mmHg to 24 ± 4 mmHg ($p = 0.02$) and an increase in the LVAD flow index. Those randomised to nitrogen placebo showed no haemodynamic response, but subsequently responded to crossover therapy with iNO, with a reduction in mPAP from 31 ± 4 mmHg to 22 ± 3 mmHg ($p = 0.02$) and an increase in the LVAD flow index.

In Rajek, 2000[28] (evaluable n = 68), iNO at doses of up to 24 ppm was compared to prostaglandin E1 (PGE1) in adults undergoing heart transplantation, with treatment initiated at the end of CPB. In the iNO group, a major reduction in PVR occurred within 10 minutes of CPB (from 326 ± 21 to 180 ± 15 dynes·s·cm^{-5}), and this was statistically significant ($p < 0.0001$) compared to PGE1, where the initial reduction was relatively minor (295 ± 30 to 264 ± 27 dynes·s·cm^{-5}). The difference was still significant at one hour post-CPB but, by six hours, subjects in the PGE1 group had shown further reductions in PVR and the difference between groups was no longer significant.

Significant changes from baseline

Significant changes from baseline were obtained in the studies below, though no significant difference was observed between treatments (or, in the case of Winterhalter et al, iNO was significantly inferior to the active control, iloprost).[23]

Kieler-Jensen et al, 1994 (n = 12), studied iNO in the setting of pre-operative vasoreactivity testing in adults. They confirmed that iNO (ten min at each of 20, 40 and 80 ppm) is a selective vasodilator in the pulmonary circulation, lowering PVR, though it showed minimal direct effects on mPAP. The active controls, intravenous PGI2 and nitroprusside, produced a greater mPAP reduction than achieved with iNO. There was no convincing dose trend for iNO.[10]

Radovancevic et al, 2005 (n = 19), compared prostaglandin E1 (PGE1) and iNO (40, 60 and 80 ppm) during pre-operative vasoreactivity testing of heart transplant candidates with pulmonary hypertension, using an open label crossover design. This study showed positive haemodynamic results for both agents, with reductions in PVR and TPG relative to baseline, but no significant difference between the two agents. The reduction in TPG was not significant for the lowest dose of PGE1, but higher doses of PGE1 and all doses of iNO produced significant mean reductions, compared to baseline. The haemodynamic response to all doses of iNO was very similar, with no apparent dose trend across the range of 40 to 80 ppm.[29]

Schmid et al, 1999 (n = 14), used a crossover design to compare three agents, in random sequence: iNO 40 ppm, intravenous PGE1 0.1 μg·kg-1·min-1, and intravenous nitroglycerine (NTG), 3 to 5 mg·kg-1·min-1. All three agents produced a significant reduction in mPAP ($p < 0.01$), and all were effective in reducing PVR and TPG ($p = 0.003$). They differed in their effect on the systemic circulation: iNO did not produce a significant change in mSAP or systemic vascular resistance (SVR), but PGE1 and NTG did.[22]

Solina et al, 2000 (n = 45), assessed iNO at two doses (20 ppm and 40 ppm) in comparison to IV milrinone. They showed that iNO 40 ppm is broadly comparable to the intravenous vasodilator milrinone in its ability to reduce PVR. All three treatments produced a clear reduction in PVR compared to baseline. At a dose of 20 ppm, iNO was associated with a higher PVR than the other two treatments, but this could reflect pre-treatment differences.[24]

Solina et al, 2001 (n = 62), compared several different doses of iNO to milrinone. Subjects in Group 1 (n = 11) received 10 ppm, Group 2 (n = 12) received 20 ppm, Group 3 (n = 12) received 30 ppm, and Group 4 (n = 12) received 40 ppm. Subjects in Group 5 (n = 15) received milrinone initiated by bolus (50 mg/kg) 15 minutes before separation from CPB and maintained at 0.5 mg/kg/min in the operating room. All groups showed a clear and significant reduction in PVR. The percentage decrease in PVR did not show a consistent dose trend and was not significantly different between the groups by ANOVA (10 ppm = 38%, 20 ppm = 50%, 30 ppm = 44%, 40 ppm = 36%, milrinone = 58%; $p = 0.86$).[25]

Winterhalter et al, 2008 (n = 46), compared iNO to inhaled iloprost using an open label, randomised, prospective, parallel group design. Both agents produced a major, significant reduction in mPAP and PVR, relative to baseline, but the reduction in mPAP and PVR was greater with iloprost (between group mPAP difference, $p = 0.006$; PVR difference, $p = 0.013$).[23]

Negative or borderline results

Negative or borderline results were obtained for the remaining studies, though this usually reflected inadequate statistical power. None of these negative studies casts significant doubt on the efficacy of iNO.

Fattouch 2005 (n = 58) suggested that iNO 20 ppm and inhaled Prostacyclin (prostaglandin I2) (iPGI2) have similar efficacy in reducing pulmonary arterial pressure and PVR following CPB, in adults with right ventricular failure.[19] Fattouch et al, 2006 (n = 58), showed a progressive fall in mPAP during treatment with iNO, but there was no difference between iNO and intravenous controls, and many details of the paper were unclear.[20]

Giannetti et al, 2004 (n = 29), was only indirectly relevant to the proposed indication, because it did not assess the effect of iNO on pulmonary hypertension, but instead assessed its effects on markers of myocardial injury following CPB, finding significant benefits for iNO in comparison to no additional treatment.[21]

The sponsor's study INOT41 (n = 150) was a well-designed study of adult subjects undergoing LVAD insertion. It used an appropriate randomised, double blind, placebo controlled design, but in retrospect it was underpowered for its clinical endpoint ("treatment failure", largely equivalent to right ventricular dysfunction). Subjects received iNO or placebo for up to 48 hours. There was a trend suggesting superiority in the iNO group, which would be of substantial clinical worth of it were confirmed in an adequately powered study: the failure rate was 9.6% with iNO, compared to 15.6% with placebo (p not significant).

Overall, despite some flaws in the individual studies, the submitted data are strongly supportive of the efficacy of iNO in the proposed indication. The largest and best-designed

pivotal study in children, by Miller et al, 2000, produced clear evidence of a significant benefit for both clinical and haemodynamic endpoints and the remaining studies provided strong supportive evidence of haemodynamic benefit in both children and adults.

Safety

Studies providing safety data

Safety data potentially comes from 11 PD studies in the paediatric population (one of the 12 PD studies was a non-intervention study), 9 efficacy studies in the context of paediatric cardiac surgery, and 13 supportive efficacy studies in adults. One of the PD studies (INOT22) and one of the supportive adult studies (INOT41) had a sponsor driven design with comprehensive safety monitoring, but the other 32 studies were investigator-driven studies with variable and largely incomplete safety monitoring.

In the two sponsor led studies, adverse event reports were collected and grouped by organ system, and basic laboratory monitoring and vital sign reporting appeared to be comprehensive. Unfortunately, neither of these was performed in the proposed target population for the proposed indication.

In the 4 pivotal studies, safety assessments largely consisted of assays for methaemoglobin and nitrogen dioxide, along with continuous monitoring of haemodynamic profile and vital signs. Adverse events were not reported systematically, and so it is not possible to pool all the adverse events that have occurred on iNO for the proposed indication, much less compare this to the incidence of adverse events (AEs) with placebo. The number of paediatric subjects exposed to iNO in the pivotal studies was also small (Miller et al, 2000, n = 63; Russell et al, 1998, n = 18; Day et al, 2000, n = 20; Morris et al, 2000, n = 12).[11, 12, 13, 14] On the other hand, a review of the individual studies does not raise substantial new safety concerns related to the proposed indication, and the safety profile of iNO in the post-cardiac surgery setting appears to be broadly similar to that already established for the neonatal setting. There is already extensive worldwide experience with iNO in paediatric subjects, including those treated for the approved indication, PPHN, as well as subjects treated off-label for the proposed indication. The safety profile established for the original indication remains relevant to the proposed indication: both target populations consist of highly vulnerable paediatric patients in an intensive care setting.

The 13 supportive studies in adults provide indirect evidence of the safety of iNO for the proposed indication, with particular relevance to older children and teenagers. These studies include one sponsor led study (INOT41), where AE reporting was complete, and 12 investigator led studies which merely provided broad descriptions of the safety of iNO.

In many of the investigator-driven studies, particularly the PD studies, adverse events were not even mentioned. Although it seemed likely in many cases that any serious safety concerns would have been discussed, had they occurred, there was no explicit reassurance that adverse events did not occur.

In total, the sponsor considered (and the evaluator agrees) that the key safety data came from the following sources:

1. *"Safety data from studies in the proposed indication within the paediatric cardiac surgery setting (n = 10 published studies)*
2. *Safety data from studies in the paediatric cardiac setting, but not specifically for the proposed indication (company-sponsored study INOT22)*
3. *Supportive safety data from adult populations in a variety of cardiac surgery settings."*

The primary source of information of relevance to the proposed indication is therefore the 10 studies performed in the setting of paediatric cardiac surgery; this include all 9 paediatric efficacy studies (4 pivotal, 5 supportive) and one of the paediatric PD studies (Wessel et al, 1993[7]).

Known safety issues for iNO

The published experience of iNO and the previously approved PI for the existing indication suggests that the use of iNO raises a number of specific safety concerns:

- NO combines with haemoglobin (Hb) to produce methaemoglobin (metHb), which makes the haemoglobin unavailable for carrying oxygen.
- NO by-products include NO_2, and so monitoring is required to ensure that levels of NO_2 remain within safe limits.
- abrupt cessation of NO can induce rebound pulmonary hypertension.
- NO can increase left-atrial (LA) filling, potentially exacerbating cardiac failure or pulmonary oedema in susceptible individuals with pre-existing left ventricular dysfunction.
- NO could, in theory, effect platelet function.
- NO has unknown effects on the immune system.

Some of the submitted studies specifically commented on these issues. Virtually all of the studies specifically monitored and reported metHb levels, and most studies reported NO_2 levels or indicated that alarms were in place for alerting investigators to elevated levels of NO_2. MetHb levels and NO_2 are discussed further in the safety section of Attachment 2.

All authors appeared to be aware of the potential for rebound pulmonary hypertension to occur when iNO is ceased abruptly, and most study protocols avoided this with cautious weaning protocols. The ease of weaning therapy was specifically assessed in the main pivotal study, Miller et al 2000, where weaning time was considered a secondary efficacy endpoint.[11]

The sponsor's study, INOT22, provides evidence that LA filling may be excessive when iNO is administered in the setting of pre-existing left ventricular failure. This issue has been noted by previous investigators (Bocchi et al, 1994, Semigran et al, 1994)[32], [33]and is appropriately mentioned in the current and proposed PIs.

[32] Bocchi EA, et al. Inhaled nitric oxide leading to pulmonary edema in stable severe left heart failure. *Am J Cardiol* 1994; 74: 70-72

[33] Semigran MJ, et al. Hemodynamic effects of inhaled nitric oxide in heart failure. *J Am Coll Cardiol* 1994; 24: 982

Ardehali et al, 2001, also raise the following safety concern about iNO: "*The immunological properties of NO are incompletely understood. Low-level NO production appears to be necessary for maximal proliferation of lymphocytes. Furthermore, expression of inducible NO synthetase has been linked with acute solid organ rejection. On the other hand, activation of inducible NO synthetase is associated with a reduction in lymphocyte proliferation and inhibition of the expression of class II major histocompatibility complex. Further research in this area is needed to better elucidate the immune-modulating properties of inhaled NO in thoracic transplantation.*"[34]

The current safety database does not allow any substantial conclusions to be drawn about the effect of iNO on immunological function, but this should be a focus of ongoing post-marketing surveillance.

Patient exposure

Exposure to iNO in the submitted efficacy studies is summarised in the tables, with paediatric and adult subjects pooled (Table 79, Attachment 2) or considered separately (Tables 80 and 81, Attachment 2). The doses involved range from below the proposed 10 ppm starting dose, in 12 subjects, up to 80 ppm, which is well beyond the maximum recommended dose of 20 ppm. The most common exposure was to a dose of 10 to 20 ppm, used in 257 subjects, which is within the dose range recommended in the proposed PI.

For the full evaluation of Safety please see Attachment 2.

Evaluator's conclusions on safety

The use of iNO poses a number of significant but manageable safety concerns, which are acceptable in the context of a drug used in intensive care to treat and to prevent life threatening pulmonary hypertension in relation to cardiac surgery.

Levels of toxic nitric oxide by-products, including metHb and NO_2, need to be monitored in all recipients of iNO, but levels are expected to be within acceptable limits when the dose is kept ≤ 20 ppm. The proposed indication does not increase the risk of methaemoglobinaemia or elevated NO_2 compared to the existing indication. Occupational exposure to NO in medical and nursing staff is expected to be minimal.

The risk of methaemoglobinaemia can be increased by co-administration of iNO and other drugs, particularly NO donors such as nitroprusside, and some local anaesthetic agents. The PI carries warnings about this potential interaction, and monitoring for metHb would be expected to provide additional safeguards in the vent of inadvertent co-treatment with agents at risk of causing methaemoglobinaemia.

Inhaled nitric oxide causes pulmonary vasodilation, and this can have adverse consequences in patients with pre-existing left ventricular failure, or in infants relying on a particular level of cardiac shunting that could be modified by lowering resistance in the pulmonary vascular bed. This risk is intrinsic to the primary pharmacodynamic mode of action of iNO, and would be expected with any selective pulmonary vasodilator. The proposed PI carries adequate warnings about these risks, and the onus will be on

[34] Efron DT, Kirk SJ, Regan MC, et al. Nitric oxide generation from LArginine is required for optimal human peripheral blood lymphocyte DNA synthesis. Surgery 1991; 110: 327.
Kuo PC, Alfrey EJ, Krieger NR, et al. Differential localization of allograft nitric oxide synthesis: comparison of liver and heart transplantation in the rat model. Immunology 1996; 87: 647.
Albin JE, Abate JA, Henry WL. Nitric oxide production is required for murine resident peritoneal macrophage to suppress mitogen stimulated T-cell proliferation. J Immunol 1991; 147: 144.
Sichel SC, Vasquez MA, Lu CY. Inhibition of macrophage I-A expression by nitric oxide. J Immunol 1994; 163: 1293.

clinicians to use iNO in appropriately targeted patients, and to monitor for adverse haemodynamic effects.

Abrupt withdrawal of iNO can produce rebound pulmonary hypertension. This effect was not well demonstrated in the submitted studies, because clinicians specifically avoided abrupt withdrawal, but weaning times were noted to be significantly longer in the main pivotal efficacy study.

Because it is a vasodilator, iNO would be expected to have synergistic effects when combined with other vasodilators. This is not likely to be a more significant issue with iNO than other agents used to treat pulmonary hypertension, and the onus will be on clinicians to use sensible combinations of agents and to monitor for hypotension or other adverse haemodynamic effects. The PI carries appropriate warnings about this.

The submitted studies, including supportive studies in adults, only provided limited evidence about the incidence of AEs and serious adverse events (SAEs) on iNO in relation to placebo, but there does not appear to be a significantly increased risk of adverse outcomes. No study has been adequately powered to demonstrate the effects of iNO on mortality rate, but mortality in the submitted studies did not appear to be increased with iNO. Of the deaths reported in the submitted studies, no concerning patterns emerged to suggest significant safety concerns with iNO. Instead, the efficacy data revealed a significant reduction in the incidence of PHTCs in children undergoing cardiac surgery (Miller et al, 2000),[11] so there may be mortality benefits associated with the use of iNO, particularly in subjects at high risk of PHTCs.

Theoretical considerations raise the possibility of increased bleeding with iNO, but this did not emerge as a significant issue in the submitted studies. The PI already carries appropriate warnings about this.

Extensive post-marketing experience with iNO has not significantly modified the safety profile of iNO since it was first registered. The published and post-marketing experience with iNO shows broadly similar safety across several different age groups, ranging from near-term or full-term neonates to elderly adults. There is relatively little experience with teenage patients, but the extensive experience in younger and older patients allows a reasonable interpolation of the safety profile to this age group.

Overall, the safety of iNO is acceptable, but it will need to be used by staff who have been trained in its use and who are familiar with its potential problems, and adequate monitoring will need to be in place. This is already the case for the existing indication, and the proposed indication does not raise substantial new safety concerns.

First round benefit-risk assessment

First round assessment of benefits

In the context of paediatric cardiac surgery, iNO significantly reduces pulmonary hypertension with subsequent improvements in right ventricular function, and it has been shown to prevent a significant proportion of pulmonary hypertensive crises. This would be expected to produce mortality benefits, but the design of the major efficacy studies included rescue therapy with iNO, limiting the ability of the studies to show a mortality benefit.

Because iNO is selective for the pulmonary vasculature, these haemodynamic gains can be achieved without causing systemic hypotension, as has been demonstrated in several efficacy and pharmacodynamic studies. By contrast, intravenous vasodilators often produced clinically significant systemic vasodilation and systemic hypotension. This partly reflects the different routes of administration, and other pulmonary vasodilators could

offer similar benefits over intravenous agents, though none is currently registered for this indication.

Inhaled NO can also significantly improve oxygenation, presumably through improved ventilation-perfusion matching.

When used pre-operatively, as part of vasoreactivity testing, iNO can identify surgical candidates with reversible pulmonary hypertension who might otherwise be considered ineligible for surgery.

First round assessment of risks

Inhaled NO carries a number of acknowledged and manageable risks.

Of the risks identified in the submitted studies, the following are considered the most important:

- risk of NO by-products; manageable through dose restriction and monitoring for NO_2 and metHb;
- risk of adverse haemodynamic effects; manageable through patient selection and monitoring (in particular avoiding use of iNO in subjects with elevated left atrial pressure, or subjects relying on right-to-left shunting, and monitoring subjects for systemic hypotensive responses or adverse modifications of shunt haemodynamics);
- risk during pregnancy; treatment during pregnancy should be avoided because of a complete lack of information about the safety of iNO in this setting. This situation is expected to arise relatively rarely in the paediatric setting, particularly because surgery for congenital heart disease is usually performed in the first few years of life, teenagers were not commonly treated in the paediatric studies, and severe cardiac disease is likely to lower fertility. Girls of child bearing age should be screened for pregnancy as part of the cardiac surgical work-up, and decisions would need to be made about the appropriateness of continuing the pregnancy and the timing of surgery.

The risks listed below are acknowledged by the sponsor in their RMP.

Table 8: Summary of safety concerns identified in RMP

Safety concerns	
Important identified risks	Methaemoglinaemia
	Risk of acute cardiac failure with circulatory collapse in certain patient populations and Risk of heart failure or pulmonary oedema in certain patient populations
	Rebound reactions (pulmonary hypertension) with abrupt withdrawal
Important potential risks	NO_2 formation
	Increased bleeding time
	Critical failure of the delivery system

Safety concerns	
Missing information	Combined use with other vasodilators
	Use during pregnancy and lactation
	Paediatric use < 34 GA for PPHN, and patients 12 to 17 years treated for pulmonary hypertension in conjunction with heart surgery

Overall, the risks associated with iNO are adequately acknowledged in the PI and can be limited by the use of trained staff and appropriate monitoring.

First round assessment of benefit-risk balance

The benefit-risk balance of iNO in the proposed indication is favourable, because the risks that have been identified are manageable, the drug has proven efficacy in preventing or ameliorating life threatening pulmonary hypertension, and no other standard agents are registered for this indication.

There is a general lack of efficacy and safety data in the age range 12 to 17 years, but the data in younger children and older adults show consistent effects, and there is no reason to expect that the benefit-risk balance is substantially different in teenagers compared to younger and older patients. Because congenital cardiac defects are usually corrected before the age of 12, and acquired cardiac diseases often appear in older adults, this intermediate age group is under-represented in the clinical studies, and evidence in this group is likely to remain relatively limited. The potential hazard of approving iNO prior to obtaining an extensive database in this age group must be balanced against the potential hazard of denying such subjects a treatment that works in younger and older subjects, and for which there is no currently registered alternative therapy.

To optimise the benefit-risk balance, care will need to be taken to ensure appropriate patient selection and ongoing vigilance in terms of monitoring during iNO use. Inhaled NO will need to be administered by staff specifically trained in its use.

First round recommendation regarding authorisation

Inhaled nitric oxide (INOmax) should be approved for the proposed indication, following revision of the PI.

Clinical questions

As already discussed, the investigator led studies were not always clearly described in terms of their primary endpoints, blinding techniques, and safety monitoring. By contrast, the sponsor led studies had clear prospective endpoints and comprehensive safety monitoring.

It is acknowledged that, in the setting of a literature-based submission, it may be difficult for the sponsor to provide full information on studies that they did not initiate or supervise. Nonetheless, the following clinical questions represent substantial unresolved issues arising from the submission.

General questions

1. To what extent does the pulmonary selectivity of iNO reflect the proposed route of administration, rather than an intrinsic pharmacodynamic property of the drug?
2. What effects does iNO have on the immune system and are these effects likely to be clinically relevant?

Questions related to specific studies

3. Why did the pivotal study by Miller et al (2000)[11] only recruit 124 patients after sample size estimations suggested that 136 subjects would be need to reach an adequate statistical power?
4. Does the sponsor agree that, amongst time-based endpoints in the pivotal study by Miller et al (2000),[11] they have misinterpreted the study by treating the time to meeting extubation criteria and the time to meeting weaning criteria as two different endpoints when they were actually the same endpoint?
5. What statistical test was used to generate the p-value of 0.008 in the study by Russell et al (1998)[12], as cited in the abstract? "*Of the patients, 36% (n = 13) emerged from bypass with mPAP > 50% mSAP. In these patients, inhaled NO reduced mPAP by 19% (P = 0.008) versus an increase of 9% in the placebo group*." How does this p-value relate to the different p-value of 0.0016 shown for the 20 min time-point in the authors' table, reproduced below?

Table 9: Percent change in post-bypass mPAP (mPAP > 50%mSAP)

Patient	Agent	MPAP postbypass (mm Hg)	MPAP as percent of MSAP	Percent changes of MPAP (mm Hg)			
				1 min	10 min	20 min	Gas OFF
	NO	26	59	−13	−15	−35	−19
	NO	24	53	−8	−10	−8	−13
	NO	33	80	−8	−9	−15	−12
	NO	28	68	−21	−18	−29	−13
	NO	32	63	−6	0	−9	2
Mean ± SD		29 ± 4	65 ± 10	−11 ± 6	−11 ± 7	−19 ± 12	−11 ± 8
Median		28	63	−8	−10	−15	−13
P value				0.013	0.14	0.0016	0.010
	N_2	21	64	−12	−5	2	2
	N_2	25	82	8	0	16	8
	N_2	53	98	25	43	45	51
	N_2	24	59	−6	2	0	2
	N_2	29	78	2	−21	9	−5
	N_2	21	66	29	31	10	17
	N_2	32	93	9	0	−3	13
	N_2	30	59	−3	−10	−7	−3
Mean ± SD		29 ± 10	75 ± 15	6 ± 14	5 ± 21	9 ± 16	11 ± 18
Median		27	72	5	0	6	5

Bold numbers indicate patients who had pulmonary hypertension in the intensive care unit.
MSAP = mean systolic artery pressure.

6. Russell et al (2000)[12] performed a subgroup analysis in which they assessed efficacy in 13 subjects who emerged from bypass with mPAP > 50% mSAP, and the significant efficacy results cited in the abstract were confined to this subgroup. Was this analysis and the precise definition of the subgroup declared prospectively, or was the analysis performed post hoc in response to the results?
7. What was the statistical power of the study performed by Kirbas et al (2012)?[4]
8. What were the between group differences demonstrated by Fattouch et al (2005)?[19] What did the ANOVA demonstrate?
9. What drugs at what doses were administered in the study described by Fattouch et al (2006)?[20]

Several authoritative bodies have endorsed the off-label use of iNO for the proposed indication, so additional expert input is not required.

Second round evaluation of clinical data submitted in response to questions

For details of the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

The sponsor's responses have clarified a number of important issues in relation to the studies by Miller et al and Russell et al, revealing that both of these studies, flagged as pivotal by the sponsor, contained methodological flaws. These flaws mean that the proposed benefits of iNO are less statistically certain than they at first seemed, but there is no strong reason to suspect that the overall benefit-risk balance is substantially different to that described in the first round clinical evaluation report. That is, estimations of the benefit-risk balance suggest a similar overall balance, but the estimate is now surrounded by greater uncertainty.

In the case of Miller et al, the study was terminated early in response to an interim analysis showing it had achieved statistical significance; this decision means that the study had multiple potential ending times, multiple chances to achieve significance, and therefore stands in need of adjustment for multiplicity. No such adjustment was performed, and the borderline nature of the primary result ($p = 0.045$) raises the distinct possibility that the positive outcome of this study would have been negated if such an adjustment had been performed. From a purist perspective, the study should therefore be considered negative, unless the sponsor or the original authors perform a formal statistical analysis showing that the p-value remains significant after an appropriate adjustment.

The sponsor also agreed that they misinterpreted the secondary endpoints of Miller et al, but this makes no difference to the benefit-risk balance because it was assumed in the first round report that they were mistaken, and the first round clinical evaluation adopted the correct interpretation.

In the case of Russell et al, the sponsor has passed on assurances from the original author that this study's subgroup analysis was planned prospectively. No documentation was provided to back this up. This is a potential problem because positive results were only obtained in one small subgroup, subjects with elevated mean pulmonary artery pressure (mPAP) post-surgery. Given that this subgroup would be expected to be the main target group for iNO on the basis of other studies that have reached similar conclusions, this methodological flaw does not substantially change the benefit-risk balance, though it does suggest that the study lacked rigour. The original authors were also unable to explain the p-values declared in a secondary analysis, adding to the concerns about the rigour of this paper and suggesting it should be considered merely supportive. On balance, given the large number of other papers reaching similar conclusions, this does not change the benefit-risk balance.

The sponsor was unable to obtain information from the original authors in regard to three minor papers, but these papers did not contribute much to the benefit-risk assessment anyway.

With respect to safety issues, the sponsor has provided arguments suggesting that the risk of infection is not increased by iNO, and that the RMP does not need to mention theoretical concerns about the potential effects of iNO on the immune system. The evaluator concedes

that there is no positive clinical evidence of an immunosuppressive effect, but nonetheless concludes that the current clinical data is inadequate to address this risk. Some mention should be made of this theoretical issue in the RMP.

In conclusion, the benefits and risks outlined in the first round clinical evaluation appear unchanged by the new data, and remain positive. The new data reveal that no individual pivotal study demonstrated the efficacy of iNO with complete rigour, and, in particular, the response to clinical Question 3 raises concerns that the main study by Miller et al should be considered negative, from a purist statistical perspective. Despite this, the flaws in the individual studies are offset by the following:

- Multiple studies across multiple institutions, using both clinical and haemodynamic endpoints, have all been essentially concordant.
- The drug has been used off-label for a couple of decades for the proposed indication, with no concerns being raised about lack of efficacy.
- Experienced clinicians have been well placed to observe its use directly in a closely monitored intensive care setting, so the safety issues are largely known.
- Several expert bodies have supported its use after considering much the same evidence as evaluated in this report.
- Thus, despite the flaws of the individual submitted studies, the balance of evidence falls narrowly in favour of registration.
- Experienced clinicians have been well-placed to observe its use directly in a closely monitored intensive care setting, so the safety issues are largely known.
- Several expert bodies have supported its use after considering much the same evidence as evaluated in this report.

Thus, despite the flaws of the individual submitted studies, the balance of evidence falls narrowly in favour of registration.

Second round recommendation regarding authorisation

The application to register iNO should be approved, following appropriate revision of the PI and RMP.

The revisions to the PI should include those already recommended in the first round clinical evaluation, which the sponsor has accepted.

A new statement should be added to the PI that acknowledges the early termination of the pivotal study by Miller et al and the resulting uncertainty about the statistical significance of the cited results.[35]

The proposed wording of the extension of the indication is acceptable, and it is consistent with the submitted evidence. It could be argued that a formal document should not contain the split infinitive, "to selectively decrease", but the current evaluator feels that split infinitives have become part of modern English, and no changes are suggested. Similarly, it could be argued that "improve" is also part of an infinitive, and it should therefore be replaced by "to improve."

> "*INOmax, in conjunction with ventilatory support and other appropriate agents, is indicated:*

[35] Clarification: This was agreed and implemented by Sponsor

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 order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation.

as part of the treatment of peri- and post-operative pulmonary hypertension in newborn infants, infants and toddlers, children and adolescents, ages 0-17 years in conjunction with heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation."

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan EU-RMP version 2.0, dated 31 March 2014 (data lock point 31 March 2014), Australian Specific Annex version 1, dated 10 June 2014 which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 10.

Table 10: Ongoing safety concerns

Ongoing safety concerns	
Important identified risks	methaemoglobinaemia
	Risk of acute cardiac failure with circularity collapse in certain patient populations Risk of heart failure or pulmonary oedema in certain patient populations
	Rebound reactions (pulmonary hypertension) with abrupt withdrawal
Important potential risks	NO_2 formation
	Increased bleeding time
	Critical failure of the delivery system
Missing information	Combined use with other vasodilators
	Use during pregnancy and lactation
	Paediatric use < 34 GA for PPHN, and patients 12 to 17 years treated for pulmonary hypertension in conjunction with heart surgery

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance to monitor all the identified safety concerns. No additional pharmacovigilance activities are considered necessary by the sponsor.

Risk minimisation activities

The sponsor states in the EU-RMP:

> '*The drug is delivered through a NODS into the breathing circuit of the ventilation system. The combination and interaction of the three modalities (drug, NODS, and ventilation system) is critical to the safety of inhaled nitric oxide…In all countries for which LHC AB is the Marketing Authorisation Holder (MAH) all relevant healthcare staff undergoes a continuous, documented training program for both INOmax and devices based on currently approved product information*.'
>
> In addition, the sponsor has advised in the ASA that '*In Australia, the risk minimisation measures proposed for INOmax on approval of the proposed indication in the paediatric cardiac surgery setting are similar to those in the EU… At launch of the new indication, healthcare professionals who are likely to use and/or prescribe INOmax for the treatment of pulmonary hypertension associated with paediatric cardiac surgery will be provided with an educational pack*.'

Reconciliation of issues outlined in the RMP report

Table 11 summarises the first round RMP evaluation of the RMP, the sponsor's responses to issues raised and RMP evaluation of the sponsor's responses.

Table 11: Reconciliation of issues outlined in the first round RMP evaluation report

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
1. Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated TGA request for information and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	The sponsor has incorporated the majority of revisions based on safety considerations raised by the nonclinical and clinical evaluator in the revised draft PI supplied with this response. The sponsor has provided a justification for non-inclusion of the nonclinical evaluator's additional text related to an effect of NO on platelet function, thrombocytopenia as an adverse effect and listing of drugs which may potentiate methaemoglobin formation when combined with inhaled NO. These amendments are not considered relevant to the RMP at this stage but may be re-considered if the TGA Delegate's overview requests similar amendments to the PI at a later time on the evaluation process. A justification has been prepared by the sponsor for non-acceptance of the clinical evaluator's request that the RMP should include an effect of inhaled NO on the immune system. The nonclinical evaluator requested an update to a table presented in the RMP which the sponsor has responded to	The sponsor's approach is satisfactory in the context of the risk management plan. The assessment of the sponsor's response to the clinical and non-clinical evaluators' recommendations is expected to be conducted by relevant evaluators.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	in this response.	
2. The sponsor has advised that a similar application in Switzerland was withdrawn. The sponsor should clarify whether any safety related factors contributed to its decision to withdraw the application in Switzerland.	Please be advised that the application in Switzerland requested a line extension in both the adult and paediatric populations with an allowance for adults to dose escalate to 40 ppm of nitric oxide. SwissMedic had concerns primarily in the adult population regarding efficacy in the INOT41 study and lack of adequate efficacy in the published literature. Additionally, SwissMedic found the safety profile at higher doses was inconclusive. Therefore, the sponsor decided to withdraw the application.	The sponsor's response is satisfactory. Neither the patient population nor the dosage of concern appears to be relevant to the current submission in Australia.
3. It is understood that the 'certain patient populations' mentioned under 'important identified risks' include the following: Neonates known to be dependent on right-to-left, or significant left-to-right shunting of blood (contraindicated) Patients with compromised left ventricular function Patients with elevated baseline pulmonary capillary pressure. The sponsor should clarify whether there are other patient populations that are also at a higher risk.	The sponsor confirms that these are the three groups of "certain patient populations" mentioned under "important identified risks". No other patient populations are considered appropriate for this classification.	The sponsor's response is satisfactory.
4. It is recommended that the following safety concerns mentioned in the Australian PI be added in the ASA as these can be life threatening in neonates and young children: Bacteraemia and/or local infection occurred in 13% of patients in the treatment group compared to 6% in the placebo group; Cellulitis occurred in 5% of patients in the treatment group compared to 0% in the placebo group;	Section 3.1 of the ASA entitled "Risk minimisation activities in Australia" states that routine risk minimization activities are based on "Text included in the approved PI on the identified safety concerns'. The sponsor does not agree that the individual adverse effects listed above should be listed as individual safety concerns in the ASA Table; instead the ASA Table 1 has been revised to include "11. Adverse effects specified in Australian PI." In the prospectively designed, double blind and placebo controlled studies, such as CINRGI and NINOS, supporting initial Hypoxic Respiratory Failure indication registration, evaluation of incidence of infections was conducted. The suspected	The sponsor's response is acceptable. It is noted that 'adverse effects specified in the Australian PI' has been added to the list of safety concerns in the updated ASA.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
Thrombocytopenia occurred in more than 10% of patients in the CINRGI trial; Hypotension occurred in 13% of patients in the treatment group compared to 10% in the placebo group in clinical trials.	sepsis cases in CINRGI study were 59 out of 89 (66.3%) in placebo treated arm and 54 out of 97 (55.7%) in iNO treated arm. Additionally, the number of subjects with positive blood cultures in the first week was almost identical between the treatment arms (10.1% in placebo treated arm and 10.3% in iNO treated arm) (Refer to CINRGI CSR; Table 68). The suspected or proven sepsis/infection as cause of death in NINOS study was 6 out of 20 (30%) in placebo treated arm and 5 out of 16 (31%) in iNO treated arm (Refer to NINOS Abbreviated CSR; Table 33). Based on this clinical data, there is no evidence of increased risk for infection/bacteraemia in subject's treated with iNO. Hypotension has been already listed in the Australian PI.	
5. Long-term safety following treatment should be added as 'missing information'. Although the sponsor claims that valid conclusion cannot be drawn due to lack of dose response relationship and the low follow-up rate, data from one year and five year follow-up studies have found higher incidence of hearing loss; 4% in treatment group compared to 0% in placebo group; cerebral palsy; 4% in treatment group compared to 1% in placebo group; neurological impairment; 23% in treatment group compared to 14% in placebo group; and gait disturbance; 16% in treatment group compared to 2% in placebo group.	In the NINOS study, follow-up exams were performed at 18 to 24 months for infants enrolled in the 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 (EU RMP). 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. Based on this low follow-up rate and inability to come to valid conclusion with available follow-up data, the sponsor does not consider these as valid safety concerns to be added to the ASA table. However, the sponsor will continue to monitor these through routine pharmacovigilance.	The sponsor's response is acceptable.
6. The safety concern list should include risks related to both ingredients and the delivery system. The risk of 'abrupt discontinuation of INOmax therapy in the event of critical failure of the delivery system' and	As INOmax delivery system is registered and approved as a medical device, it has its own risk assessment and management documents as required by ISO 14971 and Australian medical device regulations. With regard to "abrupt discontinuation of INOmax therapy", the sponsor wishes to draw attention to item 4 on the ASA table,	The sponsor's approach in amending the PI document to provide warning against the risk of abrupt discontinuation of

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
'dose errors associated with the delivery system' should also be added as important identified risks in the ASA.	which discusses rebound pulmonary hypertension following abrupt withdrawal of INOmax, regardless of causes, as an important identified risk. Additionally, item 7 on the ASA discusses critical failure which includes device failures. Therefore, the sponsor believes that, although the ASA table currently describes such a risk, the PI describing the nitric oxide delivery system should be amended to describe important device safety requirements engineered into the INOmax DSIR to mitigate these risks. The abrupt discontinuation of INOmax therapy may be caused at least by two reasons: Use error when the instruction to gradually wean off INOmax in the PI is not followed. INOmax delivery device defect. To mitigate the risk of abrupt discontinuation of INOmax therapy, INOmax delivery system has 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 the INOblender, that is mounted below the primary delivery system on the "cart" containing the delivery system and drug cylinders, and is able to deliver nitric oxide while the patient is manually ventilated. Both back-up systems are pneumatic, thus being able to operate without main electrical power or battery power. In the interest of patient safety, and in order to minimize the risk of rebound pulmonary hypertension, all Ikaria nitric oxide delivery systems provided to hospitals have an integrated and independent back-up system. In this way, if the primary delivery fails, the INOmax delivery system alerts users in order to initiate one of the two back-up delivery approaches. Ikaria Australia has been providing user training routinely to relevant hospital personnel, and ongoing 24 hour, 7 days a week technical support service, on the proper use of INOmax delivery system to mitigate patient risks. With regard to "dose errors associated with the delivery system", the sponsor wishes to draw attention to Section 3.4 of ASA, which	INOmax therapy in the event of critical failure of the delivery system' is acceptable. However, it should be noted that following the first round RMP evaluation report dated 18 December 2014 in which the relevant recommendations were first made, the UK regulator MHRA published a drug safety update for INOmax on 16 February 2015.[36] This update confirmed the issue of potential failure of the delivery system raised in the RMP evaluation report and provided warning against the risk of 'valve defect stopping gas delivery early in some cylinders'. Users were reminded to '*always have a full spare cylinder loaded on the delivery device so the cylinders can be switched without delay*'. It is recommended that the Delegate considers the adequacy of PI in the context of the recommendations made by the RMP evaluator and the MHRA drug safety

[36] https://www.gov.uk/drug-safety-update/inomax-nitric-oxide-cylinders-valve-defect-might-stop-gas-delivery-early-in-some-cylinders

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
	discusses potential for medication errors. There is very low to negligible potential for medication error including dose error for the following reasons: To ensure accurate INOmax dose is delivered, INOmax delivery system has a specially designed injector module and an internal flow sensor, which enables tracking of the ventilator waveforms and the delivery of a synchronized and proportional dose of NO. The INOmax delivery system has integrated monitoring of NO level of patient's inspired gas. Every INOmax delivery system is/shall be calibrated with NO Cal gas. When monitored NO level is not consistent with set NO dose, the INOmax delivery system alerts users for system check. INOmax is supplied as a single strength product in Australia. Ikaria Australia provides relevant hospital personnel training, and ongoing 24 hour, 7 days a week technical support service, on the proper use of INOmax delivery system to mitigate patient risks including dose errors. Therefore, the sponsor believes no addition shall be made to ASA.	update. The sponsor's response regarding 'dose errors associated with the delivery system' is acceptable.
7. The pharmacovigilance and risk minimisation sections should be updated accordingly to provide plans for managing these safety issues.	Please refer to the revised ASA (Version 2 dated 06 March 2015), clean and annotated versions) attached to this response.	The sponsor's response is acceptable.
8. The sponsor should clarify whether the additional education materials are provided to the healthcare professionals for the treatment of PPHN.	The healthcare professionals who will receive the educational pack are cardiothoracic surgeons and other health care professionals such as anaesthetists, and paediatric intensivists who work with the paediatric cardiac surgery team and who manage patients who are planned to have surgery for congenital heart disease.	The sponsor's response is satisfactory.
9. The sponsor should explain the difference between a test gas cylinder and a treatment gas cylinder; and the safety issues related to using a test gas cylinder for treatment purpose. The sponsor should clarify whether test	Test gas cylinders are available in Australia but there is no risk of using test gas cylinders for treatment purposes or accidental exposure of health staff to INOmax during the training process, for the reasons outlined below: Test gas cylinders are used to calibrate the delivery device (INOmax DSIR). It is not possible to connect these cylinders to the	The sponsor's response is satisfactory.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
gas cylinders are available in Australia. If so, how it plans to mitigate the risk of using test gas cylinders for treatment purpose and the risk of accidental exposure of health staff to INOmax during the training process.	delivery device in any way that gas could be delivered to a patient. When the device is in calibration mode and test gas is connected, delivery to a patient is not possible. Test gas cylinders are kept outside of the intensive care unit. The size of test gas cylinder is 39 litres. The size of treatment cylinder is 1963 litres for "88" cylinder and 353 litres for "D" size cylinder. The monitoring CPU acts completely independently to the delivery CPU – there is no crossover of gas between these two systems in the delivery device. The test gas is connected to the monitoring CPU only through a luer lock sample port. The test gas cylinders have a reverse (left hand) thread on them so the regulators from the DSIR are unable to connect to them. The infra-red capability of the DSIR recognises whether the treatment cylinder is INOmax and will not deliver any other gas.	
10. The sponsor has stated in the EU-RMP that the additional education includes the following: A continuous, documented training program for both INOmax and devices An instruction for use manual An operations manual for the device A technical operations manual including customer-specific detailed medical device training. The sponsor should clarify whether the Australian educational program contains the same elements. If not, the sponsor should provide justification to the differences.	The sponsor confirms that the additional education package supplied in Australia contains the above elements as described in the EU-RMP.	The sponsor's response is satisfactory. The evaluator has noted the changes made in the updated draft PI document.
11. The sponsor has advised that the risk of 'combined use with other vasodilators that act on cGMP or cyclic adenosine monophosphate (cAMP)' is not incorporated	Based on the recommendation of the RMP evaluator, the sponsor has incorporated the text regarding "combined use with other vasodilators" into the section of the revised PI supplied with this response.	The sponsor's response is satisfactory.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
in the Australian PI. However, this risk is relevant to the use of the product in Australia settings and is listed as missing information in the RMP. It is recommended to the Delegate that the following information about the risk is provided in the PI: 'The combined used with other vasodilators (for example 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.' (as in the SmPC).		

Summary of recommendations

It is considered that the sponsor's response to the TGA request for information has adequately addressed most of the issues identified in the RMP evaluation report. An outstanding issue is discussed below.

Recommendation 6:

The sponsor's approach in amending the PI document to provide warning against the risk of 'abrupt discontinuation of INOmax therapy in the event of critical failure of the delivery system' is acceptable.

However, it should be noted that following the first round RMP evaluation report (dated 18 December 2014) in which the relevant recommendations were made, the UK regulator MHRA published a drug safety update for INOmax on 16 February 2015.[36]

This update confirmed the issue of potential failure of the delivery system, raised in the RMP evaluation report and provided warning against the risk of 'valve defect stopping gas delivery early in some cylinders'. Users were reminded to 'always have a full spare cylinder loaded on the delivery device so the cylinders can be switched without delay'.

It is recommended that the Delegate considers the adequacy of PI in the context of the recommendations made by the RMP evaluator and the MHRA drug safety update. The sponsor's response regarding 'dose errors associated with the delivery system' is acceptable.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

Implement EU-RMP version 2.0, dated 31 March 2014 (data lock point 31 March 2014) with Australian Specific Annex version 2, dated 6 March 2015 and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

The nonclinical evaluation had no objections to the extension of indications for INOmax on nonclinical grounds. The evaluator noted that methhaemoglobinaemia was the primary adverse effect of inhaled nitric oxide (iNO) in a sheep repeat dose toxicity study. The evaluator was concerned that the highest levels, 12%, may not be well tolerated in individuals with compromised oxygenation and/or oxygen carrying capacity. The nonclinical evaluator has made recommendations that the potential for nitric oxide to modulate platelet function via the guanylate cyclase signalling pathway should be added to the PI and that there should be modification of the section describing interactions with medicines that cause methhaemoglobinaemia.

Clinical

Pharmacology

The following is a summary of the known pharmacokinetics of iNO.

- NO is inhaled, absorption occurs in aerated alveoli by diffusion into alveolar capillaries and is taken up rapidly into haemoglobin (Hb) (velocity constant 280 fold greater than oxygen).
- When Hb is 60 to 100% saturated iNO combines with oxyHb to produce metHb and nitrate. At low oxygen saturations it can combine with deoxyHb to form nitrosyl haemoglobin which converts to nitrogen dioxide and metHb on exposure to oxygen.
- Half-life of 0.46 sec to a 'few seconds'.
- Predominant metabolite is nitrate, which is excreted in urine.
- Uptake and metabolism is not affected by gender or genetics but may decrease with age. No major differences were expected in the paediatric surgical population compared with other populations.

- Concentration of iNO in the lung depends on the administered dose (in ppm), and absorption from the alveolus depends on the minute ventilation.

New pharmacodynamic data were submitted including literature and a sponsor-led study (INOT22) and showed:

- Inhaled nitric oxide, via activation of guanylate cyclase resulting in the formation of cGMP, causes smooth muscle relaxation and vasodilation.
- Inhaled nitric oxide causes pulmonary vasodilation, a reduction of pulmonary artery pressure and unloading of the right ventricle.
- The effect is expected to be greater in areas of ventilated lung, improving ventilation perfusion mismatch.
- The onset of action is rapid, and within several minutes.
- A secondary PD effect makes patient at risk of rebound pulmonary hypertension and this can last for hours after cessation of therapy, therefore a slow weaning process is recommended.
- There is no clear dose response relationship, and it is likely that other factors such as the degree of deficiency in endogenous NO and other patient factors are likely to be important. The lowest effective dose was not well demonstrated in the studies, but there was limited evidence that incremental improvement is not achieved with doses greater than 40 ppm.

Efficacy[37]

Published literature was presented in support of the efficacy of iNO in management of pulmonary hypertension in the peri- and post-operative setting in patients undergoing cardiac surgery. The clinical evaluator considered that although there were flaws in the individual studies included in the submission, but that multiple studies from multiple institutions using both clinical and haemodynamic endpoints have provided essentially concordant results. The evaluator concluded that the balance of evidence falls narrowly in favour of registration.

Nine randomised controlled trials (RCTs) evaluating the effects of iNO in treating pulmonary hypertension in children undergoing cardiac surgery were included. Four studies (two placebo controlled and two with conventional therapy as controls) evaluated clinical endpoints as well as haemodynamic endpoints and the remaining 5 further studies had active controls and were considered directly supportive. Four of 9 efficacy studies in children were designated as "pivotal", because the control group received placebo or standard care in a randomised prospective design, but the studies by Day et al and Morris et al used an open label design.[13, 14] Additional supportive studies were provided in adult populations. Many of the studies listed as efficacy studies were small and used iNO for only short periods to gauge the short term haemodynamic response.

Miller et al (2000)[11] reported a prospective, randomised, double blind study of the efficacy of iNO 10 ppm versus placebo in 124 infants (median age 3 months [interquartile range (IQR) 1 to 5 months]) with large ventricular, atrioventricular septal defects, truncus arteriosus or total anomalous pulmonary venous drainage with high pulmonary flow, pressure or both, undergoing corrective surgery for congenital heart disease administered iNO or nitrogen (placebo) for up to 7 days. Randomisation was stratified by diagnosed

[37] Clarification: Regarding this dossier, the use of INOmax in this orphan indication has been primarily supported by published literature. As such, a literature based submission does not usually have the same coordination of study design and endpoints as a sponsor executed development plan. The following comments should be interpreted with this information in mind.

Down's syndrome and occurred prior to surgery. A sample size of 136 patients was required to provide 80% power to detect a 50% reduction in the number of PHTC events with a two sided significance level of 0.05. Clinically important pulmonary hypertension (PAP/SAP > 0.5 with haemodynamic instability or > 0.75 at any time) was managed by a standardised protocol of sedation and muscle relaxation, intermittent positive pressure ventilation (IPPV), vasopressors, and vasodilators, and additional open label iNO if required. Patients were well matched for demographic characteristics type of cardiac lesion and baseline haemodynamics. There were no withdrawals during the study. The study was discontinued prematurely because of logistical reasons (both the principal research fellow and the principal investigator were due to leave the country in which the study was conducted) and a blinded evaluation of the data by the data safety monitoring committee that determined there was a statistically significant difference of the primary endpoint with the lower number of subjects.

The primary endpoint was the number of PHTCs in the treatment period, which lasted for up to 7 days. Infants who received iNO had significantly fewer PHTCs (median 4 events [IQR 0 to 12]) than infants receiving nitrogen placebo (median 7 events PHTCs [IQR 1 to 19]; unadjusted relative risk 0·66 [95%CI 0·59 to 0·74] p < 0·001; adjusted for dispersion 0·65 [0·43 to 0·99], p = 0·045).

The iNO patients reached extubation criteria significantly sooner (80 h [IQR 38 to 121] versus 122 h [63 to 164], p = 0.019). Most (82%) of the infants in the study weaned off the study gas in < 7 days, and the remainder (6 in the iNO group and 15 in the placebo group) weaned at 7 days per protocol. The iNO patients spent less time overall on study gas (87 h [IQR43-125] versus 117 h [67 to 168], p = 0.023). The PVRI measured every 12 hours during study gas administration was also significantly lower in the iNO group (p < 0·001).

The studies by Russell et al (1998)[12] and Morris et al (2000)[14] were listed as pivotal but they used haemodynamic endpoints rather than clinical endpoints, and the iNO treatment duration was brief (≤ 30 min). Russell et al (n = 40 studies in 39 children, 3 sets of measurements excluded) conducted a double blind placebo controlled study of the measurements of mPAP in children undergoing cardiac surgery for congenital heart defects with preoperative pulmonary hypertension given inhaled iNO 80 ppm or placebo at fraction of inspired oxygen FiO_2 of 0.9. Measurements were taken at baseline, after 1, 10 and 20 minutes of study gas and 1 minute after the discontinuation of study gas. A significant haemodynamic effect for iNO over 20 min compared to placebo, was seen in the subset of the study population consisting of 13 subjects with elevated PAP, (5 received iNO). mPAP was reduced by 19% (range 80 to 35% at 20 minutes) with iNO (p = 0.008) and increased by 9% with placebo. Oxygenation was not changed during the study period.

Morris et al (2000)[14]conducted a small randomised, controlled, open label crossover study (n = 12) of children aged 0.1 to 17.7 years to compare the haemodynamic effects of iNO (5 ppm for 15 minutes then 40 ppm for 15 minutes) with hyperventilation induced alkalosis (HV) to a pH of 7.5 in children recovering from biventricular repair and CPB. After the randomised treatment each group received a combination of iNO and HV. Subjects received treatments for 30 minutes in random order with a 30 minutes washout between treatments. All children received sedation and muscle relaxation, inotropes and other medications as indicated. Eight of the 12 patients received sodium nitroprusside at baseline. No significant changes were observed in PVRI and mPAP with both treatments, relative to baseline, but some improvement could have been due to recovery from CPB with time. There was a decrease in PAP/SAP with iNO compared with baseline but this was not different from HV.

The open label study by Day et al[13] of patients after biventricular repair or heart transplantation with a PAP > 50% of SAP after successful removal from CPB (n = 40 samples from 38 patients) compared the efficacy of iNO 20 ppm with conventional therapy (determined by the treating clinician, using a variety of regimens). The median age in

control subjects was 6 months (range 1 day to 3 years) and in the iNO subjects 7 months (range 1 day to 20 years). The baseline PAP was 47 ± 2 mm of Mercury (mmHg) and in the iNO group 52 ± 3 mmHg. The difference did not reach statistical significance but equalled the size of the treatment effect in the iNO group. The primary endpoint, PHTC, occurred in 4 control patients and in 3 iNO patients, a difference that was not statistically significant. There were no statistical differences between treatments for the major secondary endpoints of changes in haemodynamic parameters, but the trends were favourable. Systolic pulmonary arterial pressure (SPAP) in the control group started relatively low and increased after an hour, whereas SPAP in the iNO group started relatively high and decreased by approximately 10%. The changes in ratio of systolic pulmonary and systemic arterial pressures were greater with iNO than with conventional therapy, and this comparison approached statistical significance (p = 0.066).

The remaining 5 efficacy studies in children compared iNO to active alternatives. These studies were not specifically powered to demonstrate differences between iNO compared to the active alternative.

- Cai et al, 2008 (n = 46)[15], was an open label, parallel group study in which iNO at a starting dose of 10 ppm and continued for at least 24 hours was compared to intravenous milrinone 0.5 $mcg.kg^{-1}.min^{-1}$ and a combination of the two treatments in children with pulmonary hypertension after a Fontan procedure. In a 3 group, open label design, each agent was compared to the other agent and to the combination of both agents. Inhaled NO was significantly superior to milrinone for the study's main measure of PVR, and transpulmonary gradient (TPG). An improvement in oxygenation was shown in all groups, but greatest in the groups using iNO.
- Goldman et al, 1995 (n = 13)[16], was a small, brief, open label crossover study, which showed that iNO 20 ppm was significantly superior to intravenous prostacyclin 20 ng per kg per minute in the short term (10 minute) treatment of severe pulmonary hypertension in paediatric subjects after cardiac surgery. mPAP was reduced by 33% during iNO treatment (95%CI, -24% to -51%), compared to a reduction of 15% during prostacyclin treatment (95%Cl, -4% to -38%; p < 0.01).
- Kirbas et al, 2012 (n = 16)[4], was a small, open label study in paediatric cardiac surgery patients found no difference between the efficacy of iNO 20 ppm (n = 8) and aerosolised iloprost (n = 8) in the treatment of pulmonary hypertension. Favourable reductions in PAP and in PAP/SAP ratio were observed in both groups.
- Loukanov et al, 2011 (n = 15)[5], was a small, open label pilot study comparing iNO 10 ppm and aerosolised iloprost 0.5 µg/kg every 2 h in infants aged 77 to 257 days, 73% of whom had trisomy 21. Similar efficacy between iNO and iloprost to prevent PHTCs was suggested but the study was not adequately powered to demonstrate equivalence. Trends in mPAP were weakly in favour of iNO.
- Stocker et al, 2003 (evaluable n = 15)[17], compared iNO 20 ppm and intravenous sildenafil 0.35 mg/kg in a small, open label crossover study in infant cardiac surgery patients, showing that the two drugs were similar in their ability to lower mPAP and PVRI. In the iNO-first group, mPAP had fallen after 20 min of therapy, reducing by 1.4 ± 0.4 mmHg (by 7.8 ± 2.1%; p = 0.008). The subsequent addition of sildenafil did not further lower PA pressure. In the sildenafil-first group, mPAP had also fallen by 20 minutes; the reduction seen with sildenafil was numerically greater than that seen in the iNO-first group when expressed as a percentage of baseline, but the fall was not statistically significant (reduction of 10 ± 4.1%; p = 0.055). The subsequent addition of iNO produced a further fall in mPAP. The authors noted that iNO had greater pulmonary selectivity.

The remaining 13 efficacy studies were performed in adults. The studies included a sponsor led study of 150 adults (study INOT41) undergoing LVAD placement given iNO at

a dose of 40 ppm or placebo for up to 48 hours. These studies showed similar haemodynamic changes to those observed in children. Many were small and had issues with sample size and/or methodology but were overall supportive of the efficacy of iNO in adult with cardiac abnormalities and pulmonary hypertension.

Safety

In the studies submitted in support this application 288 children were exposed to iNO and 134 were exposed to the proposed dose range of 10 to 20 ppm. An additional 155 adults were also exposed with an additional 123 exposed to the proposed dose range. In the post-market setting an estimated 603,449 patients has been exposed since 1999, with the majority of those in the USA. One sponsor led PD study and one of the supportive adult studies were sponsor led had comprehensive safety monitoring, however the majority were investigator led, and many published more than a decade ago. There was no systematic reporting of adverse events in the published literature. Deaths were reported by Miller et al (1 patient: PHTC associated with a pneumothorax),[11] Goldman et al (3 deaths: 1 delayed PHTC 2 days after cessation of iNO, 1 multiple organ failure, 1 from underlying lung disease)[16] and Kirbas et al (1 patient from chronic respiratory failure).[4] In the sponsor led PD study (INOT22) 3 deaths were reported; 1 after accidental extubation with resultant severe hypotension, hypoxia and bradycardia, and subsequent refractory pulmonary hypertension and right ventricular failure, 1 due to accidental perforation of the aortic valve during catheterisation, and 1 from refractory pulmonary hypertension that commenced 30 minutes after withdrawal of the study drug. He had received iNO at 80 ppm for 79 minutes. Two of the 6 adult deaths from the adult literature occurred within 30 days of cessation of the study drug. Another 2 adult patients with cardiomyopathy undergoing LVAD (study INOT41) died of right ventricular failure and a further 2 died from multiple organ failure. SAEs or permanent discontinuations were reported in 3 of the 10 patients in study INOT22 in patients with elevated PCWP at baseline compared with 6.5% of the full study cohort.

The following is a summary from safety issues for iNO the current and previous submissions:

- Nitrogen dioxide production: This is produced at low levels when iNO and O_2 are combined, and can cause airway irritation, chemical pneumonitis, and asthma in susceptible individuals. The highest reported level in a child in the submitted literature was 2.1 ppm. The sponsor has recommended dose reduction if NO_2 is detected at > 0.5 ppm.
- Methaemoglobinaemia is a recognised risk with iNO for which monitoring was mentioned in most of the submitted studies. The highest reported metHb % was 8% (Goldman et al 1995)[16] with a 20 ppm dose, and decreased to 4% when the iNO dose was reduced to 15 ppm. The sponsor has recommended dose adjustment if metHb is > 2.5%.
- Rebound pulmonary hypertension is a well described phenomenon with abrupt withdrawal of iNO. It can result in bradycardia and circulatory collapse.
- Other cardiovascular effects can result from increased blood flow through the lungs to the left atrium, increasing left atrial filling and left ventricular pre-load. In a setting of left ventricular dysfunction pulmonary oedema can result and was seen in study INOT22. Changes produced by iNO in the relative pressures in the right and left sides of the heart could also reverse or worsen shunting in patients with cardiac malformations, with negative haemodynamic consequences.
- Drug-drug interactions: The risk of methaemoglobinaemia can be increased by co-administration of iNO and other drugs, particularly NO donors such as

nitroprusside, and some local anaesthetic agents. Synergistic vasodilatory effects with other agents may result in amplification of the pharmacodynamic effects of iNO.

- Possible mechanism for reduced platelet function because of the action of iNO on guanylate cyclase this did not emerge as a safety signal from the studies. Increased bleeding risk did not emerge as a safety signal in the submission, but may not have been specifically sought as an outcome.
- The impact of iNO on immune function is unknown.

A review of the post-market did not reveal any new safety signals. A possible signal for retinopathy of prematurity associated with iNO was investigated and not supported by the sponsor's analysis.

Risk management plan

The RMP evaluator has accepted EU-RMP version 2.0, dated 31 March 2014 (data lock point 31 March 2014) with Australian Specific Annex version 2 dated 6 March 2015. There are no outstanding matters for consideration.

Risk-benefit analysis

Delegate's considerations

Efficacy

The sponsor has provided a hybrid submission of clinical studies and literature in support of the extension of indication. Of the two sponsor led studies one was of relevance for the pharmacodynamics of nitric oxide and the other was not of direct relevance to the requested indication. The study by Miller et al was considered a pivotal study and included both clinical (PHTCs) and haemodynamic endpoints.[11] The outcomes of the study should be interpreted in the context of the reasons for its premature discontinuation. The majority of the remainder of the efficacy studies are small, and have differences in dose, duration of therapy and the type of comparator (active or placebo). There are also methodological concerns with a number of the studies. However, the effect of iNO on haemodynamic parameters was well demonstrated, and some studies demonstrated clinical endpoints such as a reduction in the number of PHTCs. Additional support for the efficacy of iNO was derived from studies of iNO in adult cardiac surgery patients in the pre- and immediate post-operative setting. Considered as a whole, the efficacy evidence is considered just sufficient to support the extension of indication for use in children undergoing cardiac surgery to manage pulmonary hypertension.

Safety and RMP

The safety information in this submission is viewed in the context of international experience with the proposed indication, off-label use for the proposed indication, the relevance of the safety data from the initial registration of INOmax for the proposed population. Although the safety data are limited, reported adverse effects were consistent with the known risk profile for iNO for children for the approved population. None of the studies was of sufficient size to detect uncommon or rare events. The majority of the reported safety experience is with infants, young children and adults, but there is very limited experience in the adolescents. Given the likely mechanisms of toxicity it is reasonable to extrapolate the safety data to this population. The impact of repeated use in children has not been investigated and the long term consequences for pulmonary and neurodevelopment outcomes were not addressed in this submission. The sponsor has

proposed the use by cardiothoracic anaesthetists and intensivists. This restriction is appropriate given the likely clinical scenarios for its use and its risks.

Dose

The starting dose is 10 ppm, and titrating up to 20 ppm if necessary and 20 ppm is the maximum dose recommended. Although higher doses were used in some studies the proposed doses were equated with acceptable efficacy and a lower risk of methaemoglobinaemia. The sponsor is requested to comment on the safety margins and other safeguards in its delivery system to ensure the selected dose is not exceeded.

Indication

No change to the wording of the indication is recommended at this time; however the ACPM is requested to provide a comment.

Data deficiencies

This was predominantly a literature based submission. Data submitted were of variable quality and although requested, additional information was not available for all studies to address the questions posed by the clinical evaluator. Limited data were submitted for the use in children aged 12 to 17 years. The individual studies were not of sufficient size to detect uncommon or rare adverse effects. No safety data with repeated or prolonged use were provided and any potential impact of such exposure on the growth and development of children is unknown.

Conditions of registration

The following are proposed as conditions of registration:

Implement EU-RMP version 2.0, dated 31 March 2014 (data lock point 31 March 2014) with Australian Specific Annex version 2, dated 6 March 2015 and any future updates as a condition of registration.

Questions

1. Please indicate whether INOmax cylinders can only be used with the delivery system provided by the sponsor or if other nitric oxide delivery systems can be used. If not, is the technical support mentioned in the PI available to all prescribers of INOmax?
2. Does the delivery system allow manual ventilation while maintaining the same dose of iNO? Can iNO be delivered via BVM ventilation using the delivery system?
3. Other international regulators issued warnings in early 2015 about device failures with delivery systems for INOmax. Although the INOmax delivery system is not the subject of this submission reliable delivery is an important safety and efficacy consideration. Please provide an update on the sponsor's activities to ensure the identified failure mode of these devices is not applicable to the delivery system devices supplied to the Australian market.

Summary of Issues

- Whether the evidence from this literature based submission is sufficient to support the requested extension of indication.
- Whether all the efficacy claims included in the indication can be supported by the evidence.

Proposed action

The Delegate had no reason to say, at this time, that the application for INOmax should not be approved for registration.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Does the committee consider that the sponsor has satisfactorily demonstrated the efficacy and safety of inhaled nitric oxide to support the proposed indication? If so, is there sufficient evidence to include the efficacy claims in the wording of the indication?
2. Are the recommendations for monitoring for methaemoglobin and nitrogen dioxide consistent with current clinical practice? If not, what amendments should be made to these recommendations?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

TGA Delegate's overview – advice sought from ACPM

1. *Does the committee consider the sponsor has satisfactorily demonstrated the efficacy and safety of iNO to support proposed indication? If so, is there sufficient evidence to support the efficacy claims in the wording of the indication?*

The sponsor believes that sufficient evidence has been provided to demonstrate efficacy and safety in a rare paediatric indication that was granted Orphan Drug Designation by the TGA in September 2013. The proposed wording is identical to the approved orphan drug indication. Furthermore, in pre-submission discussions with the sponsor, the TGA agreed that a literature based submission was a suitable registration strategy for this orphan drug indication in a paediatric population. This agreement indicates a recognition by the TGA of the established safety profile of inhaled NO over several decades of clinical use and the fact that a sponsor conducted complete clinical trial program of randomised, controlled studies would never be conducted, either on ethical grounds or patient availability, based on the supportive clinical data which already existed in the published literature. In this current application; 288 children were exposed to inhaled NO and 134 to the proposed dose range of 10 to 20 ppm. These are significant numbers in an orphan drug indication and the published results are in line with current clinical practice.

The sponsor also brings to the attention of the ACPM that a similar registration package supporting the registration of INOmax for the same indication was approved by the EMA in 2011. Annual Periodic Safety Update Reports (PSUR) produced by the sponsor confirms the on-going safety profile of INOmax in all approved indications worldwide. The clinical overview of the current application indicated that an estimated over 603,000 subjects (of all ages) over all time periods were exposed to iNO; some of these patients were administered the medicinal product off-label in relation to cardiac surgery (PSUR reports for the total period of 24 December 2005 to 23 December 2013).

The sponsor believes that INOmax is used off-label in Australia for the proposed paediatric cardiac surgery indication and wishes to bring any such use under the control of a TGA approved indication so that appropriate dosage regimen and safety monitoring can be implemented by sponsor.

2. *Are the recommendations for monitoring for methaemoglobin and Nitrogen dioxide consistent with current clinical practice – if not what amendments should be made to these recommendations?*

The sponsor believes that the recommendations for monitoring for MetHb and NO_2 are consistent with current clinical practice. An extensive monitoring guideline already exists in the current TGA approved PI for INOmax for the existing indication (pulmonary hypertension in neonates). The monitoring guidelines are strongly enforced by the

sponsor and there have been no significant safety issues since first Australian registration of INOmax in 2007. As mentioned previously, approval of the paediatric cardiac surgery indication would allow the sponsor to bring any current off-label use in this indication under the monitoring controls specified in the INOmax PI. Specific product training, as outlined in the ASA to the EU RMP, would be implemented for cardiac anaesthetists/ intensivists. The ASA also outlines the sponsor's comprehensive safety monitoring system. The wording of the proposed PI provides further control over safe use by stating:

> *"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 administered under close monitoring of haemodynamics and oxygenation."*

Conditions of registration

1. *Implement EU-RMP version 2.0, dated 31 March 2014 (data lock point 31 March 2014) with Australian Specific Annex version 2, dated 6 March and any future updates as a condition of registration*

The sponsor provides an assurance that the EU-RMP V2.0 (dated 31 March 2014) with Australian Specific Annex V2 (6 March 2015) and any future updates, will be implemented post-approval.

Specific questions

1. *Please indicate whether INOmax cylinders can only be used with the delivery system provided by the sponsor or if other nitric oxide delivery systems can be used. If not, is the technical support mentioned in the PI available to all prescribers of INOmax?*

Technically the INOmax cylinder could be used with another nitric oxide delivery device if that device could interface with a CGA 626 valve outlet. However, the CGA 626 valve outlet is not a standard Australian valve outlet per AS 2473 Valves for compressed gas cylinders Part 3: Outlet connections for medical gases; therefore, the likelihood of encountering a nitric oxide delivery device that would interface with the INOmax CGA 626 fitting in Australia is highly unlikely. Regardless, the sponsor agrees that the delivery device is extremely important to the safe use of INOmax; therefore, Ikaria provides the delivery device, all the associated disposable parts, calibration gas, ongoing training, etc. as part of a complete package with the purchase of the drug, INOmax. With this unique product offering, all INOmax customers are provided a fleet of INOmax DSIR systems to accommodate their INOmax usage and maintain a backup device. This drug, device, service, support model is in place to assure that INOmax cylinders are used with INOmax DSIR delivery systems.

If an INOmax cylinder is used with another NO delivery system, our technical support would not be able to provide assistance for another company's NO delivery system. However, because we provide the INOmax DSIR system as part of a complete product offering, there is no reason for our customers to purchase, maintain or use other nitric oxide delivery systems.

2. *Does the delivery system allow manual ventilation while maintaining the same dose of iNO? Can iNO be delivered via BVM ventilation using the delivery system?*

The INOmax DSIR does allow for manual ventilation at the same dose. The INOmax DSIR delivery system includes an INOblender, for delivery of INOmax, specifically designed for short term attended use with a BVM. The INOblender delivers NO doses from 5 to 80 ppm at 5 to 14 litres per minute and can be ready for use in less than 1 minute. The blender is completely pneumatic and does not require power to operate. While it is possible to use

the main delivery system by attaching the BVM to the systems injector module, almost all clinicians use the INOblender for this purpose.

3. *Other international regulators issued warnings in early 2015 about device failures with delivery systems for INOmax. Although the INOmax delivery system is not the subject of this submission, reliable delivery is an important safety and efficacy consideration. Please provide an update on the sponsor's activities to ensure the identified failure mode of these devices is not applicable to the delivery system devices supplied to the Australian market.*

The field action reported to the US FDA involved a software version incompatibility with a new display assembly sourced by Ikaria Inc USA when the originally specified display was made obsolete and no longer available from our vendor. This issue resulted from the difference in current required to operate the display, which was significantly lower than that required with the original display. The issue was detected soon after release of the new display as a result of tracking and trending mechanisms put in place by Ikaria. None of the new displays were sent to Australia, however a courtesy notification was provided to TGA at the time the field action was reported to the US FDA.

Since the anomaly can only occur when a specific display is installed in an INOmax DSIR with a specific software version, this configuration has not been, and will not be, possible with devices made available to the Australian market.

4. *The sponsor is requested to comment on safety margins and other safeguards in its delivery system to ensure the selected dose is not exceeded.*

The INOmax DSIR uses a "dual channel" design to ensure the safe delivery of INOmax. The first channel has the delivery CPU, the flow controller and the injector module to ensure the accurate delivery of NO. The second channel is the monitoring system, which includes a separate monitor CPU, the gas cells (NO, NO_2 and O_2 cells) and the user interface including the display and alarms. The dual-channel approach to delivery and monitoring permits INOmax delivery independent of monitoring but also allows the monitoring system to shutdown INOmax delivery if it detects a fault in the delivery system such that the NO concentration could become greater than 100 ppm for 12 consecutive seconds. The delivery system can also shut down delivery if it detects certain serious problems with the monitoring system. The primary NO control is based on a volumetric calculation of the breathing circuit flow and the NO flow. If the calculation shows that delivery is not within the acceptable range, the device will alarm and/or shut down.

The resulting NO concentration is also monitored with the independent NO gas monitoring sensor. The NO concentration alarms are user settable and will alarm if the measured NO concentration in the patient circuit goes out of range.

The INOmax DSIR Hazard and Risk Analyses are conducted in accordance with ISO 14971: 2012. As such, risks associated with the use of the device are brought to acceptable levels as established in the RMP. The user is provided with relevant information regarding mechanisms employed to reduce risk in product labelling. High Priority Alarms associated with over-delivery, and under-delivery, conditions are described in some detail in the device Operator's Manual. Included in the alarm handling strategies are mechanisms by which drug delivery may be interrupted if the delivered dose exceeds the set dose. Labelling and training instruct the user in addressing and resolving over- and under-delivery conditions. The labelling includes instructions for use of backup drug delivery mechanisms.

5. *Clinical Evaluation Report 2nd Round Evaluation.* After assessing the sponsor's response to the original question *"What effect does iNO have on the immune system and are these effects likely to be clinically relevant?',* the Clinical Evaluator makes the following comment*: In conclusion, the sponsor's response on this issue was acceptable,*

and this theoretical safety concern should not be a barrier to registration, provided the Pre-clinical Evaluator agrees with the sponsor's assessment of the animal data. It would nonetheless be appropriate to continue to monitor this issue in post-marketing surveillance programs, and to mention the issue in the RMP. Such a mention would not have to describe the risk in strong terms, and the sponsor would be justified in stating that there is no positive clinical evidence of risk. They would not be justified in stating that there is sufficient clinical data to dismiss this theoretical risk.

The sponsor provides the following response:

A theoretical risk describes an event could happen in theory but has never occurred in reality. "Theoretical risks can never be disproved. It is not possible to prove that something can never happen (HIV testing and risks of sexual transmission February 2013 Appendix 2, page 59)". In this context, "mentioning" a theoretical risk of inhaled nitric oxide therapy on the immune systems/functions and continuing to monitor this issue in post-market surveillance program would be a reasonable advice; and "the sponsor would not be justified that there is sufficient clinical data to dismiss this theoretical risk". While the sponsor has no intention to dismiss a theoretical risk, we do not believe that a theoretical risk for inhaled nitric oxide therapy on the human immune system/function exists, after careful review the available scientific data, including the clinical data, and after careful consideration of the evaluator's comments, concerns and the conclusion.

The belief that a theoretical risk for inhaled nitric oxide on the immunity possibly stems from the interchangeable use of the following two sets of concepts, as reflected in the evaluator's concern and conclusion. Inhaled nitric oxide versus endogenous nitric oxide, and immune regulation versus immune modulation have been discussed without distinction in many scientific especially clinical reports. In several well cited reports, the authors, after comprehensive review of endogenous nitric oxide production, distribution and its biological effects in humans, have attempted to leap to the assumption that the internally produced nitric oxide redox potential and immune modulatory effect in specific in vivo micro/macro milieu would apply to inhaled nitric oxide.

Endogenous nitric oxide mostly serves as intermediary signalling molecules to modulate immunity, depending on its cellular origin and location of distribution, when environmental factors activate or suppress immune system signalling cascades. Nitric oxide per se does not initiate the activation or suppression of the innate/acquired immunity. Nitric oxide is synthesized in most nucleated cells, particularly in macrophages. As part of the innate immune defence, nitric oxide suppresses viral replication and is bactericidal. According to the evaluator's concern, "expression of inducible NO synthetase has been linked with acute solid organ rejection". Such link is not based on any detrimental effect of endogenous nitric oxide on suppression of host immune tolerance to the graft organ. Rather, reperfusion of the graft organ could activate the inducible nitric oxide synthase and increase the endogenous nitric oxide level especially at the endothelium of the host-graft vascular anastomoses thus affect the graft organ blood supply and viability.

By entering the systemic circulation, inhaled nitric oxide has been found to reduce parasitic accumulation and reduce inflammation in mice and in children with cerebral malaria. This demonstrates the protective, immune modulatory effect of inhaled nitric oxide on the immune systems/functions. Inhaled nitric oxide, as characterized under the response to question 1, has a transient and focused effect on pulmonary vasculature. Immune cells within the pulmonary circulation and in the systemic circulation have very little exposure to inhaled nitric oxide because it would be metabolized in the vascular endothelial cells. Resident immune cells within the parenchyma and the interstitium of the lungs may be exposed to inhaled nitric oxide. Any modulatory effect of inhaled nitric oxide on extravasate immune cells would depend on the state of the local immune system at the host lungs, and the redox environment at the time of NO inhalation. Nitric oxide,

regardless of its origins, achieves its biological effects through interactions with numerous signalling pathways and transcription factors. Although the signalling/transcription networks at cellular and molecular levels have been extensively studied, the exact effects of nitric oxide at the systems and organic levels (on immunity and the immune system in particular) are the functions of the environment, the dose/duration of the nitric oxide exposure and the disease state.

To date, we have not identified any scientific or clinical information that would imply any theoretical risk of detrimental/harmful effect of inhaled nitric oxide on human immune systems and functions. On the contrary, inhaled NO has been demonstrated to, in addition to its established therapeutic effects, reduce malaria parasitic accumulation and not to contribute to disease pathogeneses.[38] Therefore, any risk of inhaled nitric oxide exerting deleterious effect on human immune systems and functions, even in theory, is not founded. Mentioning "a theoretical [safety] risk" for inhaled nitric oxide therapy on immune systems and functions in the RMP is therefore not warranted at the current time.

Data deficiencies

The TGA Delegate makes the comment that "*This was predominantly a literature based submission. Data submitted were of variable quality and although requested, additional information was not available for all studies to address the questions posed by the clinical evaluator. Limited data were submitted for the use in children aged 12 to 17 years. The individual studies were not of sufficient size to detect uncommon or rare adverse effects. No safety data with repeated or prolonged use were provided and any potential effect of such exposure on the growth and development of children is unknown."*

The sponsor believes that the TGA approval for a literature based submission strategy was based on the fact that the proposed application was for an orphan drug indication, in a paediatric indication, for a product that has been registered in Australia since 2007 for a neonatal indication. The company did provide supportive safety data from two large RCTs conducted in another paediatric indication and the adult cardiac surgery indication respectively. Data from the published literature will always represent a lower level of medical evidence than the randomized, controlled clinical study programs conducted by sponsors for non-orphan drug indications in large patient populations. The (sponsor's) clinical expert stated that:

> "*The clinical documentation consists of two company sponsored clinical trials conducted by INO Therapeutics LLC, USA, and a number of published RCT. Since the majority or RCT submitted have been conducted as independent clinical trials in academic settings, the studies are heterogeneous with regard to the studied populations, endpoints, control treatments, and when in the peri-operative course treatment has been implemented. Also the duration of iNO administration varies considerably from short term exposures to treatment lasting for several days.*
>
> *Pulmonary hypertension is a severe condition and in many studies the control group has received an active treatment. This active control treatment has frequently been another off-label drug for treatment of pulmonary hypertension. A formal regulatory assessment of iNO in treatment of pulmonary hypertension is therefore difficult to conduct. On the other hand, the range of corroborative studies provides a good basis for external validity."*

The TGA Delegate has expressed a similar opinion in the overview to ACPM as follows:

[38] , J. Mannick. Immuno-regulatory and antimicrobial effects of nitrogen oxides. *Proc Am Thorac Soc*, 2006; 3: 161-165

- Considered as a whole, the efficacy evidence is considered just sufficient to support the extension of indication for use in children undergoing cardiac surgery to manage pulmonary hypertension.
- Although the safety data are limited, reported adverse effects were consistent with the known risk profile for iNO for children for the approved population. Given the likely mechanisms of toxicity, it is reasonable to extrapolate the safety data to this (proposed adolescent) population.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy and safety, agreed with the Delegate and considered INOmax Gas in Cylinders containing NO 800 ppm of nitric oxide to have an overall positive benefit–risk profile for the proposed indication and dosage;

> *INOmax, in conjunction with ventilatory support and other appropriate agents, is indicated as part of the treatment of peri- and post-operative pulmonary hypertension in newborn infants, infants and toddlers, children and adolescents, ages 0 to 17 years in conjunction with heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation.*
>
> *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. The lowest effective dose should be administered and the dose should be weaned down to 5 ppm provided that the pulmonary artery pressure and systemic arterial oxygenation remain adequate at this lower dose.*

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

Specific Advice

The ACPM advised the following in response to the delegate's specific questions on this submission:

1. *Does the committee consider that the sponsor has satisfactorily demonstrated the efficacy and safety of inhaled nitric oxide to support the proposed indication? If so, is there sufficient evidence to include the efficacy claims in the wording of the indication?*

The ACPM considered that the efficacy and safety data were adequate to support the requested indication and dosage.

2. *Are the recommendations for monitoring for methaemoglobin and nitrogen dioxide consistent with current clinical practice? If not, what amendments should be made to these recommendations?*

The ACPM was of the view that the recommendations for monitoring methaemoglobin and nitrogen dioxide were appropriate and consistent with current clinical practice, noting that inhaled nitric oxide had a history of two decades of clinical use.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of INOmax nitric oxide 800 ppm medicinal gas for inhalation cylinder indicated for:

INOmax, in conjunction with ventilatory support and other appropriate agents, is indicated

- *as part of the treatment of peri- and post-operative pulmonary hypertension in newborn infants, infants and toddlers, children and adolescents, ages 0-17 years in conjunction with heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation.*

Specific conditions of registration applying to these goods

The INOmax EU-Risk Management Plan (EU-RMP), version 2.0, dated 31 March 2014 (data lock point 31 March 2014) with Australian Specific Annex version 2, dated 6 March 2015, included with submission PM-2014-01399-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for INOmax approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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