Australian Public Assessment Report for Nitric oxide

Proprietary Product Name: INOmax

Sponsor: Ikaria Australia Pty. Ltd.

November 2019

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
ACCF	American College of Cardiology Foundation
ACM	Advisory Committee on Medicines
ACPM	Advisory Committee on Prescription Medicines
AE	Adverse event
AHA	American Heart Association
ARTG	Australian Register of Therapeutic Goods
CABG	Coronary artery bypass grafting
cGMP	Cyclic guanosine monophosphate
CHMP	Committee for Medicinal Products for Human Use
CI	Cardiac index or confidence interval
CO	Cardiac output
CPB	Cardio-pulmonary bypass
DB	Double blind
ECG	Electrocardiogram
EU	European Union
GCP	Good Clinical Practice
GTN	Glyceryl trinitrate
HR	Heart rate
IBD	International birth date
ICU	Intensive care unit
ICH	International Council for Harmonisation
iNO	Inhaled nitric oxide
iPGI2	Inhaled prostacyclin
IV	Intravenous
LVAD	Left ventricular assist device
metHB	Methaemoglobin

Abbreviation	Meaning
mmHg	Millimetres of mercury
MPAP, mPAP	Mean pulmonary artery pressure
NO	Nitric oxide
NO2	Nitrogen dioxide
NYHA	New York Heart Association
PAH	Pulmonary artery hypertension
PAP	Pulmonary artery pressure
PCWP	Pulmonary capillary wedge pressure
PGE1	Prostaglandin E1
PH	Pulmonary hypertension
PI	Product Information
PPHN	Persistent pulmonary hypertension of the newborn
ppm	Parts per million
PSUR	Periodic safety update report
PVR	Pulmonary vascular resistance
RMP	Risk management plan
RV	Right ventricular
RVEF	Right ventricular ejection fraction
RVF	Right ventricular failure
SAE	Serious adverse event
SAP	Systemic arterial pressure
SD	Standard Deviation
SPC	Summary of Product Characteristics
TGA	Therapeutic Goods Administration
TPG	Transpulmonary pressure gradient
VAD	Ventricular assist device

I. Introduction to product submission

Submission details

Type of submission:	Major variation, extension of indications
Decision:	Approved
Date of decision:	30 April 2019
Date of entry onto ARTG:	13 May 2019
ARTG number:	128136
▼ *Black Triangle Scheme*	No
Active ingredient:	Nitric oxide
Product name:	INOmax
Sponsor's name and address:	Ikaria Australia Pty Ltd Ground Floor 17 Cotham Road Kew VIC 3101
Dose form:	Medicinal gas
Strength:	800 ppm
Container:	Gas cylinder
Pack sizes:	MD 15 cylinder and 88 cylinder
Approved therapeutic use:	*INOmax, in conjunction with ventilatory support and other appropriate agents, is indicated*: *to selectively decrease pulmonary arterial pressure in patients with perioperative pulmonary hypertension in conjunction with heart surgery*
Route of administration:	Inhalation
Dosage:	Not more than 20 ppm (see Product Information (PI) for details)

Product background

This AusPAR describes the application by Ikaria Australia Pty Ltd (the sponsor) to extend the indications for INOmax nitric oxide 800 parts per million (ppm) medicinal gas to include the following indication:

> 'INOmax, in conjunction with ventilatory support and other appropriate active substances, is indicated:
>
> - as part of the treatment of patients with peri- and post-operative pulmonary hypertension in conjunction with heart surgery, to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation.'

Nitric oxide is a signalling molecule that participates in many cellular activities. In blood vessels it regulates vascular tone and blood flow by activating soluble guanylate cyclase in vascular smooth muscle.

Pulmonary hypertension arises from vasoconstriction or vascular remodelling in the pulmonary vasculature, in response to a variety of cardiopulmonary disease states including chronic hypoxia or left-to-right shunting. It may be present preoperatively in a number of cardiac surgical patients, and it may worsen peri-operatively in patients undergoing cardiac or lung surgery because of endothelial dysfunction, impairments in oxygenation, or release of vasoconstrictive mediators. The chief significance of pulmonary hypertension is that it increases afterload on the right ventricle, increasing the risk of right heart strain or right heart failure.

Cardiopulmonary bypass 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 nitric oxide appears to be a major contributor to this problem. Even without these cardiopulmonary bypass effects, many patients 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. Patients are also at risk of pulmonary hypertensive crises, 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.

A number of intravenous vasodilators have been used in the management of pulmonary hypertension in the setting of cardiac surgery. The main issue with these systemically administered agents is that they are not selective for the pulmonary vasculature, and so they lower peripheral vascular resistance, and tend to cause systemic hypotension. In patients with poor cardiac output, this may be poorly tolerated, leading to poor organ perfusion, reduced oxygenation and myocardial ischaemia.

Inhaled nitric oxide (iNO), prostaglandins, and milrinone have been explored as an alternative to intravenous vasodilators, and have generally shown pulmonary selectivity. For decades, inhaled nitric oxide has been the predominant agent used in this setting, although it has mostly been used off-label.

More recently, inhaled nitric oxide has been registered for use in children and adults. The other inhaled vasodilators are not registered for this indication. In children, the only approved inhaled vasodilator is inhaled nitric oxide.

Another nitric oxide product, Vasokinox was approved in March 2016 and entered onto the Australian Register of Therapeutic Goods (ARTG) in January 2017 for the following indication:

Vasokinox is indicated in conjunction with ventilator support and other appropriate active substances to selectively decrease pulmonary arterial pressure in patients with perioperative pulmonary hypertension in conjunction with heart surgery.

Regulatory status

The product received initial registration on the ARTG on 22 November 2007 for the persistent pulmonary hypertension of the newborn (PPHN) indication. The indications were extended in July 2015 to include the treatment of peri- and post-operative pulmonary hypertension in conjunction with heart surgery in newborn infants, infants and toddlers, children and adolescents, aged 0 to 17 years.

International regulatory status

At the time the TGA considered this application, a similar application had been approved in the European Union (EU) as described below.

Nitric oxide was registered in the EU in 2001, and currently has the following indications:

INOmax, in conjunction with ventilatory support and other appropriate active substances, is indicated:

- *for the treatment of newborn infants ≥ 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation;*

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

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. Registration time line

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 1: Timeline for Submission PM-2018-00306-1-3

Description	Date
Submission dossier accepted and first round evaluation commenced	30 April 2018
First round evaluation completed	2 October 2018
Sponsor provides responses on questions raised in first round evaluation	29 October 2018

Description	Date
Second round evaluation completed	18 December 2018
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	2 January 2019
Sponsor's pre-Advisory Committee response	11 January 2019
Advisory Committee meeting	1 February 2019
Registration decision (Outcome)	26 March 2019
Completion of administrative activities and registration on ARTG	29 March 2019
Number of working days from submission dossier acceptance to registration decision*	208

*Statutory timeframe for standard applications is 255 working days

III. Quality findings

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

IV. Nonclinical findings

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

V. Clinical findings

A summary of the clinical findings is presented in this section.

Introduction

Clinical rationale

Inhaled nitric oxide is already widely recommended for the treatment of perioperative pulmonary hypertension in adult cardiac surgical patients, and no other suitable agent is registered for this indication. For more than two decades, this drug has been widely used to vasodilate the pulmonary vasculature with the aim of preventing or reducing right heart strain. Several published studies, which are considered in this submission, have confirmed that inhaled nitric oxide reduces pulmonary vascular resistance in a relatively selective manner, and to some extent this is reflected in favourable clinical outcomes. It has already been approved for this use in paediatric patients, and the clinical rationale in adults is essentially the same as the paediatric perioperative setting (the drug also has a specific indication for perinatal pulmonary hypertension).

The sponsor now proposes formal registration of inhaled nitric oxide for the adult indication. It would primarily be administered in the operating theatre and in intensive

care units (ICU), by anaesthetists and intensive care specialists already familiar with its use, and it would meet a need that is currently being met, to a large extent, by off-label inhaled nitric oxide.

The proposed formulation of inhaled nitric oxide in adults is identical to that used in children, with a gaseous blend of inhaled nitric oxide 800 ppm diluted in pure medical grade nitrogen. The drug is administered via the inspiratory limb of the ventilator circuit, where it is further diluted with air and oxygen according to the oxygen needs of the patient, and the final delivered concentration is closely monitored. No changes are proposed to the formulation.

Guidance

The EU guidelines of relevance to this submission are:

- EMEA/CHMP/EWP/356954/2008: Guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension.

Contents of the clinical dossier

The submission contains 17 studies evaluable for efficacy. The submission is primarily a literature based submission, although one sponsor-initiated efficacy study was also included; this study was well-designed, but it proved to be underpowered and it was negative for its primary and secondary endpoints. Of the controlled studies found in the literature that were relevant to the current submission, most had been evaluated in the context of the previous INOmax submission for paediatric cardiac surgery. Four new controlled studies were identified in the more recent literature search. The submission included no new pharmacokinetic or pharmacodynamic data, and no studies with a primary focus on safety.

Paediatric data

The submission contained no paediatric data. INOmax has already been approved for use in the paediatric setting, and most of the evidence considered in the current submission was previously evaluated in the context of the paediatric submission. The current submission raises no new issues about the paediatric use of INOmax.

Good clinical practice

The sponsor-initiated study was performed in accordance with principles of Good Clinical Practice (GCP). Some published studies made mention of approval by institutional ethics committees, implying compliance with GCP, but formal statements of compliance with GCP were generally lacking.

Pharmacokinetics

No new pharmacokinetic studies have been performed, and the sponsor's updated literature search identified no relevant new publications.

Pharmacodynamics

No new pharmacodynamic information is available, and the new submission does not raise any concerns related to the pharmacodynamics of inhaled nitric oxide.

Dosage selection for the pivotal studies

No satisfactory dose-ranging study has been performed for inhaled nitric oxide, but experience with different doses has led most investigators to use doses of 20 to 40 ppm in published studies, corresponding with the dose proposed for registration.

The general principles of dosage selection for inhaled nitric oxide were discussed in the context of the previous submission for paediatric use. No study has demonstrated a clear dose-response relationship for inhaled nitric oxide, and it appears that similar efficacy is obtained over a range of doses from 10 to 80 ppm.

The accumulation of the toxic by-products nitrogen dioxide and methaemoglobin (metHB) increases with increasing dose, as shown in Figure 1.[1]

Figure 1: Levels of nitrate and methaemoglobin in response to inhaled nitric oxide
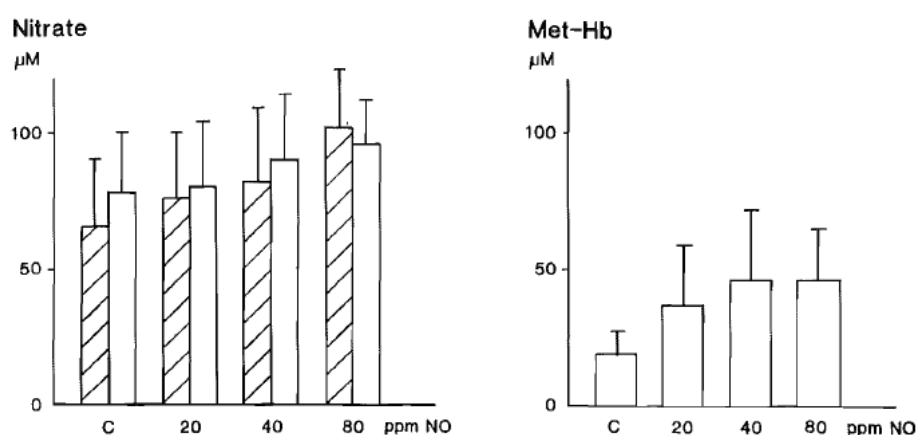
Plasma levels of nitrate *(left panel)* and methemoglobin *(Met-Hb) (right panel)* in basal state *(C)* and during inhalation of nitric oxide (NO, 20 to 80 ppm) in six patients. *Filled bars* represent pulmonary arterial blood; *open bars* represent systemic arterial blood. Data presented are mean ± standard error of the mean.

In the paediatric setting, a similar relationship between administered dose and metHb has been noted. Methaemoglobin disposition has been investigated as a function of time and nitric oxide exposure concentration in neonates with respiratory failure. The metHb concentration–time profiles during the first 12 hours of exposure to 0, 5, 20, and 80 ppm INOmax is shown in Figure 2.

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[1] Kieler-Jensen, N. et al., 1994. 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: Time course of methaemoglobin concentration upon exposure to varying levels of inhaled nitric oxide
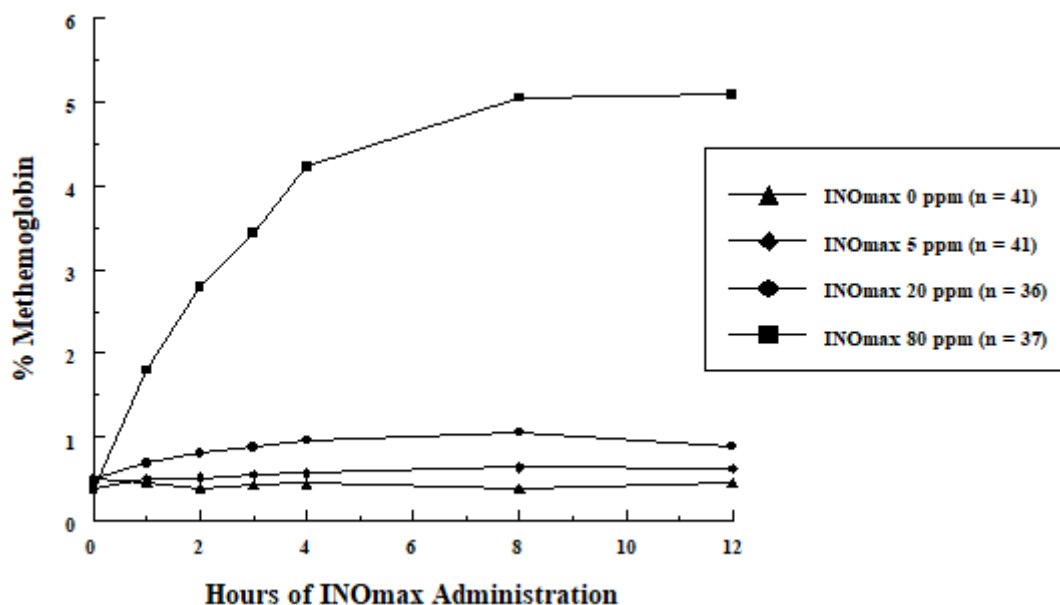
The sponsor's only efficacy study in adults, Study INOT41, used a dose of 40 ppm, which reflects the doses used in the literature. Studies using the lower dose of 20 ppm have shown broadly similar haemodynamic effects. In the absence of evidence showing better efficacy at higher doses, and given concerns about metHb and potential pulmonary toxicity of inhaled nitric oxide, it is therefore appropriate to start at approximately 20 ppm, the lowest dose for which there is adequate efficacy data. The sponsor proposes titrating upwards to 40 ppm if needed, but there is no strong basis for this suggestion in the submitted evidence.

To put the proposed dose into context, the proposed dose for adults is two-fold higher (20 ppm, increasing as needed to 40 ppm) than the INOmax dose approved in children undergoing cardiac surgery (10 ppm, increasing as needed to 20 ppm). The proposed starting dose in adults is the same as the dose approved for perinatal pulmonary hypertension, 20 ppm, but the paediatric dosing instructions advise against increases to 40 ppm, partly because of concerns about increased risk of methaemoglobinaemia at higher doses.

Of note, Vasokinox was approved for use in children and adults at a dose range that matches the dose approved for INOmax in children; the Vasokinox Product Information (PI) gives dosing instructions as follows:

> In children and adults, the recommended starting dose of inhaled nitric oxide is 10 ppm of inhaled gas. The lowest effective dose should be administered. The effects of inhaled nitric oxide are rapid [and are] usually observed within 5 to 20 minutes. In case of insufficient response, the dose may be titrated after a minimum of 10 minutes. The maximum recommended [dose] is 20 ppm.

Concerns were raised by both the non-clinical evaluator and the clinical evaluator for Vasokinox about the uncertain safety of inhaled nitric oxide at a dose of 40 ppm, and the clinical evaluator for Vasokinox noted that there is minimal evidence of superior efficacy at 40 ppm relative to 20 ppm. On this issue, the conclusions of the Australian Committee on Prescription Medicines (ACPM) are summarised in the Australian Public Assessment Report (AusPAR) for Vasokinox as follows:

The ACPM advised the evidence submitted on the proposed 40 ppm maximum dose in adults was insufficient to support efficacy of that dose in adults compared to 20 ppm (which is currently registered for VasoKINOX).

The ACPM noted there is large post-marketing safety data (n = 600,000), which shows acceptable safety, but this is predominantly in patients treated with up to 20 ppm.

The ACPM further noted that adverse events appear to be dose related.

The ACPM was of the view that the dose in adults should be limited to 20 ppm for safety reasons and it was noted that the sponsor has agreed in the pre-ACPM response to the reduction in dose for adults.

In Europe, inhaled nitric oxide has been approved for use in adults at a dose of 20 ppm, potentially increasing to 40 ppm in resistant cases.

The European Summary of Product Characteristics (SPC) for Vasokinox allows for a dose increase to 40 ppm, if needed, but it explicitly recommends a maximum of 20 ppm:

The recommended operating range is 2 to 20 ppm. The maximum recommended [dose] is 20 ppm. In adult[s], the dose may be increased up to 40 ppm if the lower dose has not provided sufficient clinical effects. In this case the patient's state should be followed up more regularly and the exposure to this higher dosage should be as limited as possible.

The European SPC for INOmax has similar wording, but it does not explicitly recommend a maximum of 20 ppm:

The starting dose of inhaled nitric oxide is 20 ppm (part per million) of inhaled gas. The dose may be increased up to 40 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.

For consistency, INOmax dosing instructions in Australia should generally match those for Vasokinox.

Efficacy

The evidence in this submission has limitations, because it relies on published studies that were small, underpowered, and often lacking in methodological rigour. Many of the published studies were of low quality, with inadequate characterisation of efficacy endpoints and incomplete reporting of safety data. Where this makes interpretation unreliable, this is pointed out within this report.

The only sponsor-initiated study was well-designed, but it proved to be underpowered and it was negative for its primary and secondary endpoints.

The sponsor's clinical overview contains some inaccurate statements, claiming significance for some outcomes that were not significant. Also, the sponsor's summaries generally emphasise within-group comparisons with baseline, even in controlled studies, rather than placing an appropriate emphasis on between-group comparisons. In some instances, this inflates the apparent efficacy of INOmax.

To some extent, these deficiencies reflect the fact that inhaled nitric oxide has been used off-label for years, and the evidence suggesting that it has efficacy in the treatment of pulmonary hypertension has slowly accumulated from small, investigator-led studies that were, individually, underpowered and lacking the rigour expected of a proper Phase III

study. The only major sponsor-initiated study was well-designed but, in retrospect, was underpowered.

Given the relatively low numbers of patients that undergo major cardiac surgery and develop pulmonary hypertension, it would be difficult and expensive to perform an adequate Phase III study for the proposed indication. Also, it would be unethical to randomise patients to placebo if they required treatment of pulmonary hypertension, and it would be difficult to find a universally accepted active comparator, given that none is registered for the proposed indication. Furthermore, it appears unlikely that inhaled nitric oxide would prove superior to any of the currently used (off-label) inhaled pulmonary vasodilators, and it would require large patient numbers to perform a meaningful non-inferiority study. Even if such a study were attempted, and showed that inhaled nitric oxide was similar in efficacy to another agent, no strong conclusions could be drawn without proof that the other agent was effective. For all of these reasons, many of the current submission's deficiencies can be understood and excused, though it remains important to correct some of the inaccuracies highlighted in this evaluation.

Studies providing efficacy data

The current submission is not based on any positive, well-designed, adequately powered sponsor-initiated studies.[2] The sponsor has submitted a single sponsor-initiated summary of Study INOT41, which was also submitted as supportive evidence for the paediatric submission, along with studies reported in the literature. Twelve of the adult studies from the literature were randomised, controlled studies that were previously assessed as supportive studies in the paediatric submission. The sponsor repeated the literature search in 2017 and uncovered four new randomised, controlled studies, one of which was merely a sub-study of Study INOT41, and contributes no new patients to the evidence base. One additional study[3] was included in the Vasokinox submission but it did not meet the selection criteria for inclusion in the current INOmax submission because it assessed combination therapy with INOmax and sildenafil, making it difficult to assess the contribution of inhaled nitric oxide to efficacy.

Thus, in total, 17 randomised, controlled studies in adults provide evaluable efficacy data for the current submission, covering 16 unique patient cohorts, as summarised in the tables below (this total comes from Study INOT41, along with 12 previously evaluated studies and 4 newly submitted studies). Indirect support also comes from the previously evaluated paediatric studies, though those studies will not be reassessed. Some uncontrolled published studies have also been assessed for safety.

Another 3 studies that had a primary focus on haemodynamics were presented and evaluated as pharmacodynamic studies within the previous paediatric submission. These have not been re-evaluated.

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[2] Clarification: The limitations of the available clinical data were identified in pre-submission discussions between the sponsor and the TGA

[3] Matamis D et al., 2012 Inhaled NO and sildenafil combination in cardiac surgery patients with out-of-proportion pulmonary hypertension: acute effects on postoperative gas exchange and hemodynamics. *Circ Heart Fail.* 2012 Jan;5(1):47-53

Table 2: Sponsor-initiated study in adult patients undergoing cardiac surgery

Study	Study design	No of patients	Primary outcome
INOT41 (Popatov et al., 2011);[4]	R, C	150	iNO reduced the incidence of right ventricular dysfunction, but not significantly. There was a trend to decrease the time required for mechanical ventilation iNO (p = 0.077)

R: randomised; C: controlled

Table 3: Published and previously evaluated studies in adult patients undergoing cardiac surgery

First author / year	Study design	No of patients	Primary outcome
Haemodynamics in adult cardiac surgery			
Girard 1992;[5]	open	6	iNO for 10 minutes improved haemodynamics in patients with mild PAH post mitral valve surgery
Lepore 2005;[6]	open	9	iNO decreased PAP and PVR by 10 ± 4% and 26 ± 12%, respectively (both p < 0.05) in potential transplant patients
Lindberg 1994;[7]	open	7	Dose response to iNO post CABG surgery – response same at all doses. Mean decrease in PAP and PVR of 11 ± 1% and 22 ± 22%, respectively, (both p < 0.05)
Cardiac surgery, various			
Fattouch 2005;[8]	R, C, DB	58	iNO was as effective in treating PAH as inhaled prostacycline. Both inhaled treatments superior to nitroprusside.
Fattouch 2006;[9]	R, C, DB	58	iNO was as effective in treating PAH as inhaled prostacycline. Both inhaled treatments were superior to nitroprusside. Inhaled treatments were superior with regards to time to weaning, intubation time and ICU stay (p < 0.05)

[4] Potapov E et al., 2011. Inhaled nitric oxide after left ventricular assist device implantation: a prospective, randomised, double-blind, multicenter, placebo-controlled trial. *Journal of Heart and Lung*, 30(8), pp. 870-878
[5] Girard C et al 1992 Inhaled nitric oxide after mitral valve replacement in patients with chronic pulmonary artery hypertension. *Anesthesiology,* 1992; 77: 880-883
[6] Lepore J et al 2005 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
[7] Lindberg L et al 1994 Nitric oxide gives maximal response after coronary artery bypass surgery. *J Cardiothorac Vasc Anesth*, 1994; 8: 182-187
[8] Fattouch K et al 2005 Inhaled prostacyclin, nitric oxide, and nitroprusside in pulmonary hypertension after mitral valve replacement. *J Card Surg*, 2005; 20: 171-176
[9] Fattouch K et al 2006 Treatment of pulmonary hypertension in patients undergoing cardiac surgery with cardiopulmonary bypass: a randomised, prospective, double-blind study. *J Cardiovasc Med* (Hagerstown), 2006; 7: 119-123

First author / year	Study design	No of patients	Primary outcome
Gianetti 2004[10]	R, C	29	Low concentration iNO can blunt release of markers of myocardial injury and antagonise LV dysfunction after CPB.
Schmid 1999[11]	R, XO	14	iNO and prostacycline IV decreased PVR and increased cardiac index
Winterhalter 2008;[12]	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 CO.
Solina 2000;[13]	R, C	45	iNO lead to lower HR, higher RV ejection fraction and lower vasopressor requirement compared to milrinone.
Solina 2001;[14]	R, C	62	Doses of iNO >10ppm showed no difference in PVR response.
Heart transplant patients			
Ardehali 2001;[15]	Pr, C	16	Post-transplant iNO significantly reduced RV stroke work and PVR. Retrospective control group.
Keiler-Jensen 1994;[1]	Pr, C	12	iNO significantly decreased PVR and increased PCWP (p < 0.01) during 20ppm iNO; with no further at 40 or 80ppm.
Rajek 2000;[16]	R, C	68	iNO (initiated at 4 ppm and titrated up to 24 ppm) caused selective reduction in PAP. iNO aided weaning from CPB more successfully than PGE1.
Radovancevic 2005;[17]	R, XO	19	iNO and PGE1 have comparable dilatory effects in PAH

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[10] Gianetti J et al 2004 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

[11] Schmid E et al 1999 Inhaled nitric oxide versus intravenous vasodilators in severe pulmonary hypertension after cardiac surgery. *Anesth Analg*, 1999; 89: 1108-1115

[12] Winterhalter M et al 2008 Comparison of inhaled iloprost and nitric oxide in patients with pulmonary hypertension during weaning from cardiopulmonary bypass in cardiac surgery: a prospective randomised trial. *J Cardiothorac Vasc Anesth*, 2008; 22: 406-401

[13] Solina A et al 2000 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.

[14] Solina A et al 2001 Dose response to nitric oxide in adult cardiac surgery patients. *J Clin Anesth*, 2001; 13: 281-286

[15] Ardehali A et al 2001 Inhaled nitric oxide for pulmonary hypertension after heart transplantation. *Transplantation,* 2001; 72: 638-641

[16] Rajek A et al 2000 Inhaled nitric oxide reduces pulmonary vascular resistance more than prostaglandin E(1) during heart transplantation. *Anesth Analg,* 2000; 90:523-530.

[17] Radovancevic B et al 2005 Nitric oxide versus prostaglandin E1 for reduction of pulmonary hypertension in heart transplant candidates. *J Heart Lung Transplant*, 2005; 24: 690-695

First author / year	Study design	No of patients	Primary outcome
Left ventricular assist device (LVAD) placement			
Argensiano 1998[18]	R, C, DB	11	iNO at 20 ppm induced significant reductions in mPAP and increases in LVAD flow index .

R: randomised; C: controlled; DB: double blind; XO: cross over; Pr: prospective

Table 4: Additional randomised studies in adult patients from the 2017 literature search

First author / year	Study design	No of patients	Primary outcome
Kukucka 2011[19]	R, C, DB LVAD	47	After LVAD implantation, marked decreases in PCWP (p < 0.01) and mean PAP (p < 0.01) were observed in iNO and placebo groups. Pulmonary vascular resistance decreased only in the iNO group (311 ± 35 to 225 ± 17, p < 0.01).
Fernandes 2011;[20]	R, Open Mitral valve surgery	29	The increase in cardiac index was significantly greater (p < 0.0001) in patients receiving iNO than in those receiving oxygen at both 24 and 48 hrs. The decrease in PVR was significantly greater (p = 0.005) in the iNO group, at 48 hrs.
Khan 2009;[21]	R, XO Heart Transplant	25	In heart transplant recipients, nitric oxide and prostacyclin similarly reduce pulmonary artery pressures and central venous pressure, and improve cardiac index and mixed venous oxygen saturation; pilot study
Knothe 1996;[22]	R, Open CABG	20	In the iNO group, PAP and PVR were significantly reduced (p < 0.05) and returned to baseline value after iNO ceased. No significant changes seen with conventional treatment

Kukucka 2011 reports on 47 patients from one centre (Berlin) participating in Study INOT41

Note that the sponsor's summaries under 'Primary outcome' in the right-hand column of Tables 3 and 4 contain several inaccuracies, particularly for Fernandes 2011;[20] [23]. All of the cited p-values refer to comparisons with baseline, not to between-group comparisons.

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[18] Argenziano M et al 1998 Randomised, double-blind trial of inhaled nitric oxide in LVAD recipients with pulmonary hypertension. *Ann Thorac Surg,* 1998; 65: 340-345

[19] Kukucka M et al., 2011. Acute impact of left ventricular unloading by left ventricular assist device on the right ventricle geometry and function: effect of nitric oxide inhalation *J Thorac Cardiovasc Surgery,* 2011; 141: 1009-1014.

[20] Fernandes J.L., et al., 2011. Comparison of inhaled nitric oxide versus oxygen on hemodynamics in patients with mitral stenosis and severe pulmonary hypertension after mitral valve surgery. *Amer J Cardiol*, 2011; 107: 1040-1045.

[21] Khan T et al 2009 A prospective, randomised, crossover pilot study of inhaled nitric oxide versus inhaled prostacyclin in heart transplant and lung transplant recipients. *J Thorac Cardiovasc Surg* 2009; 138: 1417-1420

[22] Knothe Ch et al 1996 NO inhalation in heart surgery procedures: Relevance for right-side heart function. *Anaesthesist.* 1996; 45: 240-248

[23] Clarification: some of the inaccuracies identified arose from the published reports themselves and the text of the approved PI for VasoKINOX

Evaluator's conclusions on efficacy

The current submission rests on 16 controlled studies in the literature, and a single, negative, sponsor-initiated study (Study INOT41, n = 150). In total, 709 adult patients have received controlled therapy in the submitted studies, 395 of whom were treated with inhaled nitric oxide. Control therapies in the different studies have been variable, but have included inhaled nitrogen (Study INOT41, Argenziano 1998;[18]); conventional treatment (Knothe 1996;[22]); oxygen (Fernandes 2011;[20]); intravenous (IV) milrinone (Solina 2000; [13]); IV Prostaglandin E1 (PGE1) (Schmid 1999;[11] Rajek 2000;[16]); IV nitroprusside or glyceryl trinitrate (Schmid 1999;[Error! Bookmark not defined.] Fattouch 2005;[8] Fattouch 2006;[9]); inhaled iloprost (Winterhalter 2008;[12] Khan 2009;[21]); and inhaled prostacyclin (Fattouch 2005;[8] Fattouch 2006;[9]).

In the adult studies, inhaled nitric oxide doses ranged from 4 to 40 ppm, but 20 ppm was used most commonly. The sponsor's study, Study INOT41, assessed inhaled nitric oxide (40 ppm) versus placebo (an equivalent concentration of nitrogen). In cardiac surgery patients, inhaled nitric oxide was usually commenced at the time of weaning from cardiopulmonary bypass. The duration of inhaled nitric oxide treatment was variable, and ranged from 15 minutes in acute haemodynamic studies to several hours (up to the arrival in the ICU or later). The doses of inhaled nitric oxide used in the included publications broadly support the recommended dosage of 20 ppm.

The endpoints were similar in each study, and included pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR), right ventricular ejection fraction (RVEF) or cardiac index (CI). In Study INOT41, the primary endpoint was clinical: the incidence of right ventricular dysfunction occurring within 48 hours during treatment with study drug.

The main findings and main limitations of each study are summarised in the Table 5 below. Despite the limitations noted, efficacy has been demonstrated for the key outcomes of pulmonary arterial pressure, pulmonary vascular resistance, with less convincing findings for cardiac index.

Pulmonary artery pressure

In the studies that reported changes in pulmonary arterial pressure (Argenziano 1998;[Error! Bookmark not defined.] Knothe 1996;[Error! Bookmark not defined.] Fernandes 2011;[Error! Bookmark not defined.] Fattouch 2005;[8] Fattouch 2006;[9] Solina 2000;[13] Winterhalter 2008;[12] Rajek 2000;[16] Schmid 1999;[11] Khan 2009;[21]), inhaled nitric oxide was associated with a reduction in pulmonary arterial pressure of up to 40% in adult patients with pulmonary hypertension after cardiac surgery, but this improvement generally included recovery from surgery and responses to other medications; placebo subtracted results were usually not available. Treatment with inhaled nitric oxide appeared to be more effective at reducing pulmonary arterial pressure than inactive controls, such as nitrogen (in patients undergoing left ventricular assist device insertion), and it was more pulmonary-selective than intravenous agents, such nitroprusside and glyceryl trinitrate, as shown by a higher incidence of systemic hypotension with intravenous agents. Many studies showed no major difference between inhaled nitric oxide and active comparators in their effects on pulmonary arterial pressure, but the studies were not designed as non-inferiority studies and were generally not adequately powered. The only active comparator reported to be more effective than inhaled nitric oxide in reducing pulmonary arterial pressure was inhaled iloprost (Winterhalter 2008;[12]), but inhaled nitric oxide appeared to have greater pulmonary selectivity than iloprost.

Pulmonary vascular resistance

In the studies that reported changes in pulmonary vascular resistance (Solina 2001;[14] Knothe 1996;[22] Fernandes 2011;[20] Fattouch 2005;[8] Fattouch 2006;[9] Solina 2000;[13] Winterhalter 2008;[12] Rajek 2000;[16] Schmid 1999;[11]), inhaled nitric oxide reduced the

pulmonary vascular resistance by approximately 35% to 65% and had no significant effect on systemic vascular resistance (where this was reported). Pulmonary selectivity was shown by lower pulmonary vascular resistance/systemic vascular resistance ratios seen with inhaled nitric oxide than with intravenous agents in adult patients with pulmonary hypertension after cardiac surgery. Treatment with inhaled nitric oxide appeared to be more effective at reducing pulmonary vascular resistance than oxygen, nitroprusside, and glyceryl trinitrate, and at least as effective as prostaglandin E1 (PGE1), sildenafil, milrinone and conventional treatment. The only active comparator reported to be more effective than inhaled nitric oxide in reducing pulmonary vascular resistance was iloprost (Winterhalter 2008;[12]) but iloprost also significantly reduced systemic vascular resistance, whereas inhaled nitric oxide did not.

Cardiac output and ejection fraction

Many of the studies assessed overall cardiac function or right ventricular function, as reflected in cardiac index, cardiac output, right ventricular ejection fraction, or left ventricular assist device flow index (Solina 2001;[14] Argenziano 1998;[18] Knothe 1996;[22] Fernandes 2011;[20] Fattouch 2005;[8] Fattouch 2006;[9] Solina 2000;[13] Winterhalter 2008;[12] Rajek 2000;[16] Schmid 1999;[11] Khan 2009;[21]). In most of these studies, measures of cardiac function were not significantly different in the inhaled nitric oxide group relative to comparator treatments. The sponsor's claim that the increase in cardiac index after inhaled nitric oxide was significantly greater than after oxygen, was based on the publication of Fernandes 2011;[20] however the clinical evaluator found that this statement in the publication was an error: cardiac index changes in the two groups were not significantly different. When compared to nitrogen, the increase in left ventricular assist device flow index after inhaled nitric oxide was greater than after nitrogen.[18] In patients undergoing heart transplantation for congestive heart failure, inhaled nitric oxide (4 ppm to 24 ppm, n = 34) was superior to a PGE1 infusion at a rate of 8 ng/kg/min (n = 34), with significant between-group differences for pulmonary vascular resistance, pulmonary vascular resistance/systemic vascular resistance, cardiac output and success in weaning from cardiopulmonary bypass; failures on PGE1 required rescue with inhaled nitric oxide[Error! Bookmark not defined.].[16] The increase in cardiac output after inhaled nitric oxide was significantly lower than after inhaled iloprost.[12]

In the proposed PI, the sponsor identifies 5 published studies as 'key' studies demonstrating efficacy of inhaled nitric oxide in adults undergoing cardiac surgery:

> A total of 17 prospective randomised controlled trials involving 709 adult patients (395 treated with inhaled nitric oxide) were assessed as published study reports for the indication of perioperative pulmonary hypertension in conjunction with cardiac surgery. Five of these were considered key studies: Kukucka et al 2011;[19] Argenziano et al 1998;[18] which were placebo controlled double blind studies and Knothe et al 1996;[22] Fernandes et al 2011;[20] and Rajek et al 2000;[16] which were controlled against conventional therapy.

There is no clear reason for highlighting Kukucka et al.,[19] as a key study, when it was merely a negative sub-study assessing patients from one centre during the larger parent study, Study INOT41.

Although the sponsor has provided summary tables for the submitted studies, the sponsor's tables generally highlighted changes from baseline, and failed to report on between-group comparisons except where these were positive. The table below reflects the clinical evaluator's overall conclusions about the quality of the studies and the main conclusions that can be inferred from each of them. Of the 16 controlled studies in the literature, only six showed a significant between-group difference (Schmid 1999;[11] Ardehali 2001;[15] Kieler-Jensen 1994;[1] Radovencevic 2005;[17], Rajek 2000;[16] and Fernandes

2011;[20]); these are presented in bold in Table 5, and should be considered the key studies supporting the submission.

Table 5: Summary of published studies of adult cardiac surgery patients (excluding Study INOT41)

Study and Clinical Setting	Treatments	Flaws	Results	Between-Group Comparison
Fattouch 2005;[8] Mitral valve surgery	inhaled nitric oxide 20 ppm (n = 22) inhaled PGI2 (n = 18) IV nitroprusside (n = 18)	Doses unclear Blinding uncertain No clear primary endpoint ANOVA results missing from paper Poor separation of rebound/recovery effects from efficacy effects	inhaled nitric oxide and iPGI2 both reduced pulmonary vascular resistance and mean pulmonary arterial pressure, relative to baseline	Negative
Fattouch 2006;[9] Mitral valve surgery	inhaled nitric oxide variable dose (n = 21) Inhaled PGI2 (n = 19) IV vasodilators (n = 18)	Doses and agents used unclear Unclear relationship to Fattouch 2005, with possible overlap of data Blinding uncertain Unclear statistical methods with no clear primary endpoint	inhaled nitric oxide and PGI2 were similar, reducing pulmonary vascular resistance compared to baseline	Negative
Gianetti 2004;[10] Aortic valve replacement	inhaled nitric oxide 20 ppm (n = 14) no additional inhalation treatment (n = 15)	Open-label study No clinical endpoints, and did not focus on haemodynamic effects, so not directly relevant to proposed indication	inhaled nitric oxide significantly reduced production of biochemical markers of myocardial injury	Negative
Solina 2000;[13] Cardiac surgery patients with pulmonary hypertension	inhaled nitric oxide 20 ppm (n = 15) inhaled nitric oxide 40 ppm (n = 15) IV milrinone (n = 15)	Open-label study No placebo group Active comparator not a recognised therapy Unclear separation of recovery effects from efficacy effects No sample size calculations	inhaled nitric oxide and milrinone had similar and significant effects on pulmonary vascular resistance, relative to baseline	Negative
Solina 2001;[14]	inhaled nitric oxide 10 ppm (n =	Open-label study	Percentage decrease in pulmonary	Negative

Study and Clinical Setting	Treatments	Flaws	Results	Between-Group Comparison
Cardiac surgery patients with pulmonary hypertension	11) inhaled nitric oxide 20 ppm (n = 12) inhaled nitric oxide 30 ppm (n = 12) inhaled nitric oxide 40 ppm (n = 12) milrinone (n = 15)	No placebo group Active comparator not a recognised therapy Unclear separation of recovery effects from efficacy effects	vascular resistance similar in all groups (10 ppm = 38%, 20 ppm = 50%, 30 ppm = 44%, 40 ppm = 36%, milrinone = 58%, p = 0.86)	
Schmid 1999;[11] **Cardiac surgery patients with severe pulmonary hypertension**	inhaled nitric oxide 40 ppm, IV PGE1 and IV glyceryl trinitrate, crossover (n = 14)	Open-label study No sample size calculations Results emphasise comparison with baseline rather than between-group comparisons	inhaled nitric oxide lowered pulmonary vascular resistance, TPG, relative to baseline No significant pulmonary vascular resistance difference between groups inhaled nitric oxide showed significantly greater selectivity for pulmonary circulation (pulmonary vascular resistance/systemic vascular resistance)	Reduction in pulmonary vascular resistance/systemic vascular resistance more pronounced with inhaled nitric oxide
Winterhalter 2008;[12] Cardiac surgery patients with pulmonary hypertension	inhaled nitric oxide 20 ppm (n = 23) inhaled iloprost (n = 23)	Open-label study No correction for multiplicity of secondary endpoints, but primary endpoint (pulmonary arterial pressure) clearly identified	Both drugs improved haemodynamics and lowered mean pulmonary arterial pressure and pulmonary vascular resistance, relative to baseline	Negative for inhaled nitric oxide. Iloprost produced greater reductions in pulmonary vascular resistance and pulmonary arterial pressure, and greater increases in cardiac index.
Ardehali 2001;[15] **Heart transplant patients with PH**	inhaled nitric oxide 20 ppm (n = 16) historical controls (n = 16)	No valid control group No clear primary statistical hypothesis No correction for multiplicity of endpoints	Lower incidence of RV dysfunction with inhaled nitric oxide Lower pulmonary vascular resistance at 6 hours with	Lower incidence of RV dysfunction with inhaled nitric oxide Lower pulmonary vascular resistance at 6 hours with

Study and Clinical Setting	Treatments	Flaws	Results	Between-Group Comparison
		(Does not match indication)	inhaled nitric oxide	inhaled nitric oxide
Kieler-Jensen 1994;[1] **Pre-op heart transplant candidates**	inhaled nitric oxide 20, 40 and 80 ppm, nitroprusside, prostacyclin, crossover (n = 12)	Open-label study No primary endpoint No correction for multiplicity of endpoints (Does not match indication)	pulmonary vascular resistance lowered with all treatments No dose effect across 20 ppm to 80 ppm	Greater pulmonary selectivity (pulmonary vascular resistance/systemic vascular resistance changes) with inhaled nitric oxide than intravenous agents
Radovancevic 2005;[17] **Pre-op heart transplant candidates**	inhaled nitric oxide 40, 60 and 80 ppm, PGE1, crossover (n = 19)	Open-label study No primary endpoint No correction for multiplicity No power calculations	Both agents lowered pulmonary vascular resistance and transpulmonary pressure gradient No dose effect across 40 to 80 ppm	Greater selectivity with inhaled nitric oxide - significantly less effect with inhaled nitric oxide on systemic BP, systemic vascular resistance and cardiac index
Rajek 2000;[16] **Heart transplant patients**	inhaled nitric oxide 4 to 24 ppm (n = 34) IV PGE1 (n = 34) Rescue crossover	Unclear distinction between changes from baseline and between-group comparison	pulmonary vascular resistance and pulmonary arterial pressure reduced in both groups compared to baseline, with better reductions for inhaled nitric oxide	inhaled nitric oxide showed better reduction in pulmonary vascular resistance, pulmonary arterial pressure, pulmonary vascular resistance/systemic vascular resistance, greater improvement in cardiac output, fewer rescue crossovers
Argenziano 1998;[18] Patients undergoing left ventricular assist device insertion	inhaled nitric oxide 20 ppm (n = 6) nitrogen (n = 5)	No clear primary endpoint No correction for multiplicity No power calculations	Between-group comparison unclear, but significant response to inhaled nitric oxide in placebo crossovers, with reduction in mpulmonary arterial pressure	Unclear
Kukucka 2011;[19] Substudy of INOT41,	inhaled nitric oxide 40 ppm (n = 24) placebo (n = 23)	No clear primary endpoint No correction for multiplicity of	Changes in pulmonary vascular resistance and CI relative to baseline, in both groups,	Negative

Study and Clinical Setting	Treatments	Flaws	Results	Between-Group Comparison
patients receiving left ventricular assist device		endpoints	significant in inhaled nitric oxide group, trend in favour of inhaled nitric oxide	
Fernandes 2011;[20] **Mitral valve surgery**	inhaled nitric oxide 10 ppm (n = 14) oxygen (n = 15)	Open-label study No correction for multiplicity of secondary endpoints, but clear identification of primary endpoint Unclear power calculations Significance of cardiac index results misrepresented	inhaled nitric oxide associated with reduced pulmonary vascular resistance compared to baseline, and improved cardiac index compared to baseline	Significant superiority of inhaled nitric oxide for pulmonary vascular resistance, but no significant difference for cardiac index
Khan 2009;[21] Lung and heart transplant patients	inhaled nitric oxide 20 ppm (n = 14) PGI2 (n = 11) Followed by crossover	Open label study Unclear power calculations "Baseline" after treatment	No difference between groups	Negative
Knothe 1996;[22] Cardiac surgery patients	inhaled nitric oxide 30 ppm (n = 10) standard therapy (n = 10)	Open-label study	Reductions in pulmonary arterial pressure and pulmonary vascular resistance observed, but no difference between groups	Negative

Off-label and non-trial experience

As noted for the paediatric submission, there has been extensive experience with inhaled nitric oxide over multiple decades, and inhaled nitric oxide is widely regarded as a gold-standard treatment for management of pulmonary hypertension in ventilated patients. Several authorities have recommended its use in the cardiac surgical setting, despite its off-label status, and it was registered for the proposed indication in Europe in 2011 (also, the same active agent is already approved in Australia under a different brand name Vasokinox, at a different concentration). This widespread off-label experience offsets the considerable deficiencies in the published studies evaluated here.

Conclusion

The efficacy of inhaled nitric oxide has been confirmed in a large number of small studies that are individually weak, but broadly consistent. Inhaled nitric oxide has been shown to reduce pulmonary artery pressure and pulmonary vascular resistance when given to adult subjects who exhibit pulmonary hypertension in the setting of cardiac surgery. In settings where systemic blood pressure needs to be maintained, inhaled nitric oxide has an advantage over systemic vasodilators because it is selective for the pulmonary

vasculature. The size of the effect cannot be determined accurately from the available evidence.

Safety

The safety of inhaled nitric oxide has been evaluated in the context of previous submissions including:

- the original paediatric INOmax submission seeking registration for respiratory distress associated with persistent pulmonary hypertension of the newborn;

- the INOmax submission seeking registration of INOmax for treatment of pulmonary hypertension in paediatric cardiac surgery; and

- the Vasokinox submission seeking registration of inhaled nitric oxide in both children and adults

Inhaled nitric oxide has also been registered for use in adults overseas, and it has been used off-label for more than two decades in the treatment of adults with perioperative pulmonary hypertension. The safety issues associated with this product are therefore reasonably well known, and the current submission does not present substantial new safety issues compared to those evaluated previously. Compared to the Vasokinox submission, which did not include Study INOT41/ Potapov 2011;[4] the current INOmax submission provides data on a greater number of exposures to inhaled nitric oxide 40 ppm. The current submission does not directly discuss paediatric exposure to INOmax, but the experience of using INOmax in this vulnerable population provides additional external validity and reassurance for the adult safety assessment.

Known safety issues with INOmax

At the time of the clinical evaluation for the paediatric submission, the following safety issues were identified:

- nitric oxide combines with haemoglobin (Hb) to produce metHB, which makes a proportion of the total haemoglobin unavailable for carrying oxygen;

- nitric oxide by-products include the toxic molecule nitrogen dioxide (NO_2), and so monitoring is required to ensure that levels of nitrogen dioxide remain within safe limits;

- abrupt cessation of nitric oxide can induce rebound pulmonary hypertension;

- nitric oxide can increase left atrial (LA) filling, potentially exacerbating cardiac failure or pulmonary oedema in susceptible individuals with pre-existing left ventricular dysfunction;

- nitric oxide could, in theory, effect platelet function;

- nitric oxide has unknown effects on the immune system.

The previous evaluation made the following comments in regard to these issues:

'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 nitrogen dioxide levels or indicated that alarms were in place for alerting investigators to elevated levels of nitrogen dioxide.

All authors appeared to be aware of the potential for rebound pulmonary hypertension to occur when inhaled nitric oxide 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;[24], where weaning time was considered a secondary efficacy endpoint.

The sponsor's study, Study INOT22, provides evidence that left atrial filling may be excessive when inhaled nitric oxide is administered in the setting of pre-existing left ventricular failure. This issue has been noted by previous investigators[25],[26] and is appropriately mentioned in the current and proposed PIs.

Ardehali et al. 2001;[15] also raise the following safety concern about inhaled nitric oxide:

> 'The immunological properties of nitric oxide are incompletely understood. Low-level nitric oxide production appears to be necessary for maximal proliferation of lymphocytes. Furthermore, expression of inducible nitric oxide synthetase has been linked with acute solid organ rejection. On the other hand, activation of inducible nitric oxide 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 immunomodulating properties of inhaled nitric oxide in thoracic transplantation.'[27],[28],[29],[30]

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

These comments remain broadly applicable to the current submission.

The sponsor's Risk management plan (RMP) includes the following table identifying major risks:

Table 6: Summary of known safety concerns

Summary of safety concerns	
Important identified risks	Hypoxemia from methaemoglobinemia
	Acute cardiac failure, pulmonary oedema, circulatory collapse
	Rebound pulmonary hypertension
Important potential risks	Airway injury
	Increased bleeding time
	Critical failure of the delivery system
Missing information	Combined use with other vasodilators

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

[25] Bocchi EA et al. Inhaled nitric oxide leading to pulmonary edema in stable severe heart failure. *Am J Cardiol.* 1994 Jul 1;74(1):70-2

[26] Semigran MJ et al. Hemodynamic effects of inhaled nitric oxide in heart failure. *J Am Coll Cardiol.* 1994 Oct;24(4):982-8

[27] Efron DT et al. Nitric oxide generation from LArginine is required for optimal human peripheral blood lymphocyte DNA synthesis. *Surgery* 1991; 110: 327.

[28] Kuo PC, et al. Differential localization of allograft nitric oxide synthesis: comparison of liver and heart transplantation in the rat model. *Immunology* 1996; 87: 647.

[29] Albin JE, et al. Nitric oxide production is required for murine resident peritoneal macrophage to suppress mitogen stimulated T-cell proliferation. *J Immunol* 1991; 147: 144.

[30] Sichel SC, et al. Inhibition of macrophage I-A expression by nitric oxide. *J Immunol* 1994; 163: 1293.

Summary of safety concerns	
	Use during pregnancy and lactation
	Paediatric use < 34 GA for PPHN
	Patients 12-17 years treated for pulmonary hypertension in conjunction with heart surgery

Each of these is adequately discussed in the current PI, and should be known to clinicians administering the agent. In most cases, the risks can be moderated, for instance: by monitoring levels in the case of metHB and nitrogen dioxide; by avoiding the drug in subjects likely to be intolerant of elevated left atrial filling pressures, who might be reliant on elevated pulmonary vascular resistance; and by weaning the drug slowly to avoid rebound pulmonary hypertension. Backup power and equipment should be available in the event of critical equipment failure, which could subject patients to sudden withdrawal. The potential effects of inhaled nitric oxide on bleeding time remain unconfirmed, but this issue remains under surveillance. The effects on pregnancy are likely to remain unclear, given the low incidence of pregnancy in subjects undergoing major cardiac surgery; cardiopulmonary bypass in this context would itself pose major risks to the foetus. Similarly, subjects are very unlikely to breastfeed while receiving inhaled nitric oxide, so this is not an important practical issue. The dose for the age group of 12 to17 years is somewhat uncertain, but the PI mentions this, and such subjects are beyond the scope of this evaluation.

The new submission raises no new concerns about any of these known issues.

Studies providing safety data

No submitted studies assessed safety as their primary outcome. The previously described sponsor-initiated efficacy study, Study INOT41, represents the primary study evaluable for safety, with 69 subjects exposed to inhaled nitric oxide 40 ppm. (The safety data for this study have been evaluated previously, and the relevant sections of the previous evaluation are reproduced here largely verbatim, because the data have not changed.)

Most of the other studies included in the current submission were small and safety monitoring was restricted to monitoring metHB, nitrogen dioxide, haemodynamic profile and vital signs. The studies had inconsistent or non-existent reporting of adverse events. Most of these studies have already been evaluated, and the conclusions reached in the previous evaluation are merely summarised in this report.

Of the four new controlled studies found in the 2017 literature search, one (Kukucka 2011;[19]) was a substudy of Study INOT41 and involved no new exposures; it raised no new safety concerns. The safety findings of the other three new studies are discussed below. Several additional uncontrolled or retrospective studies were identified in the 2017 literature search; these studies were not evaluable for efficacy, because of their uncontrolled nature, but they add to the safety database. Their uncontrolled nature limits their utility for safety analysis, particularly as the studies were performed in cardiac surgery patients with a high background incidence of adverse events and comorbidities.

Seven case reports were identified in the 2017 literature search; these were surveyed by the sponsor for previously unreported adverse events (AEs), and no new issues were identified.

In addition to published studies, there has been extensive post marketing and off-label exposure to inhaled nitric oxide. The sponsor states: 'The estimated cumulative number of exposed subjects or patients (of all ages) over all periodic safety update report (PSUR) time periods is estimated to be approximately 877,196 patients.'

Patient exposure

Patient exposure to inhaled nitric oxide in the published literature is summarised in the tables below, including Study INOT41 and some uncontrolled studies only evaluable for safety. The total number of adult subjects in published studies exposed to any dose of inhaled nitric oxide is 562; of these, most patients were exposed for < 48 hours, and 150 were exposed for < 1 hour, as shown in the tables below. Published reports of exposure to the maximum recommended dose, 40 ppm, consists of 154 patients, including 69 from Study INOT41 who received inhaled nitric oxide in a randomised, controlled study and smaller numbers of subjects from 7 separate published studies, some of which were controlled.

Table 7: Dose of nitric oxide across published studies, including Study INOT41

Dossier	Publication	Dose of iNO (ppm)	No.Pts receiving 40ppm iNO
PM-2014-01399-1-3 Prior evaluation by TGA	Fattouch 2005	20	
	Fattouch 2006		
	Gianetti 2004		
	Winterhalter 2008		
	Ardehali 2001		
	Argenziano 1998		
	Rajek 2000	4 – 24	
	INOT41	40	69
	Schmid 1999	40	14
	Solina 2000	20, 40	15
	Solina 2001	10, 20, 30, 40	12
	Kieler-Jensen 1994	*20, 40, 80*	*12*
	Radovancevic 2005	*40, 60, 80*	*19*
Current dossier for adult cardiac surgery indication	Fernandes, 2011	10	
	Khan, 2009	20	
	Razzaq, 2009[†]		
	Makker, 2006[†]		
	MacDonald, 1998[†]		
	Kieler-Jensen, 1995[†]	5, 10, 20	
	Beck, 1999[†]	*20 – 40*	*34*
	Fullerton, 1998[†]	*20, 40*	*20*
	Knothe, 1996	30	
	*Kukucka, 2011**	*40*	
	Elahi, 2009[†]	5, 20	
	Maxey, 2006*	20	
	McGinn, 2016*	Up to 40	

† *non-randomised studies* * *retrospective studies*
* *Note: Kukucka 2011 reports on a subset of patients from the INOT 41 study*

References in the above table are as follows: Fattouch 2005;[8] Fattouch 2006;[9] Gianetti 2004;[10] Winterhalter 2008;[12] Ardelhali 2001;[15] Argenziano 1998;[18] Rajek 2000;[16] INOT 41; Schmid 1999;[11] Solina 2001;[14] Kieler-Jensen 1994;[1] Radovancevic 2005;[17] Fernandes 2011;[20] Kahn 2009;[21] Razzaq 2009;[31] Makker 2006;[32] MacDonald 1998;[33] Kieler-Jensen

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[31] Razzaq RZ et al., 2009. Variable response to inhaled nitric oxide in postoperative patients of mitral stenosis with pulmonary hypertension J Ayub Medical College, Abbottabad *JAMC,* 2009; 21:98-102

1995;[34] Beck 1999;[35] Fullerton 1998;[36] Knothe 1996;[22] Kukucka 2011;[19] Elahi 2009;[37] Maxey 2006;[38] McGinn 2016;[39].

Table 8: Exposure by duration in all published studies

	iNO patients (study ref)				
Duration	< 10 ppm	10-20 ppm	21-40 ppm	41-80 ppm	Total Any Dose
0 < Dur ≤ 1 hour	0	22 (Fattouch, et al., 2005) 30 (Razzaq et al, 2009) 20 (Fullerton et al, 1996) 9 (Kieler Jensen et al, 1995) 12 (Kieler-Jensen, et al., 1994) **93 in total**	3 (INOT41, 2009) 12 (Kieler-Jensen, et al., 1994) 10 (Knothe 1996) 20 (Fullerton et al, 1996) **45 in total**	12 (Kieler-Jensen, et al., 1994) **12 in total**	150
1 < Dur ≤ 2 hour	0	0	2 (INOT41, 2009)	0	
2 < Dur ≤ 4 hour	0	10 (Elahi et al, 2009)	2 (INOT41, 2009)	0	
4 < Dur ≤ 12 hour	0	14 (Khan 2009) 49 (McGinn et al 2016)	13 (INOT41, 2009)	0	135
12 < Dur ≤ 24 hour	0	14 (Gianetti, et al., 2004) **87 in total**	31 (INOT41, 2009) **48 in total**	0	
24 < Dur ≤ 48 hours	0	15 (Solina, et al., 2000) 14 (Fernandes et al, 2011) 34 (Beck et al, 1999) 7 (Macdonald et al, 1998) 17 (Maxey et al, 2002) **87 in total**	15 (Solina, et al., 2000) 13 (INOT41, 2009) **28 in total**	0	115
48 < Dur ≤ 96 hours	0	0	4 (INOT41, 2009) **4 in total**	0	4
Mixed	0	21 (Fattouch, et al., 2006) 23 (Solina, et al., 2001) 16 (Ardehali, et al., 2001) **60 in total**	14 (Schmid, et al., 1999) 24 (Solina, et al., 2001) 23 (Winterhalter, et al., 2008) 19 (Radovancevic, et al., 2005) **80 in total**	19 (Radovancevic, et al., 2005) **19 in total**	159
Total Any Duration	**0**	327	205	31	562

[32] Makker R., et al 2006. Therapeutic application of inhaled nitric oxide in adult cardiac surgical patients. *Indian Heart Journal*, 2006; 58: 432-436

[33] Macdonald P.S., et al., 1998. Adjunctive use of inhaled nitric oxide during implantation of a left ventricular assist device. *J Heart Lung Transplant* 1998; 17: 312-16.

[34] Kieler-Jensen N., et al, 1995. Vasodilator therapy after heart transplantation: Effects of inhaled nitric oxide and intravenous prostacyclin, prostaglandin E1, and sodium nitroprusside. *J Heart Lung Transplant,* 1995; 14: 436-443

[35] Beck JR. et al., 1999. Inhaled nitric oxide improves hemodynamics in patients with acute pulmonary hypertension after high-risk cardiac surgery. *Perfusion*, 1999; 14: 37-42

[36] Fullerton D.A., et al., 1996. Effective control of pulmonary vascular resistance with inhaled nitric oxide after cardiac operation. J Thorac Cardiovasc Surg, 1996; 111: 753-763

[37] Elahi MM. et al., 2009. Inspired nitric oxide and modulation of oxidative stress during cardiac surgery. *Current Drug Safety*,2009; 4: 188-198

[38] Maxey TS et al., 2002. Beneficial effects of inhaled nitric oxide in adult cardiac surgical patients. *Ann Thorac Surg*, 73(2), pp.529-32; discussion, pp.532-33

[39] McGinn K., Reichert M., 2016. A comparison of inhaled nitric oxide versus inhaled epoprostenol for acute pulmonary hypertension following cardiac surgery. *Ann Pharmacother*,2016; 50: 22-26.

Table 9: Exposure by duration in Study INOT41

Duration	INO treated pts Dose 40 ppm	iNO open label
0 < Dur ≤ 1 hour	3	In open label phase, patients could be treated with iNO for up to 14 days
1 < Dur ≤ 2 hour	2	
2 < Dur ≤ 4 hour	2	
4 < Dur ≤ 12 hour	13	
12 < Dur ≤ 24 hour	31	
24 < Dur ≤ 48 hours	13	
48 < Dur ≤ 96 hours	4	
Total Any Duration	**69**	**34**
Mean duration	19 hours	65.6 hours
Median duration	15.2 hours	44.8 hours
Range	0-48 hours	5-624 hours

Table 10: Exposure to inhaled nitric oxide 40 ppm in published studies

Study	No. pts treatedwith iNO 40 ppm
INOT41	69
Kieler-Jensen 1994	12
Radovancevic 2005	19
Beck 1999	34
Fullerton 1998	20
Total	**154**

Safety issues with the potential for major regulatory impact

Serious adverse events (SAE) from the sponsor-initiated Study INOT41, are summarised below. In general, SAEs were more commonly observed with placebo than with inhaled nitric oxide during the double-blind phase. Open-label treatment with inhaled nitric oxide was associated with a higher incidence of SAEs, reflecting a longer duration of treatment and a sicker underlying population. The most common SAEs consisted of a need for renal replacement therapy, haemorrhage, and pyrexia; these AEs are likely to reflect the underlying disease (severe cardiac failure) and the procedure (left ventricular assist device insertion). The incidence of individual SAEs was generally similar in the inhaled nitric oxide and placebo groups. The only SAE that occurred slightly more frequently in the inhaled nitric oxide group was renal replacement therapy, but the incidence was actually similar to that observed in the placebo group (inhaled nitric oxide, 10 of 69 subjects, 14.1%; placebo 8 of 68 subjects, 11.4%), with no significant difference.

In the published studies, SAEs and AEs were not distinguished.

Deaths

Four deaths occurred in Study INOT41, as summarised in the table below.

Table 11: Deaths in Study INOT41

Trial	Centre	ID	Age	Sex	Dose	Duration	Diagnosis	COD	Medications	Other Pathologies	Loc of Narrative Description
(INOT41, 2009)	N/S		63y	F	40 ppm	Placebo DB for 10.4 hrs then OL iNO for 91.8h	Cardiomyopathy	Severe Renal failure and MOF	N/S	Valvular heart disease, Cardiomyopathy, AF and VT	INOT41 Clinical Study Report p66
(INOT41, 2009)	N/S		69y	M	40 ppm	iNO 4h (DB) 140h (OL)	Cardiomyopathy	RVF	N/S	DM, Renal Failure, AAA Tricuspid Regurgitation, MI, Hypertension and Valvular disease	INOT41 Clinical Study Report p66
(INOT41, 2009)	N/S		56y	M	40 ppm	iNO 0.5h (DB) 624h (OL)	Cardiomyopathy	MOF	N/S	Ischaemia, MI, Hypertension, Renal Failure,	INOT41 Clinical Study Report p66
(INOT41, 2009)	N/S		75y	F	40 ppm	Placebo DB for 1 hr then OL iNO for 7.8h	Cardiomyopathy	RVF	N/S	End-stage heart failure, hypertension	INOT41 Clinical Study Report p66

Note: Under the ID column, patient identifiers have been redacted.

From the previous clinical evaluation: In Study INOT41, two deaths occurred due to right ventricular failure during double blind treatment, but they were balanced across treatment groups: 1 of 69 (1.4%) in the inhaled nitric oxide group and 1 of 68 (1.5%) in the placebo group. The death in the inhaled nitric oxide recipient was considered 'remotely' related to study drug, and while the death in the placebo recipient was considered unrelated. Overall, right ventricular failure was less frequent with inhaled nitric oxide.

Two more deaths occurred during open label inhaled nitric oxide treatment. Both deaths were attributed to multi-organ failure and were considered to be 'remotely' related to study drug. There is no evidence of a causal relation between inhaled nitric oxide treatment and the deaths.

Table 12: Adverse events with a fatal outcome during treatment, Study INOT41

MedDRA System Organ Class Preferred term	N (%) of subjects who died during:		
	Double-Blind		Open-Label
	INO (N = 69)	Placebo (N = 68)	INOmax (N = 34)
Total n (%) of subjects who died[a]	1 (1.4%)	1 (1.5%)	2 (5.9%)
Cardiac Disorders	**1 (1.4%)**	**1 (1.5%)**	**0 (0.0%)**
Right ventricular failure	1 (1.4%)	1 (1.5%)	0 (0.0%)
General Disorders and Administration Site Conditions	**0 (0.0%)**	**0 (0.0%)**	**2 (5.9%)**
Multiorgan failure	0 (0.0%)	0 (0.0%)	2 (5.9%)
Renal and Urinary Disorders	**0 (0.0%)**	**0 (0.0%)**	**1 (2.9%)**
Renal failure	0 (0.0%)	0 (0.0%)	1 (2.9%)
Respiratory, Thoracic and Mediastinal Disorders	**0 (0.0%)**	**1 (1.5%)**	**0 (0.0%)**
Respiratory disorder	0 (0.0%)	1 (1.5%)	0 (0.0%)

[a] Subjects may fall into more than one category.

Liver function and liver toxicity

There is no evidence of significant liver toxicity related to inhaled nitric oxide. As noted in the previous clinical evaluation, many subjects showed improved liver function after cardiac surgery, reflecting improved liver perfusion and reduced hepatic engorgement. However, in Study INOT41, a total of 14 subjects receiving inhaled nitric oxide and 12 subjects receiving placebo had aspartate transaminase or alanine aminotransferase values that were at least 10 times the upper limit of normal at baseline or at sporadic post-baseline time points. There was no apparent correlation with administration of inhaled nitric oxide, and in many cases the abnormal liver function tests are likely to reflect cardiac and multi-organ dysfunction in the setting of major concurrent comorbidities.

Renal function and renal toxicity

There is no evidence of renal toxicity with inhaled nitric oxide, and laboratory monitoring in Study INOT41 did not raise concerns related to biochemical markers of renal dysfunction.

Other clinical chemistry

Apart from metHB and nitrogen dioxide, discussed above, the use of inhaled nitric oxide is not known to cause other abnormalities of clinical chemistry.

Haematology and haematological toxicity

There were no major haematological abnormalities noted in inhaled nitric oxide recipients in Study INOT41, and the published literature does not raise any significant concerns about haematological toxicity. As noted in the previous clinical evaluation for INOmax, concerns were raised by Ardehali et al, 2001;[15] about the theoretical potential of nitric oxide to modify immune function; these concerns have not been substantiated in ongoing safety monitoring for inhaled nitric oxide.

Similarly, theoretical concerns have been raised about whether inhaled nitric oxide might have an effect on platelets, and animal models suggest a possible increase in bleeding time, but evidence from Study INOT41, the published studies, and post-marketing surveillance show no concerning safety signals with respect to bleeding or thrombocytopaenia. The sponsor notes:

> 'Nitric oxide activates cyclic GMP and thus inhaled nitric oxide may have an effect on platelets. However, it is rapidly taken up by haemoglobin forming metHB. However, data from humans have not identified signs or signals of an increased risk of bleeding from the administration of low clinical doses of inhaled nitric oxide. Similarly a low dose of 30 ppm inhaled nitric oxide in healthy volunteers did not cause significant change in bleeding time or platelet function as compared to placebo, while active control with aspirin caused an expected change in both parameters.[40,41,42]'

The approved PI already contains a warning about this issue:

> Bleeding time
>
> Animal models have shown that nitric oxide may interact with haemostasis, resulting in an increased bleeding time. Nitric oxide may modulate platelet function via the guanylate cyclase signalling pathway. Data in adult humans are

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[40] Albert J et al. 1999 Inhaled nitric oxide does not influence bleeding time or platelet function in healthy volunteers, *Eur J Clin Invest*. 1999; 29: 953-959

[41] Mellgren K et al. 1998 Effect of nitric oxide gas on platelets during open heart operations. *Ann Thorac Surg*. 1998; 65: 1335-1341

[42] de Mol AC et al. 2007 Abnormalities of coagulation related to the use of inhaled nitric oxide before extracorporeal membrane oxygenation, *Pediatr Crit Care Med*. 2007; 8: 261-263

conflicting, and there has been no increase in bleeding complications in randomised controlled trials in term and near-term neonates with hypoxic respiratory failure.

Other laboratory tests

No additional concerns arise from other laboratory tests.

Electrocardiograph findings and cardiovascular safety

Inhaled nitric oxide can increase left atrial (LA) filling, potentially exacerbating cardiac failure or pulmonary oedema in susceptible individuals with pre-existing left ventricular dysfunction; this issue is well known and it is highlighted in the current PI.

In Study INOT41, use of inhaled nitric oxide was not associated with abnormalities of the electrocardiogram (ECG). Cardiovascular safety has been closely monitored in the submitted studies, and was usually the main focus of efficacy assessments. No concerning signals were detected, apart from the previously discussed risk in subjects intolerant of increased left atrial filling.

Vital signs and clinical examination findings

Study INOT41 did not raise any concerns related to vital signs or examination findings, and the published studies have not raised any concerning safety signals in this regard.

Immunogenicity and immunological events

Inhaled nitric oxide has not been associated with immunogenicity.

Serious skin reactions

Inhaled nitric oxide has not been associated with serious skin reactions or rashes.

Safety of 40 ppm relative to 20 ppm

The sponsor makes reference to an issue that arose during evaluation of the competing inhaled nitric oxide product, Vasokinox, as shown below. Essentially, the non-clinical evaluator for Vasokinox noted that higher doses of inhaled nitric oxide caused pulmonary toxicity in animal models when inhaled nitric oxide was administered with high concentrations of oxygen, and the clinical evaluator for Vasokinox expressed concern that only 27 subjects in the studies under evaluation had been exposed to doses of 40 ppm.

The sponsor for INOmax makes the following observations:

> 'The AusPAR for Vasokinox indicates that the TGA did not approve the 40 ppm dose for the adult population, based on concerns regarding pulmonary toxicity at higher doses expressed by the non-clinical evaluator. The clinical evaluator notes that, in the 6 studies identified as major by the Vasokinox sponsor, only 27 of the 274 exposed patients received 40 ppm dose of inhaled nitric oxide; an additional 14 patients were reported by Schmid 1999.[11] The clinical evaluator concluded that 'the robust clinical data required to address the nonclinical evaluator's concerns about inhaled nitric oxide doses higher than 20 ppm is lacking in the submission.'

> The current INOmax dossier presents additional efficacy and safety data in terms of the 40 ppm dose of inhaled nitric oxide from 5 studies that were not included in the Vasokinox dossier. These additional studies represent an additional 154 patients exposed to inhaled nitric oxide 40 ppm, compared to the Vasokinox dossier.

> In this INOmax dossier, comprehensive safety data for the 40 ppm dose is provided by the sponsored Study INOT41 which was a prospective, multicentre, double blind, placebo controlled study of INOmax (40 ppm) versus placebo (inhaled nitrogen). The safety population consisted of 137 patients (INOmax n = 69;

placebo n = 68) who received 48 hours treatment in a double blind fashion and could be crossed to open label INOmax for a further 14 days if clinically indicated.

In the safety analysis of Study INOT41, inhaled nitric oxide at a dose of 40 ppm was shown to be well tolerated and the safety profiles of inhaled nitric oxide and placebo were similar.'

Generally, the lowest effective dose of inhaled nitric oxide should be sought and dosing should always be titrated against each patient's individual clinical responses. Dosing must take into account both the clinical effect and the risk of side effects. Methaemoglobin levels must also be considered to ensure the safe use. In studies of inhaled nitric oxide doses up to 40 ppm increases in metHB have been rarely reported.

As noted by the sponsor, inclusion of the INOT41 data means that exposure to inhaled nitric oxide at doses of 40 ppm exceeds the exposure considered in the Vasokinox clinical evaluation, and no evidence of pulmonary toxicity has arisen. Nonetheless, pulmonary toxicity could be difficult to identify in subjects undergoing major thoracic surgery and mechanical ventilation, because a high incidence of pulmonary dysfunction would be expected in this population anyway, due to atelectasis, cardiac insufficiency, ventilator-associated pneumonia, and so on. The PI should provide a full disclosure of the problems identified during pre-clinical evaluation, underscoring the need to use the lowest effective dose. This is particularly important because there is no efficacy data at all, in any published study, suggesting that inhaled nitric oxide is more effective at 40 ppm than at 20 ppm.

Safety in special populations

As noted in the previous clinical evaluation, inhaled nitric oxide carries a risk of exacerbating left ventricular dysfunction in patients with left heart failure who may be intolerant of the elevated left atrial filling that can follow reduction of pulmonary vascular resistance. This issue is already noted in the PI.

Safety related to drug-drug interactions and other interactions

Pharmacodynamic interactions would be expected if inhaled nitric oxide were used in conjunction with other pulmonary vasodilators and, despite its relative pulmonary selectivity, it would need to be used with caution when combined with systemic vasodilating agents, because of the risk of synergistic increases in the overall vasodilatory response.

Also, inhaled nitric oxide combines with haemoglobin to produce metHB, so the risk of significant methaemoglobinaemia would be increased if it were used in conjunction with other drugs that encourage formation of metHB. Such drugs include other nitrogen-based compounds (sodium nitroprusside, glyceryl trinitrate) as well as many local anaesthetic agents, such as prilocaine, and also sulfonamides. This should also be a feature of post-marketing education programs.

Post marketing data

There has been extensive post-marketing experience with inhaled nitric oxide in the paediatric population in Australia, as well as the adult cardiac surgery population in Europe. The sponsor has submitted periodic safety updates as follows:

Since the Australian approval on 16 November 2007, four annual PSURs have been submitted to the TGA which fulfilled the sponsor's PSUR reporting obligations as listed below:

- First PSUR: 24 December 2006 to 23 December 2007 (submitted to TGA on 2 December 2008)

- Second PSUR: 24 December 2007 to 23 December 2008 (submitted to TGA on 4 March 2009)

- Third PSUR: 24 December 2008 to 23 December 2009 (submitted to TGA on 15 March 2010)

- Fourth PSUR: 24 December 2009 to 23 December 2010 (submitted to TGA on 10 May 2011),

For the application for paediatric cardiac surgery indication approved by the TGA the sponsor included the following PSURs:

- Fifth PSUR: 24 December 20010 to 23 December 2011

- Sixth PSUR: 24 December 2011 to 23 December 2012

- Seventh PSUR: 24 December 2012 to 23 December 2013

- Eighth PSUR: 24 December 2013 to 23 December 2014.

Post-marketing exposure since the international birth date (IBD) of inhaled nitric oxide is summarised in the table below, by country. The subsequent table lists AEs reported from post-marketing exposure. Without a control therapy, it is impossible to put these reports into context but, overall, no new safety signals have emerged during post-marketing use of inhaled nitric oxide.

Table 13: Cumulative estimated patient exposure from marketing experience

	US	Canada	South America	Australia	Mexico	Japan	South Korea	Thai-land	Malaysia	Total
No. cylinders returned	689,304	23,781	7,069	8,241	3,831	16,381	862	174	97	749,740
Estimated patient exposure	806,486	27,824	8,271	9,642	4,482	19,166	1,009	203	113	877,196

Table 14: Interval (24 December 2015 to 23 December 2016) and cumulative (23 December 1999 to 23 December 2016) summary tabulations of serious and non-serious adverse events by System Organ Class from post-marketing data sources

System Organ Classification Preferred Term	Spontaneous					Solicited	
	Serious		Non-serious		Total	Serious	
	Interval	Cumul	Interval	Cumul	Cumul	Interval	Cumul
Blood and lymphatic system disorders	4	20	0	17	37	0	3
Cardiac disorders	5	254	0	4	258	0	48
Congenital, familial and genetic disorders	1	38	0	0	38	0	10
Eye disorders	0	2	0	14	16	0	2
Gastrointestinal disorders	0	3	9	38	41		5
General disorders and administration site conditions	38	430	9	127	557	1	34
Hepatobiliary disorders							
Immune system disorders	0	4	0	0	4	0	1
Infections and infestations	7	55	0	1	56	1	23
Injury, poisoning and procedural complications	0	51	27	349	400	0	2
Investigations	11	208	2	105	313	0	34
Metabolism and nutrition disorders	0	6	0	0	6	0	6
Musculoskeletal and connective tissue disorders	0	1	0	1	2	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	2	0	0	2	0	2
Nervous system disorders	2	24	10	122	146	2	25
Pregnancy, puerperium and perinatal conditions	1	14	0	0	14	0	12
Product issues	4	31	8	160	191	0	0
Psychiatric disorders	0	0	1	4	4	0	2
Renal and urinary disorders	1	6	0	0	6	0	1
Reproductive system and breast disordees	0	0	0	2	2	0	0
Respiratory, thoracic and mediastinal disorders	8	201	2	30	231	3	55
Skin and subcutaneous tissue disorders	0	2	0	9	11	0	1
Social circumstances	0	0	0	2	2	0	0
Surgical and medical procedures	0	35	0	1	36	0	2
Vascular disorders	0	26	1	5	31	0	10
Grand Total	83	1413	69	991	2404	7	278

Evaluator's conclusions on safety

The proposed extension of indications to include adult cardiac surgery patients does not raise any substantial new safety concerns, and most of the safety data were already submitted as part of the previous INOmax submission.

The main safety issues related to inhaled nitric oxide are those already highlighted in previous evaluations and mentioned in the current PI:

- Potential accumulation of nitrogen dioxide.

- Rebound pulmonary hypertension

- Acute cardiac failure in subjects relying on pulmonary vascular resistance and intolerant of increased left atrial filling

Potential safety issues include theoretical concerns about the effects of inhaled nitric oxide on bleeding time and potential airway injury from exposure to inhaled nitric oxide, but there is no direct evidence showing that inhaled nitric oxide has clinically relevant effects on bleeding time or produces airway toxicity.

Safety during pregnancy and lactation is unknown, but cardiac surgery is itself relatively contraindicated in pregnant patients.

First round benefit-risk assessment

First round assessment of benefits

Table 15: First round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
Inhaled nitric oxide offers the following benefits: • Produces pulmonary vasodilation, resulting in significant decrease in pulmonary arterial pressure and pulmonary vascular resistance • Reversible, with quick onset and offset of action, allowing titration to desired effect • Selective for pulmonary vasculature, with minimal effects on systemic arterial pressure (SAP) and systemic vascular resistance The evidence for these benefits comes from the following positive studies: **Schmid 1999**;[11] Cardiac surgery patients with severe pulmonary hypertension, inhaled nitric oxide 40 ppm, PGE1 and glyceryl trinitrate, open-label crossover (n = 14). Reduction in pulmonary vascular resistance/systemic vascular resistance more pronounced with inhaled nitric oxide **Ardehali 2001**;[15] Heart transplant patients with pulmonary hypertension. Open label, inhaled nitric oxide 20 ppm (n = 16), historical controls (n = 16). Lower incidence of RV dysfunction with inhaled nitric oxide, Lower pulmonary vascular resistance at 6 hours with inhaled nitric oxide **Kieler-Jensen 1994**;[1] Pre-op heart transplant candidates, inhaled nitric oxide 20, 40 and 80 ppm, nitroprusside, prostacyclin, crossover (n =	**Strengths** Many investigator studies over two decades have been broadly consistent with each other and have generally shown the haemodynamic changes claimed for inhaled nitric oxide (reduced pulmonary arterial pressure or pulmonary vascular resistance). Although the between-group comparisons have often not achieved statistical significance within individual studies, the collective evidence is much stronger than suggested by any individual study. **Uncertainties** The evidence for benefit is limited, because: • The only sponsor-initiated study was negative (possibly because it was underpowered). • Many of the studies in the literature were negative or methodologically unsound, and all were small • Positive endpoints in adult studies are largely limited to haemodynamic changes, without clear changes in clinical outcomes • No clear benefit has been shown for cardiac index, right-ventricular function, mortality, or time in ICU. • Equivalent or superior benefit relative

Indication	
Benefits	**Strengths and Uncertainties**
12), Greater pulmonary selectivity (pulmonary vascular resistance/systemic vascular resistance changes) with inhaled nitric oxide than IV agents **Radovancevic 2005;**[17] Pre-op heart transplant candidates, inhaled nitric oxide 40, 60 and 80 ppm, PGE1, crossover (n = 19). Greater selectivity with inhaled nitric oxide - significantly less effect with inhaled nitric oxide on systemic BP, systemic vascular resistance and cardiac index **Rajek 2000;**[16] Heart transplant patients, inhaled nitric oxide 4 to24 ppm (n = 34), PGE1 (n = 34). inhaled nitric oxide showed better reduction in pulmonary vascular resistance, pulmonary arterial pressure, pulmonary vascular resistance/systemic vascular resistance, greater improvement in cardiac output, fewer rescue crossovers **Fernandes 2011;**[20]Mitral valve surgery, inhaled nitric oxide 10 ppm (n = 14), oxygen (n = 15). Significant superiority of inhaled nitric oxide for pulmonary vascular resistance, but no significant difference for cardiac index.	to other active agents has not been demonstrated. • There is no clear evidence showing that inhaled nitric oxide 40 ppm is superior to 20 ppm, and yet the PI recommends increasing to 40 ppm if needed.

First round assessment of risks

Table 16: First round assessment of risks

Risks	Strengths and Uncertainties
The risks of INOmax in the proposed usage are: • Rebound pulmonary hypertension on sudden cessation, making any interruption to treatment hazardous, including unplanned interruption due to equipment failure. • Increased left atrial filling in response to reduced pulmonary vascular resistance may cause cardiac failure and pulmonary oedema in adults with underlying left ventricular dysfunction. • Treatment produces toxic by-products: methaemoglobinaemia, which may cause hypoxaemia, and nitrogen dioxide • Animal studies have suggested a potential risk of increased bleeding	**Uncertainties** The submission is based on a heterogeneous mix of small studies with widely variable control therapies Poor or absent documentation of adverse events in most published studies. Overall exposure in controlled studies has been too limited to allow identification of rare safety problems. Relative safety of 40 ppm versus 20 ppm is unknown. **Strengths** One sponsor-initiated study (Study INOT41) showed no major safety issues in comparison to nitrogen placebo There has been extensive post-marketing and off-label exposure to inhaled nitric

Risks	Strengths and Uncertainties
(although this has not been directly observed in the submitted studies, none of the studies was adequately powered to assess differences in bleeding and none had bleeding as a focus).	oxide, so most of the risks associated with its use are likely to have been identified.

First round assessment of benefit-risk balance

The precise benefit-risk balance for inhaled nitric oxide has not been defined with rigor, but within the limitations of the available evidence, the balance appears to be positive overall. There are substantial residual uncertainties about the efficacy and safety of its use in adult patients, and in particular the utility of doses beyond 20 ppm has not been established. Collectively, the submitted studies make it very likely that inhaled nitric oxide acts as a selective pulmonary vasodilator, lowering pulmonary arterial pressure and pulmonary vascular resistance, and despite the methodological flaws of the submitted studies, this effect is not really in doubt. Clinicians have used the drug for more than two decades in closely monitored environments, and they have directly observed the haemodynamic changes that result from administering inhaled nitric oxide. The rapid onset of action and rapidly reversible nature of the drug's haemodynamic effects make it very easy for anaesthetists and intensivists using the drug to confirm that nitric oxide causes pulmonary vasodilation, and where pulmonary arterial pressure and pulmonary vascular resistance have been studied in comparison to placebo agents in controlled studies, the vasodilatory effect has been reproduced, though the studies have often been underpowered.

It has not been established, in adults, that the haemodynamic effects translate into favourable clinical outcomes, but the previous paediatric submission included studies with clinical endpoints (such as Miller, 2000;[24]), and these showed that treatment of pulmonary hypertension in paediatric cardiac surgery patients reduced the incidence of pulmonary hypertensive crises and shortened time on ventilation. It is not certain that these results reflect the situation in adults, but it appears likely.

The important question is whether it is realistic to expect positive studies with clinical endpoints in cardiac surgical patients. It would be unethical to deny cardiac surgical patients with pulmonary hypertension access to pulmonary vasodilators in situations where clinicians thought such treatments were indicated, leaving them on placebo until they demonstrated a potentially dangerous clinical decline, so any studies assessing inhaled nitric oxide would need to take at least one of the following approaches:

- Use haemodynamic endpoints and brief exposures to randomised treatment, rather than allowing patients to continue randomised therapy until they suffer adverse clinical outcomes.

- Use rescue therapy to prevent adverse clinical outcomes.

- Use acceptable active control therapies to manage pulmonary hypertension, randomising patients to inhaled nitric oxide or active controls only when there is genuine clinical equipoise in selecting between the two agents.

The submitted studies have taken a mix of these approaches, but each strategy compromises the demonstration of a clear cut benefit for inhaled nitric oxide using clinical outcomes. Even in the sponsor's own study, Study INOT41, the use of rescue therapies meant that a clear comparison between treatment arms was difficult; relatively few

recipients of placebo were allowed to reach the clinical endpoint of right ventricular dysfunction and some were instead switched to active open-label inhaled nitric oxide.

If there were an accepted, gold-standard, registered treatment for pulmonary hypertension in the cardiac surgical setting, it might be reasonable to design a non-inferiority study intending to show that inhaled nitric oxide was acceptably similar to that gold-standard treatment, but no such alternative treatment exists. Also, the number of patients required to demonstrate equivalence between two active treatments would probably be prohibitively large. If strong clinical endpoints were used, such as deaths or episodes of severe right heart failure, then these endpoints would be reached relatively infrequently (as shown in the sponsor's Study INOT41), and this would reduce the statistical power to show that two agents were equally effective. It has already been shown that inhaled nitric oxide is less likely to produce systemic hypotension than IV vasodilators, and it appears very likely that the unintended systemic hypotension associated with systemic vasodilation would produce adverse clinical outcomes if it were left uncorrected. It would be unethical to enforce a study design that encouraged clinicians to wait until adverse haemodynamic endpoints produced unfavourable clinical outcomes. Finally, in cardiac surgical patients, who are a clinically vulnerable patient population, many cases of poor clinical outcome could occur that had nothing to do with the (presumably minor) differences between one inhaled pulmonary vasodilator and another, and so the signal-to-noise ratio in such studies for non-haemodynamic endpoints such as death or time in ICU would be low.

The uncertainties surrounding the safety data pose similar problems. The target population is likely to have a very large number of AEs and SAEs in the perioperative period, as a result of: their underlying cardiac disease; the highly invasive surgery and cardiopulmonary bypass; the invasive mechanical ventilation in ICU; and their other comorbidities. In this setting, it is inherently difficult to identify safety signals solely attributable to inhaled nitric oxide. Furthermore, it is unlikely that a large randomised study comparing inhaled nitric oxide with "placebo" (that is, a treatment arm banning use of active pulmonary vasodilators) would be considered ethical or could ever reach its recruitment targets. It is therefore unlikely that clear identification of the incidence of AEs attributable to inhaled nitric oxide will ever be possible. Instead, the safety of inhaled nitric oxide must be inferred from post-marketing data and uncontrolled or spontaneously reported observations. So far, this evidence suggests that the safety of inhaled nitric oxide is acceptable, despite several important risks associated with the treatment, as outlined above.

Finally, despite substantial residual uncertainties surrounding the efficacy and safety of INOmax, it is basically the same drug as Vasokinox, differing only in the storage concentration of inhaled nitric oxide (800 ppm for INOmax, 450 ppm for Vasokinox). Although the clinical evaluator for Vasokinox had a number of concerns about the quality of the evidence supporting inhaled nitric oxide in adults (concerns shared by the current Evaluator), the overall benefit-risk of Vasokinox was eventually considered acceptable for adult cardiac surgical patients with pulmonary hypertension, largely on the basis of the same evidence considered in this report. In addition to that previously evaluated evidence, the sponsor has also submitted the study INOT41. Although this sponsor-initiated study was negative for its efficacy endpoints, probably because it was underpowered, it had favourable efficacy trends, and it extended the safety data, including exposure to 40 ppm.

The current evaluator accepts that it is not realistic to expect a traditional, large, adequately powered Phase III study with clinical endpoints to be conducted, so the existing deficiencies in the evidence cannot be easily remedied, and a decision must be made on the balance of probabilities after reviewing multiple limited studies, rather than on more straightforward statistical evidence. Overall, then, despite the deficiencies in the evidence, the benefit-risk balance for inhaled nitric oxide in the proposed usage appears to

be favourable. The most important residual uncertainty relates to the efficacy and safety of 40 ppm compared to 20 ppm.

First round recommendation regarding authorisation

The sponsor's proposal to register INOmax for the proposed indication should be approved, as reproduced below, but only after satisfactory revisions have been made to the PI and following clarification of the need for a 40 ppm dose.

INOmax, in conjunction with ventilatory support and other appropriate active substances, is indicated:

> *as part of the treatment of patients with peri- and post-operative pulmonary hypertension in conjunction with heart surgery, to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation.*

Clinical questions and second round evaluation

Question 1

> *Please provide a brief summary of the evidence supporting the use of inhaled nitric oxide at a dose of 40 ppm, rather than 20 ppm as used in most clinical studies. Include efficacy and safety data. Should the PI recommend a maximum dose of 20 ppm?*

Summary of sponsor's response

Table 17: Published experience with inhaled nitric oxide at a dose of 40 ppm

Publication	Dose of iNO (ppm)	Pts on 40ppm
INOT41 (Potapov 2011; Kukucka 2011)	40	69
Schmid 1999	40	14
Solina 2000	20, 40	15
Solina 2001	10, 20, 30, 40	12
Kieler-Jensen 1994	20, 40, 80	12
Radovancevic 2005	40, 60, 80	19
Beck, 1999[+]	20 – 40	34
Fullerton, 1996[+]	20, 40	20
McGinn, 2016[*]	5 to 40	(98) - dose breakdown not provided
Total no. of patients		**195**

[+] *non-randomised studies* [*] *retrospective studies*

References for Table 18: Popatov 2011;[4] Kukucka 2011;[19] Schmid 1999;[11] Solina 2000;[13] Solina 2001;[14] Kieler-Jensen 1994;[1] Radovacevic 2005;[17] Beck 1999;[35] Fullerton 1996;[36] McGinn 2016;[39]

The total of 195 subjects mentioned in the table above does not include the patients in McGinn et al, 2016.[39] This study was retrospective and did not provide a dose breakdown, so it does not provide any useful efficacy or safety comparisons of inhaled nitric oxide 40 ppm compared to inhaled nitric oxide 20 ppm. Accordingly, it was not submitted in detail nor evaluated in the first round clinical evaluation report. Similarly, Beck et al, 1999;[35] and Fullerton et al, 1996;[36] were non-randomised studies, so they provide no reliable comparison of 20 ppm and 40 ppm. The sponsor notes that Fullerton et al failed to report any safety findings, so this study is of very limited value in choosing a maximum

inhaled nitric oxide dose. The sponsor reports that, for Beck et al;[35] "the number of patients requiring up-titration to 40 ppm is not specified in the report," so this study is also not useful in the current context, and provides no basis for comparing the two doses.[43]

Most of the remainder of the sponsor's response consists of a brief inline text description of the studies listed above, and an appendix summarising the same studies (included as a table, below). Excluding the retrospective and non-randomised studies, the other studies listed in the table above have already been described in this report. In many cases, they were open-label, or had other significant methodological flaws. They provide only limited information relevant to choosing a maximum inhaled nitric oxide dose, and none of them provides a robust efficacy and safety comparison of 20 ppm and 40 ppm. Of the three controlled, randomised studies assessing inhaled nitric oxide at both 20 ppm and 40 ppm (Solina et al, 2000[Error! Bookmark not defined.]; Solina et al, 2001;[14] Kieler-Jensen, 1994[1]), none provides a robust comparison of safety at the two doses and none shows evidence of a dose trend in efficacy (with the possible exception of Solina et al, 2000, which suffered from significant baseline mismatch, as discussed below).

The sponsor-initiated Study INOT41, provides placebo controlled safety data for 69 subjects exposed to inhaled nitric oxide 40 ppm, and this study provides the main source of new information since the Vasokinox submission. Study INOT41 assessed the use of inhaled nitric oxide to prevent right ventricular dysfunction in the setting of left ventricular assist device insertion in adults with cardiac failure, but it showed no significant efficacy benefits of inhaled nitric oxide over placebo for the primary endpoint of right ventricular dysfunction.

In their response to this question, the sponsor's description of INOT41 was broadly accurate:

In the sponsor-initiated study INOT 41 (Potapov et al., 2011;[4]) the use of inhaled nitric oxide at 40 ppm in the perioperative phase of left ventricular assist device implantation did not achieve significance for the primary end point of reduction in right ventricular dysfunction. A trend was established regarding the influence of inhaled nitric oxide on mechanical ventilation and the need for right ventricular assist device support after left ventricular assist device placement. In the controlled phase of study INOT41, inhaled nitric oxide 40 ppm was given for a median duration of 19 hours (range 0 to 48 h). In the open label phase of Study INOT41 where patients could be treated for up to 14 days, the median duration of inhaled nitric oxide 40 ppm was 65.6 hours (range 5 to 624 hours), thus providing safety evidence for prolonged administration of inhaled nitric oxide 40 ppm.

The safety data from INOT41 raised no specific concerns about pulmonary toxicity at an inhaled nitric oxide dose of 40 ppm, but the study was not specifically powered for safety comparisons, and pulmonary toxicity could have been difficult to identify in the study population, given the fact that all subjects had baseline cardiac failure and all subjects underwent major invasive thoracic surgery and mechanical ventilation, so some degree of pulmonary dysfunction was expected in all patients. This study also lacked a 20 ppm control group, so it provides no direct comparison of the safety of 40 ppm relative to lower doses. Given that no significant efficacy benefit was demonstrated for inhaled nitric oxide 40 ppm over placebo, the study does not provide any support for the notion that there is a dose trend for efficacy in the range of 20 ppm to 40 ppm.

The other studies described in the sponsor's response were already available at the time of the Vasokinox evaluation, at which time they were deemed to provide inadequate support for the 40 ppm dose. The sponsor's description of these studies raises no substantive new issues or new argument in favour of the 40 ppm dose. In particular, the

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[43] Clarification: The Beck et al and Fullerton et al studies were not reviewed by the clinical evaluator.

sponsor's descriptions of the other studies do not address the specific issue of how efficacy or safety at 40 ppm compares to efficacy at 20 ppm, but merely summarise, for each study, how haemodynamic results in the inhaled nitric oxide treatment arm compared to those in the non-inhaled nitric oxide control arm. In some cases, the sponsor appears to infer inhaled nitric oxide efficacy from haemodynamic changes with respect to baseline, without considering the extent to which these changes could have been due to other factors, such as recovery from surgery and other treatments provided in ICU. (As already noted throughout this report, the control groups of most studies also often showed substantial improvements relative to baseline.)

As is evident from the table below, most of the studies included in the sponsor's response lacked safety reporting, so they do not adequately address the safety of inhaled nitric oxide 40 ppm at all, let alone in comparison to 20 ppm. In particular, all three of the studies that assessed both 20 ppm and 40 ppm (Solina et al, 2000;[13] Solina et al, 2001;[14] Kieler-Jensen, 1994[1]) lacked safety reporting. None of the three studies assessing both doses showed superior efficacy for 40 ppm relative to 20 ppm (with the possible exception of Solina et al 2000, which suffered from baseline mismatch).

Table 18: Outcomes from clinical studies using 40 ppm inhaled nitric oxide

Publication	Dose of iNO (ppm)	Pts on 40 ppm	Study design	Efficacy outcomes	Safety outcomes
INOT41	40	69	Prospective, placebo-controlled RCT in adults after LVAD implantation	Use of iNO at 40 ppm in the perioperative phase of LVAD implantation did not achieve significance for the primary end point of reduction in RVD. A trend was established regarding the influence of iNO on mechanical ventilation and the need for RVAD support after LVAD placement.	In the safety analysis of INOT41, iNO at a dose of 40 ppm was shown to be well tolerated and the safety profiles of iNO and placebo were similar
Schmid 1999	40	14	Prospective, RCT in adults with severe pulmonary hypertension but preserved RVF after cardiac surgery	iNO was not superior to IV prostaglandin E1 with regard to cardiac index and right ventricular performance.	In-hospital outcome was favourable in all patients and all were discharged in good condition.
Solina 2000	20, 40	15	iNO group randomized to 20 ppm (n = 15) or 40 ppm (n = 15) of iNO on termination of CPB). iNO was continued for first 24 hours in the ICU.	The treatment of pulmonary hypertension in adult cardiac surgery patients with inhaled NO was associated with a favourable effect on RVEF and a reduced requirement for treatment with pressor agents when compared with milrinone treatment. Similar effects seen with 20 ppm or 40 ppm iNO.	No safety findings reported
Solina 2001	10, 20, 30, 40	12	Dose comparison study	In this dose comparison, the % decrease in PVR with iNO as compared to baseline values was not significantly different among the groups (10 ppm 38%, 20 ppm 50%, 30 ppm 44%, 40 ppm 36%, milrinone 58%, p 0.86).	No safety findings reported
Kieler-Jensen 1994	20, 40, 80	12	To assess pulmonary vasodilator potential in heart transplant candidates	The maximal effect on PVR in adult patients could be obtained at a dose of 20 ppm with no further effect at higher dose levels (40 and 80 ppm)	No safety findings reported
Radovancevic 2005	40, 60, 80	19	To assess pulmonary vasodilator potential in heart transplant	Both the transpulmonary gradient and PVR decreased promptly with the lowest dose of NO (40 ppm) and remained relatively unaffected by additional increases to 60 ppm and 3480 ppm. On the other hand, NO therapy failed to decrease systolic PAP regardless of the dose administered.	No safety findings reported
Beck, 1999[*]	20 – 40	34	Dose started at 20ppm and titrated until response was noted or 40 ppm reached	Patients receiving iNO exhibited substantial reductions in mPAP) (34.6 ± 2.0 to 26.0 ± 1.7 mmHg, $p < 0.0001$), with improvements in systemic hemodynamics, mean arterial pressure (68 ± 3.1 to 75.9 ± 2.0 mmHg, $p = 0.006$). The dose as used in this study is in line with proposed PI; the number of patients requiring up-titration to 40 ppm is not specified in the report	Six deaths in 34 patients due to multisystem organ failure (n=3), unresponsive hypoxia (n=1), coagulopathy and bleeding (n=1) and fatal PE (n=1) several days post-op.
Fullerton, 1996[*]	20, 40	20		iNO produced a significant reduction in both PAP and PVR in patients after cardiac surgery without reducing SAP or SVR. There were ni differences in haemodynamic effects of 20 and 40 ppm. In patients with higher OVR and PAP concentrations as high as 80 ppm may be required.	No safety findings reported
Kukucka, 2011*	40		Report on a single centre cohort from Study INOt41	After LVAD implantation marked decreases in pulmonary capillary wedge pressure (P<.01) and mean pulmonary artery pressure (P<.01) were observed in both groups. Pulmonary vascular resistance decreased only in the iNO group (311 ` 35 to 225 ` 17, P<.01).	One patient received first day postoperatively excessive transfusion because of intra-abdominal bleeding and hemorrhagic shock
McGinn, 2016*	Up to 40	Not stated	Retrospective analysis of 49 iNO patients	This published retrospective report does not provide the number of patients treated with 40 ppm iNO.	Adverse events reported in the 49 patients treated with 5-40 ppm iNO were bleeding (12%) and hypotension (8%) respectively.

These limitations of the submitted studies have been discussed elsewhere in this report, but they are reconsidered below in the context of the current clinical question, which specifically asked how the efficacy and safety of 40 ppm compared to 20 ppm.

Schmid, 1999;[11] involved very brief exposure to inhaled nitric oxide (up to 20 minutes) in a crossover design, making it impossible to draw any conclusions about the potential pulmonary toxicity of inhaled nitric oxide, and the study did not compare inhaled nitric oxide 40 ppm with inhaled nitric oxide 20 ppm.

Solina et al, 2000;[13] compared inhaled nitric oxide at 20 ppm and 40 ppm, but the study had an open label design, and the groups were poorly matched at baseline, as noted in the abstract: 'The group receiving 40 ppm nitric oxide had a significantly higher (p < 0.05) right ventricular ejection fraction on arrival in the intensive care unit (40% versus 30% for the milrinone group and 33% for the nitric oxide 20 ppm group).'

In their description of this study, the sponsor writes:

'Solina et al., 2000;[13] assessed inhaled nitric oxide at 20 and 40 ppm in comparison to IV milrinone. The study showed that inhaled nitric oxide 40 ppm is broadly comparable to the intravenous vasodilator milrinone in its ability to decrease pulmonary vascular resistance. All three treatments produced a clear reduction in pulmonary vascular resistance compared to baseline. At a dose of 40 ppm, inhaled nitric oxide was associated with a higher pulmonary vascular resistance than the other two treatments but this may have reflected pre-treatment differences.'

Although the sponsor acknowledges that pre-treatment differences may have played a role in this study, their summary, reproduced above, does not acknowledge that the treatment groups were already significantly different at baseline in terms of their right ventricular ejection fraction, completely invalidating efficacy comparisons between doses.

Solina et al, 2001;[14] was a small, open-label study, with very few patients assigned to each dose group. The abstract states: 'Subjects in Group 1 (n = 11) received 10 ppm of inhaled nitric oxide, Group 2 subjects (n = 12) received 20 ppm, Group 3 subjects (n = 12) received 30 ppm, and Group 4 subjects (n = 12) received 40 ppm. The fifth group (n = 15) received no nitric oxide [but received milrinone].' This study was far too small to provide a meaningful comparison of the relative safety of inhaled nitric oxide at doses of 20 ppm and 40 ppm.

Also, it did not suggest any efficacy difference across the dose-range assessed, as noted in the abstract: 'There were no significant differences found in demographic data, baseline hemodynamic data, surgical treatment, conduct of cardiopulmonary bypass, or the use of inotropic or vasoactive drugs among the five treatment groups. The percentage decrease in pulmonary vascular resistance on treatment with nitric oxide as compared to baseline values was not significantly different among the groups (10 ppm = 38%, 20 ppm = 50%, 30 ppm = 44%, 40 ppm = 36%, milrinone = 58%, p = 0.86).'

Kieler-Jensen, 1994[1], was another small, open label study (n = 12). It used a crossover design to compare the haemodynamic effects of increasing concentrations of inhaled nitric oxide (20, 40 and 80 ppm) with intravenous vasodilators, sodium nitroprusside and prostacyclin (PGI2), in subjects with elevated pulmonary vascular resistance undergoing diagnostic right heart catheterisation in a preoperative setting. All subjects received inhaled nitric oxide for a very short period (10 minutes at each dose). The short duration of treatment means that the study did not address the question of whether prolonged inhaled nitric oxide treatment causes pulmonary toxicity, and the fact that all subjects received inhaled nitric oxide at all three doses means that there is no adequate control group for safety comparisons. Preclinical considerations suggest that pulmonary toxicity with inhaled nitric oxide would be more likely with prolonged therapy and concurrent high-flow oxygen, so the brief pre-operative exposure reported in this study does not provide an adequate safety assessment of inhaled nitric oxide 40 ppm. Furthermore, this study showed no dose trend for the haemodynamic effects of inhaled nitric oxide across the range of 20 ppm to 80 ppm.

Radovancevic et al, 2005;[17] assessed inhaled nitric oxide versus prostaglandin E1 in heart transplant candidates in a preoperative setting, so (like Kieler-Jensen 1994;[1]) it did not directly assess the proposed indication. Furthermore, it was small (n = 19), open-label, and it used a crossover design in which all subjects were exposed to inhaled nitric oxide 40 ppm. The crossover design provides no basis for comparing the pulmonary safety of inhaled nitric oxide with non-inhaled nitric oxide-based treatments. Also, the study did not include the main proposed dose for registration (20 ppm), so it does not address the question of whether there are efficacy advantages in increasing the inhaled nitric oxide dose from 20 ppm to 40 ppm.

The remaining parts of the sponsor's response to this question consisted of the following comments:

'The studies shown in [the table above] have shown no evidence of an increased toxicity of inhaled nitric oxide at a dose of 40 ppm. This conclusion is supported by a review by Griffiths et al., 2005[44] that cited published studies as follows:

- Although a massive overdose of inhaled nitric oxide (500 to 1000 ppm) is rapidly fatal, studies in animals have provided reassuring data indicating that nitric oxide has minimal pulmonary toxicity when it is inhaled at a concentration of less than 40 ppm for up to six months (Hugod et al., 1979;[45]).

- A Phase II US study in the indication of adult respiratory distress syndrome that was not statistically powered to demonstrate a benefit in mortality rate reported that doses of 1.25 to 40 ppm of inhaled nitric oxide were well tolerated (Dellinger et al., 1998;[46]).

Troncy et al., 1997;[47] stated that "Concentrations of inhaled nitric oxide as high as tens of ppm have been given to patients for weeks without apparent toxic pulmonary effects, and 80 ppm inhaled nitric oxide in healthy volunteers or in patients with chronic obstructive pulmonary disease did not affect airway conductance.[48]

Further evidence of the safety profile of the 40 ppm dose of inhaled nitric oxide is provided by post-marketing experience as presented in PSUR/PBRER included in the registration application. INOmax has been approved in Japan, EU and Mexico at a dosage of 20 to 40 ppm as part of the treatment of patients with peri- and post-operative pulmonary hypertension in conjunction with heart surgery, to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation.

It is estimated that 877,196 patients worldwide have been treated with inhaled nitric oxide within the dose range of the proposed labelling (20 to 40 ppm) and there have been no reports suggesting lack of efficacy or drug-related adverse events that would alter its current benefits/risk profile.

While there are relatively few studies actually comparing different doses on which a formal evaluation of appropriate dosing may be based, inhaled nitric oxide (20 to 40 ppm) has been commonly used and recommended in clinical practice since 1999.

Paediatric Pulmonary Hypertension Guidelines from the American Heart Association/American Thoracic Society;[49] states that 'inhaled nitric oxide is commonly used to treat postoperative pulmonary hypertension in patients with congenital heart disease at doses between 2 and 80 ppm.'

Evaluator's comments

As already noted, the submitted studies listed in Table 18, above, provide no clear basis for concluding that inhaled nitric oxide at a dose of 40 ppm offers benefits compared to inhaled nitric oxide at 20 ppm, and this situation has not materially changed since the Vasokinox submission. In the sponsor-initiated Study INOT41, an additional 69 subjects (who were not considered in the Vasokinox submission) have been exposed to inhaled nitric oxide 40 ppm. These subjects received inhaled nitric oxide 40 ppm without obvious toxicity, but the study was not specifically powered for a comparison of potential

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[44] Griffiths, M. and Evans, T., 2005. Inhaled nitric oxide therapy in adults. *N Engl J Med*, 2005; 353: 2683-2695
[45] Hugod C Effect of exposure to 43 ppm nitric oxide and 3.6 ppm nitrogen dioxide on rabbit lung: a light and electron microscopic study. *Int Arch Occup Environ Health* 1979; 42: 159-167
[46] Dellinger RP, et al. 1998 Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. *Crit Care Med* 1998; 26: 15-20
[47] Troncy, E. et al., 1997. Inhaled nitric oxide: clinical applications, indications, and toxicology. *Can J Anaesth*, 1997; 44: 973-988
[48] Hogman M, 1993et al. Inhalation of nitric oxide modulates adult human bronvchial tone *Am Rev Resp Dis* 1993; 148: 1474-8
[49] Abman, SH. et al., 2015. Pediatric Pulmonary Hypertension Guidelines from the American Heart Association/American Thoracic Society *Circulation* 2015. 132(21), pp. 2037-99

pulmonary side effects, and the treatment was administered to a population in whom pulmonary dysfunction would have been common and variable, making attribution difficult. Median blinded exposure was only 19 hours.

According to the sponsor, some isolated reviews and small studies (Griffiths et al, 2005[50]; Hugod et al, 1979;[45] Dellinger et al, 1998;[46] Hogman et al, 1993;[48]) have suggested that pulmonary safety with inhaled nitric oxide is acceptable, although this line of evidence is largely indirect and the sponsor's treatment of these sources was very brief (consisting only of the comments above).

Four of the references mentioned above (Hugod et al, 1979;[45] Dellinger et al, 1998;[46] Hogman et al, 1993;[48;] Abman et al, 2015;[49]) were submitted as part of the sponsor's response, and were therefore evaluated by the clinical evaluator. Griffiths et al, 2005;[50] and Troncy et al, 1997;[47] were not evaluated.[51]

Hugod et al, 1979;[45] is a very old pre-clinical paper, which assessed inhaled nitric oxide at a dose of 43 ppm, administered to six rabbits in comparison to six untreated rabbits, as described in the abstract below. No evidence of lung toxicity was observed. As the authors note, the findings were not consistent with other reported pre-clinical findings. An exploration of the differences between various pre-clinical studies is beyond the scope of this report, but it has previously been suggested that inhaled nitric oxide could produce pulmonary toxicity by oxidising to nitrogen dioxide, in conjunction with high-flow oxygen, which this study did not use. In general, once pre-clinical studies have raised concerns, a small negative pre-clinical study merely suggests that the response may be heterogeneous, and is not sufficient to allay those concerns, particularly when viewed in isolation.

Dellinger et al, 1998;[46] (n = 177) assessed inhaled nitric oxide at a range of doses up to 80 ppm in comparison to placebo, in patients with adult respiratory distress syndrome (ARDS). The authors' primary hypothesis was that inhaled nitric oxide might improve ventilation-perfusion matching, increasing blood flow to well-ventilated sections of lung, and improving oxygenation. Only a small proportion of subjects received 40 ppm (n = 27), and an even smaller proportion received 80 ppm (n = 8), with all remaining subjects receiving lower doses, as shown in the table below. Patients were treated with study drug until the end of the study, or until they achieved adequate oxygenation. The median duration of treatment was not clearly stated.

Although the sponsor reports that inhaled nitric oxide was well tolerated in this study, deaths were almost twice as common in the nitric oxide group (inhaled nitric oxide 20% versus placebo 11%), so the study is not particularly reassuring with respect to the pulmonary safety of inhaled nitric oxide. No efficacy advantages were noted for higher doses over lower doses, but the study was concerned with oxygenation rather than haemodynamic endpoints, and subjects were not specifically treated for pulmonary hypertension.

This was a Phase II study for an indication completely different to that proposed for registration, so it is only indirectly supportive of the safety of inhaled nitric oxide 40 ppm, and it does not provide any rationale for recommending a maximum dose of 40 ppm instead of 20 ppm.

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[50] Griffiths, M. & Evans, T., 2005. Inhaled nitric oxide therapy in adults. *N Engl J Med*, 353(25), pp.2683-95
[51] Clarification; the Griffiths et al, 2005 and Troncy et al, 1997 publications although provided were not reviewed by the clinical evaluator.

Table 19: Causes of acute respiratory distress disorder (ARD) by treatment group; Dellinger et al, 1998;[46]

	Placebo (n = 57)	NO Group					Pooled NO (n = 120)
		1.25 ppm (n = 22)	5 ppm (n = 34)	20 ppm (n = 29)	40 ppm (n = 27)	80 ppm (n = 8)	
Pneumonia	22 (39)	'10 (45)	17 (49)	10 (34)	13 (48)	5 (62)	55 (46)
Aspiration	11 (19)	5 (23)	8 (24)	5 (17)	3 (11)	1 (13)	22 (18)
Pulmonary contusion	5 (9)	0 (0)	1 (3)	2 (7)	2 (7)	0 (0)	5 (4)
Multiple trauma	9 (16)	2 (9)	5 (15)	4 (14)	4 (15)	0 (0)	15 (13)
Surgery	6 (11)	5 (23)	3 (9)	6 (21)	3 (11)	1 (13)	18 (15)
other	4 (6)	0 (0)	0 (0)	2 (7)	2 (7)	1 (13)	5 (4)

NO, nitric oride.
Numbers in parentheses indicate percentages.

Hogman et al, 1993;[48] performed a small study (n = 31) of acute inhaled nitric oxide exposure in subjects with and without airways disease. No direct effect on bronchial tone was observed with a dose of 80 ppm, but inhaled nitric oxide modulated the airway response to a methacholine challenge. The study did not investigate chronic exposure to inhaled nitric oxide (inhaled nitric oxide was administered for only 10 minutes), and it did not administer inhaled nitric oxide with high-flow oxygen (the inspired fraction of oxygen was only 21%), so it has limited relevance to the preclinical concerns about pulmonary toxicity.

Abman et al, 2015;[49] was the final paper submitted by the sponsor in response to this clinical question. This paper was titled 'Pediatric Pulmonary Hypertension Guidelines from the American Heart Association and American Thoracic Society', and its main purpose was to give recommendations for treatment of pulmonary hypertension in the paediatric population. The paper discusses many treatments for pulmonary hypertension, including inhaled nitric oxide, so its treatment of the relative benefits of different inhaled nitric oxide doses was brief.

In the context of treating persistent pulmonary hypertension of the newborn (PPHN), it states: 'Doses of inhaled nitric oxide > 20 ppm do not enhance oxygenation or other outcomes and will increase the risk of methaemoglobinaemia and other complications.'

In the context of post-operative pulmonary hypertension in children, which has direct relevance to the proposed indication in adults, Abman et al;[49] state: 'inhaled nitric oxide is commonly used to treat postoperative pulmonary hypertension in patients with congenital heart disease at doses between 2 and 80 ppm. Doses of inhaled nitric oxide > 20 ppm rarely have additional benefit on pulmonary hypertension, and lower doses (< 10 ppm) are useful for improving gas exchange.'

Note that the sponsor quoted the first part of this paragraph as evidence of a consensus in favour of higher doses, but not the next sentence, which suggests that there is no known benefit of higher doses, and there are reasons to suspect some advantages of lower doses (improved gas exchange). The authors merely note that the practice of using higher doses is common, not that it is appropriate. Taken in context, the very section that the sponsor has quoted in favour of a maximum dose of 40 ppm instead sounds more like a warning to keep doses lower.

Conclusion

The sponsor has not provided any evidence that inhaled nitric oxide is more effective at 40 ppm than at 20 ppm, and the studies that have been performed with this dose do not allow

a robust comparison of the relative safety of the two doses. The sponsor-initiated study, INOT41, adds 69 patients to the exposure database for inhaled nitric oxide 40 ppm, but this study was not powered for an assessment of pulmonary toxicity and it did not include a 20 ppm dose group for comparison. This study failed to show an efficacy benefit of inhaled nitric oxide 40 ppm over placebo, so it provides no support for the idea that there is a dose-response curve at the doses of interest. The only studies to compare 20 ppm and 40 ppm were small and underpowered, and they did not show superiority of the higher dose.

The additional, new references cited by the sponsor in support of higher doses do not provide evidence of superior efficacy of doses > 20 ppm. The recommendations of the American Heart Association for treatment of paediatric pulmonary hypertension do not support use of a higher dose, and the sponsor's quotation of the American Heart Association (AHA) guidelines is incomplete.

Post-marketing surveillance has not directly demonstrated major safety issues with an inhaled nitric oxide dose of 40 ppm, but it is not clear that pulmonary toxicity would be easily recognised in a population where pulmonary dysfunction is already expected to be prevalent, without an appropriate control group and a randomised, double blind, prospective methodology.

Overall, there is no clear efficacy benefit for doses of inhaled nitric oxide > 20 ppm, and the safety of higher doses has not been assessed for long enough, in enough patients, with sufficient rigour, to address non-clinical concerns.

Question 2

Why did the Efficacy section of the PI exclude mention of Study INOT41, the single-most important study assessing efficacy of inhaled nitric oxide in adults?[52]

Sponsor's response

The sponsor did not intentionally exclude the results of Study INOT41 as the proposed PI included a summary of the publication by Kukucka et al., 2011;[19] that reported on a group of 49 patients treated at one centre in Study INOT41. In view of the clinical evaluator's comments, a summary of the findings of the complete Study INOT41 is now included in the revised PI, making the inclusion of the subset study unnecessary.[19]

Evaluator's comments

The sponsor's explanation of the omission of Study INOT41 from the PI appears to be that the omission was not intentional.[53]

The sponsor acknowledged this omission and now proposes including Study INOT41 in the PI, and dropping mention of the minor substudy by Kukucka et al;[19] this seems appropriate.[54]

Second round benefit-risk assessment

The second round benefit-risk assessment is not substantially different from the first round assessment.

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[52] Clarification: The sponsor does not agree that Study INOT41 is the 'single most important study' for efficacy as the study was underpowered; it was a key study for safety findings particularly at the dose of 40 ppm
[53] Clarification: the sponsor included the published study by Kukucka, 2011 (reporting a sub-study of Study INOT41) on the basis that the Clinical Trials section of the approved PI for VasoKINOX included published study reports for the other 4 controlled studies cited.
[54] Clarification: Note: The dose of 40 ppm inhaled NO was not recommended by ACPM so the approved INOmax Product Information contains no reference to Study INOT4.

The sponsor's response to clinical Question 1 has provided a chance to revisit the issue of whether a maximum dose of 40 ppm is appropriate. There is no evidence that inhaled nitric oxide at 40 ppm is more effective than 20 ppm, so there are no known benefits of the higher dose compared to the lower dose. Because the dose-response curve has not been adequately defined, it remains possible that individual patients might show a different response to the two doses.

There is no satisfactory safety data allowing comparison of the 40 ppm dose with the 20 ppm dose, so the risks of the higher dose remain unclear. Most toxic effects known or suspected to be associated with inhaled nitric oxide are dose-related, so it is appropriate to recommend the lowest effective dose.

Compared to when the Vasokinox submission was evaluated, there is very little new information, but 69 subjects were exposed to inhaled nitric oxide 40 ppm in the sponsor initiated Study INOT41. This study was negative for its efficacy endpoints and it did not involve a control group receiving 20 ppm, so it does not provide a strong basis for preferring the 40 ppm dose over 20 ppm.

In isolated cases with refractory pulmonary hypertension, the potential risks of pulmonary toxicity with inhaled nitric oxide 40 ppm could be considered clinically acceptable, and a trial of increasing from 20 ppm to 40 ppm might be appropriate. (This is the approach taken in the EU, on the basis of the same evidence considered in this report.) The PI should make it clear, however, that such an increase is not backed by any robust trial data, that there is no evidence of a dose-response curve between 20 ppm and 40 ppm, and that exposure to higher doses might cause pulmonary inflammation. Exposure to higher doses should be limited in duration where possible. Caution in this is particularly appropriate given that other inhaled pulmonary vasodilators are available, and switching to alternative agents should be considered in refractory cases (precise recommendations on alternatives cannot be made, given the lack of robust trial data.)

VI. Pharmacovigilance findings

Summary of RMP evaluation[55]

The sponsor has applied to extend the indications of nitric oxide (INOmax) which is currently approved for the treatment of pulmonary hypertension in neonates and children as an inhaled medical gas at a concentration of 5 to 20 ppm. The current submission seeks to extend the indications to include use in adults as part of the treatment of pulmonary hypertension associated with heart surgery.

The most recently evaluated EU-RMP was version 2.0 (31 March 2014; data lock point (DLP) 31 March 2014) and ASA version 2 (6 March 2015). In support of the extended indications, the sponsor has submitted Australian RMP version 3.0 (4 April 2018; DLP 31 January 2018) and Australian RMP version 4.0; (23 October 2018; DLP 31 January 2018).

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[55] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Risk management plan

Table 20: Risk management plan

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Hypoxemia from methaemoglobinaemia	✓	–	✓	–*
	Acute cardiac failure, pulmonary oedema, circulatory collapse	✓	–	✓	–
	Rebound pulmonary hypertension	✓	–	✓	–*
Important potential risks	Airway injury	✓	–	✓	–*
	Increased bleeding time	✓	–	✓	–*
	Critical failure of the delivery system	✓	–	✓	–*
Missing information	Combined use with other vasodilators	✓	–	✓	–
	Use during pregnancy and lactation	✓	–	✓	–
	Paediatric Use < 34 gestational age for persistent pulmonary hypertension of the newborn	✓	–	✓	–
	Patients 12 to17 years treated for pulmonary hypertension in conjunction with heart surgery	✓	–	✓	–

* Sponsor has included distribution of a health care professional letter at launch of the extended indication

- No additional pharmacovigilance activities are proposed. This is acceptable for the nature of the safety concerns.

- The sponsor has amended the additional risk minimisation activity of providing an 'education pack' to health professionals to providing a 'health care professional letter' at launch of the extended indication. This is acceptable in the context of continuing to provide broader education activities on the use of the product and device.

New and outstanding recommendations from second round evaluation

There are two outstanding recommendations which should not delay any decisions regarding product registration:

- The sponsor should provide a copy of the health care professional letter to the TGA for review and approval prior to product launch. This should not delay any decisions regarding product registration.

- The sponsor is requested to provide more information on the evaluation of the additional risk minimisation activities. Measures to evaluate the effectiveness of the health care professional letter could include distribution, reach and targets for success. Measures for product/device training for the extended indication could include reach, site training frequency, pocket guide distribution, health care professional knowledge and targets for success. The sponsor should provide this information and details of how and when the evaluation findings will be reported to the TGA, prior to product launch. (See section 5.1 for additional information).

The sponsor should also commit to incorporating this information in the next updated version of the RMP, including an updated table (summary of risk minimisation activities measures) allocating these activities as additional risk minimisation activities against the appropriate safety concerns.[56]

Proposed wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

> The INOmax Australian Risk Management Plan (RMP) (version 4, dated 23 October 2018, data lock point 31 January 2018) included with submission PM-2018-00306-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

> The following wording is recommended for the PSUR requirement:

> An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

> Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

> The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

> Additional activities for compliance monitoring

The sponsor has been requested to provide the following prior to product launch:

- a copy of the health care professional letter to the TGA for review and approval; and

- more information on the evaluation of the additional risk minimisation activities and details of how and when the evaluation findings will be reported to the TGA.

The sponsor has been requested to commit to incorporating the information in the next updated version of the RMP, including an updated table (summary of risk minimisation activities measures) allocating these activities as additional risk minimisation activities against the appropriate safety concerns.

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[56] Comment: The above recommendations were addressed by the sponsor prior to approval

VII. 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

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

No new non-clinical data were included in this submission. It is noted there were concerns in previous evaluations for nitric oxide regarding pulmonary toxicity at higher doses, and specifically recommending a limitation to 20 ppm.

Clinical

The sponsor provided literature based submission and a single clinical study to support their requested extension of the indications for nitric oxide (INOmax). The evaluator found that most of the controlled studies reported in the literature component of the submission had been previously evaluated in the INOmax paediatric submission. This submission included four additional publications of controlled studies.

Pharmacology

Pharmacokinetics

The pharmacokinetics of nitric oxide has been previously described. No new literature describing the pharmacokinetics of nitric oxide was identified by the sponsor for inclusion in this submission.

Pharmacodynamics

Three studies reporting the haemodynamic effects of small numbers of patients in open-label studies were provided in the previous submission for INOmax. No new specifically pharmacodynamic studies were included in this submission however pharmacodynamic endpoints were measured in a number of the clinical studies.

Efficacy

The efficacy studies included Study INOT41 and 15 other published studies. As noted above four new publications were included in this submission and the remainder had been evaluated previously.

Study INOT41 was evaluated as supportive study in the previous submission. As noted by the clinical evaluator this was considered a supportive study in the previous submission both because of the age of patients and because the study was negative for both primary and secondary endpoints. This was a randomised, double blind, study in adults with cardiac failure and left ventricular assist device (left ventricular assist device) insertion with cardiopulmonary bypass who exhibited preoperative increased pulmonary vascular resistance (pulmonary vascular resistance) conducted in 150 patients the USA and Germany between 2003 and 2008. Patients were randomised 1:1to inhaled nitric oxide 40 ppm or matching placebo. Inclusion criteria were adult patients undergoing their first left ventricular assist device implantation or an left ventricular assist device implantation

6 months after explantation of a previous left ventricular assist device, and pulmonary vascular resistance of ≥ 2.5 Wood units (200 dynes/sec/cm[5]) in the 30 day period prior to left ventricular assist device placement. Patients were excluded if they were pregnancy, were undergoing biventricular assist device surgery or were currently using a temporary biventricular assist device, received inhaled nitric oxide within 24 hours before study onset, had cardiac failure due to giant cell myocarditis or restrictive cardiomyopathy or had other investigational drugs that could change systemic vascular resistance or pulmonary vascular resistance.

Thirteen randomised patients did not receive treatment, 35 switched to open label inhaled nitric oxide, which was allowed in the protocol after failure to respond to treatment after completing the blinded study treatment. Fifteen of the switched patients (9 placebo and 6 inhaled nitric oxide patients) had not completed the blinded period and an additional 3 inhaled nitric oxide patients switched without meeting the right ventricular dysfunction criteria.

Protocol violations were reported for 6 patients; 2 patients from each group did not have a pulmonary vascular resistance of ≥ 2.5 Wood units in the qualifying period; 1 placebo patient underwent left ventricular assist device without cardiopulmonary bypass, and 1 had received inhaled nitric oxide within 24 hours of study commencement. None of these violations were considered likely to have positively influenced the outcome.

The sample size of 55 patients per group to give an 80% power was based on the assumption of a 50% failure in the placebo group and a 25% failure in the inhaled nitric oxide group, however the failure rate in the placebo group was 15.6% and the study was underpowered.

In the inhaled nitric oxide and placebo groups, respectively, patients were of mean age 57.6 and 54.0 years, 64% and 65% male, and were predominantly of white race. There were no statistically significant differences between the groups for underlying diagnosis, left ventricular assist device type used, use of an intra-aortic balloon pump, organ dysfunction of baseline haemodynamics with the exception of pulmonary capillary wedge pressure (mean (SD) 23.0 (8.31) in the inhaled nitric oxide groups and 26.7 (9.19) in the placebo group).

Primary efficacy outcome

The primary endpoint was right ventricular failure (based on 2 or more of left ventricular flow rate index ≤ 2.0 L/min/m^{2}; administration of ≥ 20 inotropic equivalents; mean arterial pressure ≤ 55 millimetres of mercury (mmHg); central venous pressure ≥ 16 mmHg; percentage of mixed venous oxygen saturation (SvO_2) of ≤ 55%) for more than 15 minutes after the removal of cardiopulmonary bypass support or failure to wean from cardiopulmonary bypass at least once due to haemodynamic failure (but not including recommencement of cardiopulmonary bypass to correct bleeding or technical device issues); or death.

There was no difference between the two groups for treatment failure (9.6% with inhaled nitric oxide and 15.6% with placebo). Time to failure was lower in placebo (0.6 hours) versus inhaled nitric oxide (3.6 hours) but this was not statistically significant. The outcome was favourable for women but not men, however the numbers of women were small and the study was not powered for the comparison. Blood products use, the presence of myocardial infarction and gender were not significant covariates for the outcome in the logistic regression model provided as a supplementary analysis. Numerical but not statistically significant differences were seen in primary endpoint when patients were stratified by pulmonary vascular resistance index ≥ 270.5 (14.3% inhaled nitric oxide versus 71.4% placebo), although there were only 7 patients in each group. The evaluator noted patients at higher risk of failure or exhibiting early failure switched to open label inhaled nitric oxide were included in the analysis for their originally

randomised group, and that inclusion of treated patients in the placebo group for analysis may have influenced the outcome.

Secondary endpoints in hierarchical order included duration of mechanical ventilation, number of ICU days, number of patients requiring renal replacement therapy (RRT), quantity of blood products used, Day 28 survival and number of patients requiring a right ventricular assist device by Day 28. There were no statistically significant differences between the two groups for the secondary outcomes.

New literature

The previous submission included literature related to adult use in inhaled nitric oxide. The sponsor included new literature in this submission.

Kukucka et al 2011;[19] was a substudy of 47 adult patients (24 and 23 patients each from the inhaled nitric oxide and placebo groups, respectively) from Study INOT41 conducted in a single centre. The inhaled nitric oxide dosing was the same as Study INOT41. The study reported trans-oesophageal echocardiographic assessments pre- and post-operatively to assess whether inhaled nitric oxide improved right ventricular geometry. The inhaled nitric oxide group compared to the placebo group had higher baseline pulmonary vascular resistance (311 ± 35 versus 298 ± 26) and lower cardiac index (1.94 ± 0.09 versus 2.19 ± 0.12). Relative to baseline significant improvements were shown for pulmonary vascular resistance for the inhaled nitric oxide group and cardiac index, pulmonary capillary wedge pressure and mean pulmonary arterial pressure for both groups. There were no statistically significant differences between the groups for clinical outcomes. Numerically, median ventilation times were shorter in the inhaled nitric oxide group (51 hours (interquartile range 24 to 334) versus 74 hours (interquartile range 28 to 605)) but median ICU stays were longer in the inhaled nitric oxide group (17 days (interquartile range 10 to 27) versus 15 days (interquartile range 9 to 40)). Three inhaled nitric oxide and 1 placebo patients developed right ventricular failure, and the 30 day mortality was 21% (5 patients) in the inhaled nitric oxide group and 13% (3 patients) in the placebo group.

Fernandes et al 2011;[20] was an open label randomised controlled study of 29 adult cardiac surgical patients with symptomatic mitral stenosis, severe pulmonary hypertension systolic pulmonary arterial pressure > 60 mmHg) undergoing cardiac surgery, to measure baseline adjusted differences in haemodynamics and short term clinical outcome. The study compared inhaled nitric oxide 10 ppm starting immediately before weaning from cardiopulmonary bypass (n = 14) with oxygen (n = 15). Those assigned to inhaled nitric oxide were less likely to be in New York Heart Association (NYHA) functional Class II (21%, compared to 40% of those assigned to oxygen), and more likely to be NYHA functional Class III (72% versus 47%);[57] had more severe elevations of pulmonary vascular resistance (mean 341 ± 183, compared to mean 264 ± 133 in the oxygen group), and were an average of 4 years older (44 ± 11 years versus 44 ± 13 years) although the between groups differences were not statistically significant. The primary endpoints were the change in cardiac index and pulmonary vascular resistance from baseline to 48 hours. CI increased from baseline in both groups at 24 hours but was sustained at 48 hours in the inhaled nitric oxide group with a mean increase of 1.58 L/min/m^2 of (95% confidence interval (CI); 1.0 to 2.16, p < 0.0001) versus 0.4L/min/m^2 (95% CI 0.01 to 0.81 L/min/m^2, p < 0.06) in the oxygen group. Compared to baseline, pulmonary vascular resistance reductions were significant at 24 and 48 hours for the inhaled nitric oxide group only (34%, p < 0.005). Both groups showed reductions in the secondary endpoints were changes in systolic pulmonary arterial pressure, pulmonary capillary wedge pressure

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[57] NYHA functional Class II: Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea (shortness of breath). NYHA functional Class III: Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea.

without statistically significant differences between the groups. Clinical outcomes were similar between the two groups. Total ICU stay was shorter (2.0 days (interquartile range 0.25) days versus 3.0 (interquartile range 7.0) days), and the number of systemic vasoactive drugs was smaller in the inhaled nitric oxide group. There were fewer predefined complications in the inhaled nitric oxide group 29% versus 60%. The evaluator had several issues with this paper because of internal inconsistencies in the reporting and interpretation of the results by the authors.

Khan et al. 2009;[21] was a prospective, crossover study comparing inhaled nitric oxide 20 ppm and inhaled prostacyclin (20 μg/mL) in 25 adult patients (aged 59 ± 2 years) undergoing heart (n = 6) or lung (n = 19) transplant. Patients received the allocated treatment for 6 hours then, after a 30 minute washout, switched to the alternative treatment. Treatment thereafter was at the treating physician's discretion. An initial 32 patients were randomised but only those receiving the randomised therapy at 6 hours were included in the analysis (3 patients from each group withdrawn because of early haemodynamic improvement). There were no significant differences between the treatments for haemodynamic parameters, oxygenation, or 30 days survival (which was 100%). Median ICU stay was 3 days and no patient required invasive treatment to manage pulmonary hypertension or right ventricular dysfunction. The evaluator noted methodological issues with this study.

Knothe et al. 1996;[22] was a randomised study to investigate the effect of inhaled nitric oxide 30 ppm compared with conventional treatment in 10 patients undergoing valve replacement surgery requiring extracorporeal membrane oxygenation support, with a mean pulmonary arterial pressure > 25 mmHg 10 minutes after returning to conventional ventilation with 10 controls receiving standard of care. Treatment with inhaled nitric oxide for 20 minutes significantly reduced mean pulmonary arterial pressure and pulmonary vascular resistance, compared to baseline. Systemic vascular resistance increased from baseline in both groups, statistically significantly in the inhaled nitric oxide group, without a difference in cardiac index, central venous pressure, pulmonary capillary wedge pressure.

Previously evaluated literature

The evaluator reconsidered 12 studies[58] that had been submitted in the previous submission for the extension of indications for use in paediatric patients undergoing cardiac surgery as supportive studies. The studies considered by the evaluator of direct relevance to the requested indication are summarised below.

Fattouch et al. 2005

Fattouch et al. 2005;[8] was a single centre study, three way crossover study investigating inhaled nitric oxide 20 ppm, inhaled prostacyclin and IV nitroprusside (control) used in 58 patients admitted to ICU after mitral stenosis repair and pulmonary vascular resistance > 200 dynes/sec/cm[5] and/or transpulmonary pressure gradient > 10 mmHg. Study medication was given for 30 minutes with a 15 minute washout between treatments. There were reductions in pulmonary vascular resistance (45%/50%/45%), transpulmonary pressure gradient (62%/64%/44%) and in mean pulmonary arterial pressure (19%/20%/21%) in the inhaled nitric oxide/prostacyclin/nitroprusside groups. Cardiac output and stroke volume were not significantly changed in the inhaled nitric oxide group and were increased in the prostacyclin group. The evaluator found methodological issues with this paper, and uncertainties in the manner in which the results were presented.

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[58] Clarifications: Gianetti J et al 2004 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 was not included in the Delegate's overview.

Fattouch et al. 2006

Fattouch et al. 2006;[9] of very similar design, size, treatment groups, study centre to the study above found that the inhaled drug groups were more easily weaned from bypass (p = 0.04), had a shorter intubation time (p = 0.03) and a shorter ICU time (p = 0.02) compared to the IV nitroprusside group. Both inhaled agents compared to IV nitroprusside improved right ventricular ejection fraction (p < 0.05). Compared to prostacyclin inhaled nitric oxide increased in Pa02 but had a lesser reduction in pulmonary vascular resistance and pulmonary arterial pressure, but unlike inhaled nitric oxide, prostacyclin reduced systemic vascular resistance and increased heart rate and cardiac output.

Solina et al. 2000

Solina et al. 2000;[13] was a single centre, open label, randomised study comparing inhaled nitric oxide 20 ppm (n = 15) and inhaled nitric oxide 40 ppm (n = 15) with IV milrinone (n = 15) in 45 adults with preoperative pulmonary hypertension (pulmonary vascular resistance > 125 dynes/sec/cm^5 undergoing cardiac surgery with cardiopulmonary bypass. After the administration of anaesthesia, the mean pulmonary arterial pressure and pulmonary vascular resistance were significantly greater in the inhaled nitric oxide 20 ppm group but other baseline characteristics were similar. After initiation of treatment, at the termination of cardiopulmonary bypass, there were no differences in pulmonary vascular resistance, systemic vascular resistance or cardiac index. At arrival in ICU, the inhaled nitric oxide 20 ppm group had a significantly higher mean arterial pressure, and the inhaled nitric oxide 40 ppm group had a higher right ventricular ejection fraction (RVEF). The milrinone group received significantly more support of systemic blood pressure with adjuvant phenylephrine. The evaluator noted this study was not powered to show differences between the relative efficacy of the agents. Similarly, it was not powered to show differences in efficacy between the two doses of inhaled nitric oxide.

Solina et al. 2001

Solina et al. 2001;[14] was a dose-response study comparing inhaled nitric oxide 10 ppm (n = 11), 20 ppm (n = 12), 30 ppm (n = 12) and 40 ppm (n = 2) with milrinone 0.5 μg/kg/min (n = 15) in adult cardiac surgery patients aged 66 to 73 years with immediate preoperative pulmonary hypertension (PH) (pulmonary vascular resistance 125 dyne/sec/cm^5), from the separation from cardiopulmonary bypass to the arrival of the patient in ICU. The patient had similar baseline characteristics except for less fentanyl use in the 30 ppm group and more valve replacement surgeries in the milrinone and 20 ppm groups. Percentage reductions of pulmonary vascular resistance from baseline were 38% (10 ppm), 50% (20 ppm), 44% (30 ppm), 36% (40 ppm) and 58% (milrinone), and were not statistically significantly different between the groups (p = 0.86). Other haemodynamic variables were also not statistically significantly different between the groups.

Schmid et al. 1999

Schmid et al. 1999;[11] was a single centre, open label, prospective, randomised, crossover study comparing inhaled nitric oxide 40 ppm, IV prostaglandin E1 (PGE1) 0.1 μg/kg/min and IV glyceryl trinitrate (GTN) 3 to 5 μg/kg/min in 14 adults aged 25 to 76 years, with persistent pulmonary hypertension (mean pulmonary arterial pressure >30 mmHg or pulmonary vascular resistance > 300 dyne/sec/cm^5) administered in the first 24 hours after cardiac surgery (mostly for mitral valve replacement). Each treatment was administered for 15 to 20 minutes followed by a washout period of 20 minutes. Haemodynamic parameters were measured. At study completion all patients were given PGE1. Each treatment resulted in reductions in mean pulmonary arterial pressure, pulmonary vascular resistance and transpulmonary pressure gradient. PGE1 and glyceryl trinitrate significantly reduced systemic arterial pressure and systemic vascular resistance (serious hypotension occurred in 3 glyceryl trinitrate and 2 PGE1 patients). Inhaled nitric

oxide and PGE1 but not glyceryl trinitrate significantly increased cardiac index, and PGE1, but not inhaled nitric oxide or glyceryl trinitrate increased right ventricular ejection fraction. Compared to baseline no intrapulmonary shunting was demonstrated with inhaled nitric oxide but was demonstrated with PGE1 and glyceryl trinitrate. PGE1 and glyceryl trinitrate resulted in significantly less metHB compared with inhaled nitric oxide.

Winterhalter et al. 2008

Winterhalter et al. 2008;[12] was a single-centre, randomised parallel group study comparing 30 minutes of iloprost (20 µg in 2mL saline) (n = 23) and inhaled nitric oxide 20 ppm (n = 23) in adult patients, mean age 68 to 69 years, with pulmonary hypertension (mean pulmonary arterial pressure ≥ 26 mmHg) preoperatively and during weaning from cardiopulmonary bypass after cardiac surgery. Compared with baseline, both therapies significantly reduced mean pulmonary arterial pressure and pulmonary vascular resistance and significant increased cardiac output (p < 0.0001). Iloprost compared with inhaled nitric oxide had a greater reduction in pulmonary vascular resistance (p = 0.013) and mean pulmonary arterial pressure (p = 0.0006) but inhaled nitric oxide increased arterial oxygen pressure whereas iloprost reduced it (not statistically significant for between group comparison). Iloprost significantly increased heart rate and reduced systemic vascular resistance compared with baseline. The evaluator commented that this study was adequately powered.

Ardehali et al. 2001

Ardehali et al. 2001;[15] was a single centre, non-randomised study comparing inhaled nitric oxide 20 ppm in 16 consecutive adults heart transplant recipients with mean pulmonary arterial pressure ≥ 25 mmHg with 16 historical controls given standard treatment. Treatment was continued until haemodynamic stability or the cessation of mechanical ventilation. Treatment was interrupted at 6 and 12 hours to record on-treatment then discontinued for 15 minutes to measure off-treatment haemodynamics. Acute withdrawal of inhaled nitric oxide resulted in elevations of inhaled nitric oxide, significant at 6 hours. Compared with historical controls right ventricular dysfunction was much less frequent (1 patient with inhaled nitric oxide and 6 patients with standard therapy).

Radovancevic et al. 2005

Radovancevic et al. 2005;[17] compared inhaled nitric oxide and IV PGE1 in an open label, crossover study to assess the haemodynamic effects of each in 19 adult patients, aged 20 to 63 years with pulmonary hypertension (pulmonary vascular resistance of > 4 Wood units; transpulmonary pressure gradient (TPG) of > 12 mm Hg; or systolic pulmonary artery pressure of > 60 mmHg) and a mean left ventricular ejection fraction of 21 ± 4% under consideration for a heart transplant. PGE1 was administered at a dose of 0.05, 0.2 and 0.5 µg/kg/min for 10 minutes each. Inhaled nitric oxide was administered via a tight-fitting facemask in a non-rebreathing system at doses of 40, 60 and 80 ppm. Inspired oxygen concentration was kept constant, and other management was according to standard care. Transpulmonary pressure gradient reduction was significant for the higher doses of PGE1, but not the lowest of PGE1 and for all doses of inhaled nitric oxide, compared to baseline. There was no apparent dose trend for haemodynamic response across the range of 40 to 80 ppm inhaled nitric oxide. The reductions in pulmonary vascular resistance and transpulmonary pressure gradient was not significantly different for the two agents, but were numerically greater during inhaled nitric oxide treatment. A mean reduction from baseline in Systolic pulmonary arterial pressure with PGE1 of 15% compared to 8% with inhaled nitric oxide, was not statistically significant between the groups. The two groups were significantly different for changes in systemic circulation (BP, systemic vascular resistance and cardiac index).

Kieler-Jensen et al. 1994

Kieler-Jensen et al. 1994;[1] in an open label, crossover study, compared the haemodynamic effects of inhaled nitric oxide (20, 40 and 80 ppm for 10 minutes each via tight fitting face mask) with IV sodium nitroprusside and prostacyclin (PGI2) titrated to approximately 15% reduction in mean arterial pressure (but not < 60 mmHg) in 12 patients with elevated pulmonary vascular resistance (> 2.5 Wood units) undergoing diagnostic right heart catherisation preoperatively prior to heart transplant. Pulmonary vascular resistance reduced significantly from baseline (5.9 to 3.7 Wood units) during inhaled nitric oxide therapy, beginning with 20 ppm but without further reduction with inhaled nitric oxide dose escalation. Pulmonary vascular resistance returned to baseline in the second control period. Changes in transpulmonary pressure gradient were similar to pulmonary vascular resistance, but mean pulmonary arterial pressure did not change. Both IV vasodilators reduced mean arterial pressure relative to baseline (significantly different from inhaled nitric oxide). Both also reduced pulmonary vascular resistance, with PGI2 producing numerically but not statistically significantly greater reduction than inhaled nitric oxide. Compared to baseline and to inhaled nitric oxide, the IV vasodilators significantly reduced mean pulmonary arterial pressure. The pulmonary vascular resistance/systemic vascular resistance ratio was reduced with inhaled nitric oxide but not with the IV groups and the difference between sodium nitroprusside and inhaled nitric oxide was significant.

Rajek et al. 2000

Rajek et al. 2000;[16] was a randomised, double blind study that compared IV PGE1 (n = 34) and inhaled nitric oxide (n = 34) for pulmonary hypertension in adult patients undergoing orthoptic heart transplant for ischaemic or idiopathic dilated cardiomyopathy. Both treatments started 10 minutes before weaning from cardiopulmonary bypass at 8 ng/kg/min and 4 ppm respectively, and were increased as required to a maximum of 24 ng/kg/min or 24 ppm, respectively with the aim of reduction of mean pulmonary arterial pressure to < 25 mmHg. Both treatments were stopped 6 hours postoperatively. Patients were switched to alternative treatments if the mean pulmonary arterial pressure was consistently elevated on maximal treatment with the allocated therapy, and weaning from cardiopulmonary bypass was difficult because of right heart failure. Immediately after weaning from cardiopulmonary bypass, pulmonary vascular resistance in the inhaled nitric oxide group was reduced by about half and in the PGE1 group by 10%. Mean pulmonary arterial pressure was reduced by 30% and 16% in the inhaled nitric oxide and PGE1 groups, respectively. At 6 hours after surgery, pulmonary vascular resistance and mean pulmonary arterial pressure were similar in both groups but in the PGE1 group the pulmonary vascular resistance/systemic vascular resistance ratio increased by about 30% while in the inhaled nitric oxide group the ratio reduced by about 20%. Cardiac output, heart rate, mean systemic arterial pressure, right atrial pressure and pulmonary capillary wedge pressure did not differ between the groups. Six patients were switched from the PGE1 to inhaled nitric oxide because of high pulmonary vascular resistance and right ventricular failure, and by 6 hours postoperatively these parameters had shown improvement. These patients were excluded from the analysis. Weaning from cardiopulmonary bypass was successful in all inhaled nitric oxide patients. The evaluator considered this an important study given the methodological flaws of many of the other studies.

Argenziano et al. 1998

Argenziano et al. 1998;[18] was a randomised, placebo controlled study to assess the short term haemodynamic effects of inhaled nitric oxide at 20 ppm in 11 adults with a mean age of 55 years undergoing left ventricular assist device insertion with elevated pulmonary vascular resistance (mean pulmonary artery pressure >25 mm Hg and left ventricular assist device flow rate < 2.5 L/min/m^2). Non-responders at 15 minutes were switched to

alternative therapy. mean pulmonary arterial pressure, mean arterial pressure and left ventricular assist device flow were assessed. Patients randomised to inhaled nitric oxide showed a reduction in mean pulmonary arterial pressure from 35±6 mmHg to 24 ± 4 mmHg (p = 0.02) and an increase in the left ventricular assist device flow index from 1.9 ± 0.2 L/min/m^2 to 2.7 ± 0.3 L/min/m^2 (p = 0.02). Those randomised to nitrogen placebo showed no significant haemodynamic response, but subsequently responded to crossover therapy with inhaled nitric oxide, with a reduction in mean pulmonary arterial pressure from 31 ± 4 mm Hg to 22 ± 3 mm Hg (p = 0.02) and an increase in the left ventricular assist device flow index from 2.0 ± 0.2 L/min/m^2 to 2.5 ± 0.2 L/min/m^2 (p = 0.002). Inhaled nitric oxide had no effect on systemic blood pressure.

Safety

A total of 562 adult patients were exposed to any dose of inhaled nitric oxide, of whom most were exposed for < 48 hours and 150 were exposed for < 1 hour. Three hundred and twenty-seven patients were exposed to 10 to 20 ppm. One hundred and fifty-four patients were exposed to the highest requested dose of 40 ppm, including 69 patients from Study INOT41. Thirty-one patients were exposed to more than 40 ppm.

The safety events were more comprehensively reported in the clinical study report for Study INOT41 than the publications. In this study, 69 patients received blinded inhaled nitric oxide, 68 received placebo and 34 received open label inhaled nitric oxide. AEs were in similar proportions in the inhaled nitric oxide and placebo groups (26.1% and 26.5%), and 38.2% of the open label group. Of those, 8.7%/11.8%/20.6% were severe, and 13.0%/7.4%/29.4% were considered drug related. AEs leading to dose modification occurred in 4.3%/5.9%/20.6% of the blinded inhaled nitric oxide/placebo/inhaled nitric oxide open label groups, and 4.3%/5.9%/0% lead to permanent discontinuation.

In Study INOT41 the most common treatment related AEs were right ventricular failure and post-procedural haemorrhage.

SAEs in Study INOT41 occurred in 10.1%/16.2%/17.6% of the blinded inhaled nitric oxide/placebo/inhaled nitric oxide open label groups. Renal replacement therapy (14.1%/11.4%/0%), post-procedural haemorrhage (4.3%/7.4%/5.9%), right ventricular failure (4.3%/5.9%/2.9%), and pyrexia (0%/0%/11.4%) were the most common events.

Deaths occurred in 1.4%/1.5%/5.9% in Study INOT41. Of the 4 deaths in the open label group, two had been on placebo before switching to inhaled nitric oxide 40 ppm. Two deaths were attributed to right ventricular failure (RVF), and two to multiple organ failure (one with severe renal failure). Deaths were reported in a number of publications (see Table 21), but the evaluator considered, that because these patients had severe cardiac dysfunction and had been exposed to general anaesthesia and mechanical ventilation, on balance there was no evidence that inhaled nitric oxide increased the risk of death.

Table 21: Deaths reported in the published literature

(Author, year)	Centre	ID	Age	Sex	Dose	Duration	Diagnosis	Cause of Death	Meds	Pathol	Loc of Narrative
Previously evaluated published studies											
(Fattouch, et al., 2005)	Palermo	N/S	N/S (Adult)	N/S	N/A *	N/A*	Mitral valve stenosis	RVF	N/S	N/S	Death intra-operatively before receiving INOmax
(Fattouch, et al., 2005)	Palermo	N/S	N/S (Adult)	N/S	N/S	N/S	Mitral valve stenosis	Multi organ failure	N/S	N/S	Unknown whether subjects received iNOmax
(Fattouch, et al., 2005)	Palermo	N/S	N/S (Adult)	N/S	N/S	N/S	Mitral valve stenosis	Multi organ failure	N/S	N/S	
(Fattouch, et al., 2006)	Palermo	N/S	N/S (Adult)	N/S	20 ppm	N/S	Mitral valve stenosis	Right ventricular failure	N/S	N/S	
(Rajek, et al., 2000)	Vienna	N/S	N/S	N/S	4-24 ppm	6→48h	Immediately post-transplant	Systemic sepsis	N/S	N/S	Deaths occurred after the study period but within 30 days of transplantation
(Rajek, et al., 2000)	Vienna	N/S	N/S	N/S	4-24 ppm	6→48h	Immediately post-transplant	Systemic sepsis	N/S	N/S	
Published studies from 2017 literature search											
Makker et al, 2006	India	N/S	N/S (Adult)	N/S	N/S	N/S	CABG with VSD repair	Intractable venrtricular arrhythmias	N/S	N/S	Death on Day 6 post-op
Beck et al, 1999	NYC, USA	N/S	N/S (Adult)	N/S	N/S	N/S	N/S	Multisystem organ failure	N/S	N/S	
		N/S	N/S (Adult)	N/S	N/S	N/S	N/S	Multisystem organ failure	N/S	N/S	
		N/S	N/S (Adult)	N/S	N/S	N/S	N/S	Multisystem organ failure	N/S	N/S	
		N/S	N/S (Adult)	N/S	N/S	N/S	N/S	Unresponsive hypoxia	N/S	N/S	Intra-operative
		N/S	N/S (Adult)	N/S	N/S	N/S	N/S	Uncorrectable coagulopathy & bleeding	N/S	N/S	
		N/S	N/S (Adult)	N/S	N/S	N/S	N/S	Fatal pulmonary embolism	N/S	N/S	Several days post-op
Maxey 2002	USA	N/S	N/S (Adult)	N/S	N/S	N/S	CABG	Not stated	N/S	N/S	10 hrs post-operative
Girard 1993	France	N/S	61 yrs	Male	25 ppm	48 hrs	Heart transplant	Multisystem organ failure	N/S	N/S	2 days post-iNO

The safety information in the literature was limited, and mostly referred to the known effects of metHB and nitrogen dioxide production. As examples, in Schmidt et al. 1999;[11] 40 ppm for 20 minutes maximum metHB was 1.55% (median increased from 0.64% in the control group to 1.06% with inhaled nitric oxide). Nitrogen dioxide levels of 2.4 ppm (95% CI; 1.8 to 4.2) were detected with a peak of 6.4 ppm. In Ardehali et al. 2001;[15] with exposures of 20 ppm no metHB was reported and nitrogen dioxide did not exceed 0.5 ppm. In the three new controlled studies presented in this submission metHB was not reported in Fernandes et al. 2011;[20] with 10 ppm dosing, and was not reported as having been observed in Khan et al. 2009;[21] and Knothe et al. 1996;[22] with 20 ppm and 30 ppm inhaled nitric oxide dosing, respectively. Some limited safety information was found in case reports. The evaluator noted that metHB and nitrogen dioxide production are known adverse effects of inhaled nitric oxide and are covered in the current PI.

Through activation of cyclic guanosine monophosphate (cGMP), inhaled nitric oxide may have an effect on platelets, as shown in animal models, although human data are inconsistent. In Study INOT41 and in the post-marketing surveillance safety data no signals for increased bleeding or thrombocytopaenia were detected.

Inhaled nitric oxide can increase left atrial filling potentially exacerbating cardiac failure or pulmonary oedema in patients with left ventricular dysfunction. This is already mentioned in the PI.

Rebound pulmonary hypertension is a known safety concern if the withdrawal of inhaled nitric oxide is not carefully managed. This is a known safety concern with no specific signal emerging in the adult cardiac surgical population.

Post market

From the post-marketing safety data, an estimated 877,196 patients have been exposed to inhaled nitric oxide for all approved indications. Adverse events including fatal events have occurred in association with sudden disconnection of inhaled nitric oxide or delivery device malfunction. From the review of the post-marketing data the evaluator found no new safety signals.

Risk management plan

The RMP evaluator has reviewed the INOmax Australian RMP (version 4, dated 23 October 2018, data lock point 31 January 2018). A comparison of the proposed and previously approved Summary of Safety Concerns is tabulated below.

Table 22: Summary of safety concerns

Summary of safety concerns		
Submission	Current	Previous
Important identified risks	Hypoxemia from methaemoglobinaemia	Methaemoglobinemia
	Acute cardiac failure, pulmonary oedema, circulatory collapse	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 pulmonary hypertension	Rebound reactions (pulmonary hypertension) with abrupt withdrawal
Important potential risks	Airway injury	Nitrogen dioxide formation
	Increased bleeding time	Increased bleeding time
	Critical failure of the delivery system	Critical failure of the delivery system
Missing information	Combined use with other vasodilators	Combined use with other vasodilators
	Use during pregnancy and lactation	Use during pregnancy and lactation
	Paediatric Use < 34 gestational age for persistent pulmonary hypertension of the newborn	Paediatric Use < 34 gestational age for persistent pulmonary hypertension of the newborn
	Patients 12 to17 years treated for pulmonary hypertension in conjunction with heart surgery	patients 12 to17 years treated for pulmonary hypertension in conjunction with heart surgery

At the second round there were two remaining issues identified by the evaluator. These can be summarised as the provision of the sponsor's proposed communication to health care professionals regarding the new indication prior to product launch, and the provision of the details of its plan to evaluate, evaluate, and report, the effectiveness of the additional risk minimisation activities outlined in the risk management plan. The evaluator has requested the sponsor include this information in the next updated version of the RMP, and post second round, the sponsor has advised it will provide a copy of the updated RMP incorporating further information on the additional risk minimisation activities in

February 2019. The sponsor has also advised it will provide a copy of its proposed health professional communication prior to launch of the product.[59]

This product is not proposed for the Black Triangle Scheme.

Risk-benefit analysis

The evaluator has recommended the following condition of registration:

- The INOmax Australian RMP (version 4, dated 23 October 2018, data lock point 31 January 2018) included with this submission, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

The evaluator recommended the following wording as the PSUR requirement:

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

Delegate's considerations

The sponsor has provided a largely literature based submission to support its proposed extension of indications to include adults with pulmonary hypertension in cardiac surgery. This is supplemented by a single study, Study INOT41, considered of importance by the evaluator because it was the only clinical study report to provide more detailed information, particularly about safety, than a publication.

Among the publications there was considerable heterogeneity in the study design, differences in the definition of pulmonary hypertension, differences in endpoints measured, and matters of interpretation and presentation of results that, while not unusual in literature based submissions, challenge the strength of the conclusions that can be drawn. Matters of internal inconsistency within individual papers were difficult to conclusively resolve. Many papers were reporting studies more than a decade old. Generally, the studies were small and many were underpowered for the comparisons made.

The outcomes reported were predominantly haemodynamic improvement rather than the typical harder clinical endpoints such as mortality, or number of ventilator days. Nitric oxide was frequently the 'standard of care' option when investigating a new agent so, as seen in other submissions, the study hypothesis and design was not necessarily aiming to address the question of efficacy or safety specifically for inhaled nitric oxide.

Exposure to inhaled nitric oxide was variable from 10 minutes to more than 24 hours.

Patients undergoing cardiac surgery had indications including valve replacement, heart transplant and left ventricular assist device placement. A range of ages was represented including small numbers of elderly patients.

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[59] Clarification: This was provided by the sponsor prior to TGA approval.

Many of the studies included dosing in the range of 20 to 40 ppm proposed. There was no clear dose-dependent efficacy response over the range 10 to 80 ppm.

The haemodynamic effects of inhaled nitric oxide on the pulmonary circulation and the pulmonary selectivity of inhaled nitric oxide compared with other inhaled or systemic vasodilators in adult patients undergoing has been demonstrated in Study INOT41 and in the majority of the literature. Pulmonary selectivity in adults has been shown in comparison studies with systemic vasodilators. A reduction in pulmonary vascular resistance and mean pulmonary arterial pressure in a number of settings including valve replacement, heart transplant, left ventricular assist device insertion and coronary artery bypass graft compared with baseline have been shown, and overall, the body of evidence supports this understanding and is consistent with the literature supporting the use of inhaled nitric oxide in children.

An impact on right ventricular function may be extrapolated from a reduction in pulmonary vascular resistance and mean pulmonary arterial pressure but few studies included direct measurements. Improvements in oxygenation were not a key feature of the studies included, and there are issues with other factors affecting pulmonary function in the ventilated, peri-operative patient, including fluid overload making the measurements reported more difficult to interpret, particularly as many of the studies have very small patient numbers.

Study INOT41 was underpowered and had a negative outcome for inhaled nitric oxide for the prevention of right ventricular failure. As noted by the evaluator, early switching to open-label inhaled nitric oxide before reaching the formal criteria for switching has potentially influenced the outcome of this study.

Nevertheless, Study INOT41 provides the most comprehensive assessment of safety in the adult population. Limited safety information is included from literature with additional information from case reports. Overall, the known safety concerns of rebound pulmonary hypertension and the risk of pulmonary hypertensive crisis with sudden withdrawal of inhaled nitric oxide are well known and serious AEs including deaths have resulted. Monitoring for NO_2 and metHB, both of which are potentially dose related adverse effects of inhaled nitric oxide are supported by the safety information, although this is largely extrapolated from other sources and managed as a known effect in the literature. No new safety signals were derived from the review of the literature, Study INOT41 and the PSURs.

Indication

The sponsor has requested an indication for treatment of pulmonary hypertension in all patients in the setting of peri-and postoperative setting and the range of setting is noted above and would appear representative of expected use.

The indication claims to decrease in pulmonary arterial pressure, and improve right ventricular function and oxygenation, and the ACM's advice regarding the indication is sought regarding the claims in the wording for the reasons outlined below.

Across the studies pulmonary artery pressure reduction was commonly reported, with significant reductions from baseline and against inactive comparators. These reductions were seen in a range of patients groups. The collective evidence provides sufficient support for the claim of reduction in pulmonary artery pressure proposed by the sponsor for the indication in adult patients. Pulmonary selectivity was demonstrated in a number of studies against systemic vasodilators and the collective evidence is considered sufficient to support this aspect of the indication in adult patients.

A few of the adult studies included oxygenation as a specific endpoint. As examples, in Khan;[21] inhaled nitric oxide did not affect the oxygenation index, in Knothe et al.;[22] there were no important differences between the groups in oxygenation status, and oxygenation

was improved from baseline in Winterhalter et al.;[12] but there was no difference in the between group comparison. It is unclear whether sufficient direct evidence has been provided to support this claim for the indication.

Direct measurements of right ventricular function were included in only some studies: in Study INOT41 right ventricular failure was the efficacy outcome measure, however this was a negative study with only a trend for differences between inhaled nitric oxide and placebo. Knothe et al.;[22] mentions there were no changes seen in directly measured parameters for right ventricular function, Schmid et al;[11] found no change in right ventricular ejection fraction with inhaled nitric oxide and no reduction in intrapulmonary shunting, but Fattouch et al. 2006;[9] showed improvement in right ventricular ejection fraction against control. Only a small number of patients contributed data to these findings, raising a question as to whether the evidence is sufficiently robust for these claims in adult patients. Although there are indirect measures and improvement in pulmonary vascular resistance and mean pulmonary arterial pressure may be anticipated to allow improvement in right ventricular function, but the issue is whether there has been consistent demonstration across the range of studies sufficient to support this claim in the indication.

Dose

One of the main considerations for this submission is the dosing. There was not a clear efficacy dose-response relationship demonstrated in the literature for inhaled nitric oxide.

In adults the sponsor proposes a starting dose of 20 ppm, in contrast to the 10 ppm for children. The majority of the studies in the submission have a commencing dose of 20 ppm with some including Study INOT41 starting at 40 ppm. Solina et al. 2001;[14] showed a post-baseline 38% reduction in pulmonary vascular resistance with inhaled nitric oxide 10 ppm. In that study there was no placebo group for comparison to assess whether this is reflected an expected improvement in pulmonary vascular resistance off cardiopulmonary bypass. Also, in Fernandes et al.;[20], although the evaluator took issue with the reporting of some of the results there was agreement of a significant post baseline improvement in pulmonary vascular resistance and that is reached statistical significant over placebo oxygen at 48 hours. As such, there may be a case for commencing at 10 ppm with upward titration if there is not a rapid response.

The major concern is the maximum dose. In this submission there are new data describing the use of inhaled nitric oxide at 40 ppm, particularly from Study INOT41 that provided 69 additional patients to the safety set from the literature for this dose. In this submission 154 patients were exposed to a dose of 40 ppm, including the 69 patients in Study INOT41.

There is a concern from nonclinical data the regarding possible pulmonary toxicity, in particular with doses over 20 ppm. A literature based submission limits the detail of the safety analysis to that reported in the publications and it is possible that lack of response attributed to other factors may have been related in part to pulmonary toxicity. There is no direct evidence to support this concern although none of the publications have addressed this question specifically.

In some studies, consequences of higher doses included metHB and increases in nitrogen dioxide, however these effects were not found in all studies of 40 ppm dosing, and in other studies were reported for lower doses.

Efficacy data to support the 40 ppm dose was mixed. For example, Solina et al. 2000;[13] showed improvement in right ventricular ejection fraction by the time of ICU arrival with 40 ppm over 20 ppm and milrinone but the dose was not different from the 20 ppm and milrinone comparators for the many other haemodynamic parameters measured. Efficacy (events of right ventricular failure) was also not demonstrated for 40 ppm in Study INOT41. However, Solina et al. 2001;[14] did not show benefit for pulmonary vascular

resistance reduction between the 20 ppm (50% reduction) and the 40 ppm (36% reduction) dosing groups.

The sponsor proposes, in response to the recommendations of the clinical evaluator, that although the general maximum dose is 20 ppm, under exceptional and in infrequent circumstances for patients with refractory pulmonary hypertension a dose of 40 ppm could be considered, there is limited direct evidence of use of this dose as rescue therapy. The advice of the Advisory Committee on Medicines (ACM) is sought on the adequacy of the evidence to support the 40 ppm maximum dosing as requested by the sponsor, and whether the starting dose should be the same as for children.

Data deficiencies

This is predominantly a literature based submission. Limitations of such submissions include publication bias, although with the number of negative studies presented this seems not to be an issue, inconsistent definition of the condition treated and the measurement of the endpoints used. Generally, with a literature based submission the evaluator is unable to ask further questions of the data or seek clarification regarding the results or conclusions drawn. Some of the literature is over two decades old. Standard of care, and other confounders such as patient selection for surgery, surgical and anaesthetic techniques have evolved over time, limiting the generalisability of some of these studies. While some residual uncertainty could be resolved with a large contemporary study this is unlikely to be conducted.

There are limited data on the use in pregnancy or lactating patients. Because of other risks of cardiac surgery in pregnancy it is expected that such data may be difficult to interpret.

Special populations

No new paediatric data were included however because the indication extension was specifically for adults this was noted but not considered a specific deficiency in the submission.

Conclusion

These types of submissions for indications in small patient groups in settings of off-label use over decades can be challenging when applying contemporary evidentiary standards. This submission has included a number of publications where methodological issues or lack of clarity or inconsistency in the report of results have limited the conclusions that can be drawn. Many of the studies were not designed to address the clinical efficacy of inhaled nitric oxide using hard clinical endpoints but were designed to address the utility of inhaled nitric oxide and other therapies for the short term modification of haemodynamic endpoints relating to the pulmonary vasculature.

The interpretation of the data and the contribution of each study to the overall understanding of the place of inhaled nitric oxide in peri-and post-operative cardiac surgical management takes into account, decades of use off-label, and to some extent extrapolation from knowledge in the paediatric data. Some reassurance of the similarity of the effects on the pulmonary vasculature has been demonstrated including a consistent reduction in mean pulmonary arterial pressure and pulmonary vascular resistance across broad patient groups. Data are less robust to demonstrate direct improvements in right ventricular function although it could be argued that a reduction in pulmonary vascular resistance should result in improved right ventricular ejection fraction.

Overall, and on balance, taking into consideration the evidence presented in the submission notwithstanding its limitations, decades of use internationally either approved or off-label in adults, and the proposal that use of inhaled nitric oxide is restricted to situations directly supervised by specialists experienced in managing the complexities of patient in the peri-and postoperative surgical environment, the preliminary conclusion is

favourable for inhaled nitric oxide for the proposed use. However, the advice of the ACM is sought regarding dosing and some aspects of the wording of the indication.

Summary of issues

- Whether there is sufficient evidence to support all the elements of the wording of the requested indication as it applies to adults. In particular, whether there is sufficient direct evidence of improvement in right ventricular function and oxygenation to support the claims.

- Whether sufficient evidence has been presented to support the efficacy and safety of 40 ppm as the maximum dose for adults, in the dosing regimen proposed.

- Whether the adult dosing regimen should commence with inhaled nitric oxide 10 ppm.

Conditions of registration

The following is the proposed condition of registration for nitric oxide:

> The INOmax Australian RMP (version 4, dated 23 October 2018, data lock point 31 January 2018) included with this submission, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

> An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

> Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

> The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

Questions for sponsor

1. The clinical evaluator has noted an estimate of the total of patients exposed to inhaled nitric oxide. If possible, please provide an estimate of the exposure in adults in the post-market setting. How do the adverse events differ by age?

2. Please provide an estimate of the number of patients aged > 70 years and > 80 years were included in the literature and in the safety information in the post-market setting?

3. The sponsor has included an upper limit of mean exposure to nitric oxide for personnel in the PI? Please advise whether this exposure limit is consistent with current Australian legislation.

Proposed action

The Delegate has no reason to say, at this time, that the application for nitric oxide (INOmax) should not be approved. The wording of the indication is an issue for which the ACM's advice is sought.

Request for ACM advice

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

1. Has sufficient evidence been provided to support the claim of treatment of pulmonary hypertension in adult patients undergoing cardiac surgery, or should the indication be limited to haemodynamic effects?

2. Has sufficient evidence been provided to support the proposed maximum 40 ppm dosing in adults? Should adult dosing commence at 10 ppm?

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

Question 1: Has sufficient evidence been provided to support the claim of treatment of pulmonary hypertension in adult patients undergoing cardiac surgery, or should the indication be limited to haemodynamic effects?

The sponsor believes that sufficient evidence has been provided to demonstrate efficacy and safety of INOmax for the treatment of pulmonary hypertension in adult patients undergoing cardiac surgery and therefore the indication should not be limited to haemodynamic effects only. The wording of the proposed indication is in line with the EU indication approved in 2011, current off-label clinical practice in Australia and the clinical data submitted in this application.

The clinical data consist of sponsor Study INOT41 and a number of published randomised clinical trials. Since the majority of randomised clinical trials submitted have been conducted as independent trials, they are heterogeneous with regard to populations, endpoints, control treatments, and when in the peri-operative course treatment has been implemented. Also the duration of inhaled nitric oxide administration varies from short term exposures to treatment lasting for several days. The limited size (usually 10 to 35 patients) published studies have focused on haemodynamic endpoints such as the rapid and selective effects of inhaled nitric oxide on pulmonary vascular resistance (pulmonary vascular resistance) and pulmonary arterial hypertension and oxygenation saturation. High pulmonary pressure interferes with clinical management of the patient and is a recognised marker for poor prognosis and increased morbidity and mortality.[60]

Studies investigating clinical endpoints such as the occurrence of pulmonary hypertensive crises and right ventricular failure generally require larger patient numbers to have sufficient statistical power. Still, a number of the presented studies (Study INOT41, Fattouch 2006;[9] Fernandes 2011;[20] Rajek, 2000;[16]) have shown statistically significant effects of INOmax ($p < 0.05$) for clinical endpoints such as pulmonary hypertensive crises, time to extubation, weaning rate, time in ICU, reduced use of systemic vasoactive agents.

The wording of the sponsor's proposed indication for treatment of pulmonary hypertension in adults undergoing cardiac surgery is supported by International Clinical Guidelines as follows:

- EU consensus for inhaled nitric oxide use;[61] states: 'Clinical experience suggests that in patients with confirmed right ventricular dysfunction and elevated pulmonary vascular resistance, use of inhaled nitric oxide may result in haemodynamic improvement when used during or after cardiac surgery.'

- American College of Cardiology Foundation/ American Heart Association Guidelines advocate inhaled nitric oxide as an effective short-term therapy for pulmonary

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[60] Hoskote A et al., Acute right ventricular failure after pediatric cardiac transplant: predictors and long-term outcome in current era of transplantation medicine, *J Thorac Cardiovasc Surg*. 2010; 139: 146-153.
[61] Germann et al. 2005 Inhaled nitric oxide therapy in adults: European expert recommendations, *Intensive Care Med*. 2005; 31:1029-1041

hypertension in conjunction with heart surgery: 'On balance, inhaled nitric oxide is an effective short-term strategy for the management of PH following cardiac surgery'.[62]

For the registered paediatric cardiac surgery indication based on similar standard of clinical data, TGA approved the following wording, consistent with the current proposal for the adult indication:

- as part of the treatment of peri- and post-operative pulmonary hypertension in newborn infants, infants and toddlers, children and adolescents, ages 0 to17 years in conjunction with heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation.

Question 2: Has sufficient evidence been provided to support the proposed maximum 40 ppm dosing in adults: Should adult dosing commence at 10 ppm?

The sponsor believes that the recommendations for the initial adult dose of 20 ppm to a maximum of 40 ppm only in those patients refractory to lower doses is supported by the doses used in Study INOT41 and the published literature as summarised in Table 23. Other published studies used starting doses ranging from 4 to 5 ppm titrated to 20 to 25 ppm or investigated dose comparisons of various combinations of 10, 20, 30, 40, 60 or 80 ppm. In terms of the safety of 40 ppm as a maximum dose in refractory patients, Study INOT41 in a total of 150 patients treated with 40 ppm inhaled nitric oxide or placebo showed no safety concerns, including no evidence of potential pulmonary toxicity, even though the primary efficacy outcomes were not met in this study.

Table 23: Starting dose of inhaled nitric oxide in published clinical studies in adult cardiac surgery

Publication	Total no. patients	Initial dose inhaled nitric oxide
Fernandes 2011;[20]	14	10 ppm
Khan 2009;[21] Razzaq 2009;[31] Beck 1999;[35] MacDonald 1998;[33] Maxey 2002;[38] Fattouch 2005*;[8] Fattouch 2006*;[9] Winterhalter 2008*;[12] Argenziano 1998*;[18] Ardehali 2001*;[15]	195	20 ppm
Knothe 1996;[22]	10	30 ppm
Kukucka 2011;[19] Schmid 2009;[11]	38	40 ppm

* previously evaluated by TGA

INOmax has been approved for the adult cardiac surgery indication in the EU since 2011 and the EU SmPC provides the same dosing recommendations for adults as the proposed Australian PI. In addition, the wording of the proposed PI provides further control over safe dosing, monitoring and weaning of INOmax by limiting prescription of the drug to specialist physicians experienced in cardiothoracic anaesthesia and intensive care.

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[62] McLaughlin, V. et al., 2009. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association. *J Am Coll Cardiol*, 2009; 53: 1573-1619

Conditions of registration

The sponsor provides an assurance that the Australian RMP version 4.0 (dated 23 October 2018) and any future updates will be implemented post-approval. PSURs will be submitted for not less than 3 years from date of approval and follow a time schedule based on TGA requirements rather than the EU PSUR schedule, as Ikaria Pty Ltd is not the EU sponsor for INOmax (Linde Healthcare AB).

Specific questions

1.   The clinical evaluation has noted an estimate of the total of patients exposed to inhaled nitric oxide. If possible, please provide an estimate of the exposure in adults in the post-market setting. How do the adverse events differ by age?

Sponsor response

Data about the drug exposure in adults in the post-market setting is not available. Data in relation to age was available by either recorded patient age or recorded age group (either newborn infants, child, adolescent, infant / toddler for age group 0 to17 years or adult, elderly for age group > 17 years). Therefore, the provided percentage of the events (Table 24) was calculated on the total numbers of events of the respective age group and not on the drug exposure. On the first view, the comparison of adverse events related to a specific age group shows notable differences in following System Organ Classes (SOC):

- Injury, poisoning and procedural complications: 25.05% in the adult group versus 4.58% in the age group of 0 to17 years.

- Respiratory, thoracic and mediastinal disorders: 7.46% in the adult group versus 17.19% in the age group of 0 to17 years.

Table 24: Number and % of adverse events by system organ class by age group

System Organ Class	Group 0 – 17 years		Group > 17 years	
	No. of AEs	% AEs	No. of AEs	% AEs
Blood and lymphatic system disorders	22	3.15%	6	1.15%
Cardiac disorders	120	17.19%	94	17.97%
Congenital, familial and genetic disorders	28	4.01%		
Eye disorders	3	0.43%	1	0.19%
Gastrointestinal disorders	2	0.29%	5	0.96%
General disorders & administration site conditions	143	20.49%	109	20.84%
Immune system disorders	1	0.14%	2	0.38%
Infections and infestations	29	4.15%	14	2.68%
Injury, poisoning and procedural complications	32	4.58%	131	25.05%
Investigations	125	17.91%	60	11.47%
Metabolism and nutrition disorders	4	0.57%		
Neoplasms benign, malignant and unspecified	1	0.14%	2	0.38%
Nervous system disorders	24	3.44%	25	4.78%
Pregnancy, puerperium and perinatal conditions	9	1.29%		
Product issues	16	2.29%	9	1.72%
Renal and urinary disorders	2	0.29%	3	0.57%
Respiratory, thoracic and mediastinal disorders	120	17.19%	39	7.46%
Skin and subcutaneous tissue disorders	1	0.14%	1	0.19%
Skin discolouration	1	0.14%	1	0.19%
Surgical and medical procedures	9	1.29%	15	2.87%
Vascular disorders	7	1.00%	6	1.15%
Total	**698**		**523**	

For Injury, poisoning and procedural complications in the adult group: 19.88% of events in the adult population are driven by the following Preferred Terms (PTs): accidental exposure to product (6.69%), occupational exposure to product (6.88%) and off label use (6.31%). These PTs are not adverse events according to the International Council for Harmonisation (ICH) definition. Therefore, these terms do not indicate per se a higher risk in the adult population. When disregarding these events both age groups seem to be comparable.

For Respiratory, thoracic and mediastinal disorders: 8.60% of the events in the paediatric group are driven by the following PTs: hypoxia (2.44%), neonatal respiratory failure (2.01%) and pulmonary haemorrhage (4.15%). It has to be noted that the target population for the approved paediatric indication is prone to experience such events because of their medical condition (for example, premature birth). Therefore, this could be an explanation of the observed discrepancy between the age groups, which is in favour of the proposed adult target population.

In summary, it can be concluded that except for respiratory disorders, the pattern of adverse events in the adult age group are comparable to the pattern of adverse events in the paediatric age group. The discrepancy that is seen in the SOC Respiratory, thoracic and mediastinal disorders favours the adult age group and is most probably related to medical condition of the paediatric patients.

2. Please provide an estimate of the number of patients aged >70 years and > 80 years were included in the literature and in the safety information in the post-market setting?

Published literature

A review of the published literature for the adult indication of cardiac surgery has indicated that the majority of publications provide only a mean age for patients studied, with no individual patient data available to identify patients aged over 70 or 80 years. The mean age of INOmax treated patients in the published studies evaluated by the TGA in the current application is listed in Table 25, indicating a mean age range of 48 to 64 years. Previously evaluated studies reported similar mean age values.

Table 25: Mean age of patients treated in published studies in adult cardiac surgery

Publication	No. inhaled nitric oxide patients	Age: Mean ± SD (y)
Kukucka 2011;[19]	24	56 ± 10
Fernandes 2011;[20]	14	48 ± 11
Khan 2009;[21]	14	59 ± 2
Elahi 2009;[37]	15	62 ± 4.5
Razzaq 2009;[31]	30	30.4 ± 8.9
Makker 2006;[32]	14	58.5 ± 9.0
Beck 1999;[35]	34	59.1 ± 1.6
MacDonald 1998;[33]	7	Range 19 to 64
Fullerton 1996;[36]	20	57 ± 6
Kieler-Jensen 1995;[34]	13	Range 18 to 59
McGinn 2016;[39]	49	63 ± 16
Maxey 2002;[38]	17	64

The following published studies provide data on a small number of patients aged over 70 years:

- Knothe 1996;[22] (n = 20) reported 4 patients over 70 years and 1 patient over 80 years

- Schmid 1999;[11] (n = 14) reported 1 patient over 70 years

- Solina 2000;[13] (n = 30) reported mean ages of 73 ± 11 years (20 ppm group) and 62 ± 15 years (40 ppm group)

- Solina 2001;[14] (n = 47) reported mean ages of 68 ± 6 y (10ppm); 70 ± 12 years (20 ppm); 73 ± 10 years (30 ppm) and 69 ± 10 years (40 ppm)

Study INOT41

In the sponsor initiated randomized, placebo controlled Study INOT41, the mean age was reported as 57.6 ± 9.75 and 54.0 ± 11.95 years, for 73 inhaled nitric oxide-treated and 77 placebo treated patients respectively. Study Report for INOT41 indicated that 14 of 150 (1.5%) patients were aged over 70 years and no patient was over 80 years.

Post-marketing safety database

The post-marketing experience (excluding data from clinical trials) includes a total of 30 cases with patients aged > 70 years and 7 cases with patients aged > 80 years.

3.   The sponsor has included an upper limit of mean exposure to NO for personnel in the PI? Please advise whether this exposure limit is consistent with Australian legislation.

The Safe Work Australia Workplace Exposure Standards for Airborne Contaminants (dated 27 April 2018) provide 8 Hour Time-Weighted Average (TWA) values for Nitric oxide of 25 ppm or 31 mg/m^{3}. The environmental build-up of nitric oxide in a well-ventilated ICU room can be evaluated using the calculation below.

Table 26: Environmental build-up of nitric oxide for DSIR (delivery system)

Room size	10 ft square (approx. 3 meters)
Room volume of air	27,000 L
Room ventilation at 6 room changes/hour	2,700 L/min
NO flow into the room	14 L/min at 80 ppm
Average room concentration of NO (80 x 14 / 2,700)	0.4 ppm of NO

Table 27: Environmental build-up of nitric oxide for DSIR Plus and DSIR Plus MRI (delivery system)

Room size	1000 ft^3
Room volume of air	28,300 L
Room ventilation at 6 room changes/hour	2,830 L/min
NO flow into the room	80 ppm at 14 L/min
Average room concentration of NO (80 x 14) ÷ 2,830 = 0.396 ppm	0.4 ppm of NO

This theoretic calculation can be supplemented by measurements as performed by Hess et al, 1996[63]. The nitric oxide and nitrogen dioxide concentrations were measured using a chemiluminescence analyser when 100 ppm of nitric oxide at 8 L/min was delivered into a room with no scavenging being used. The maximum nitric oxide and nitrogen dioxide concentrations measured over a one hour period were 0.12 ppm of nitric oxide and 0.03 ppm of nitrogen dioxide. Both these methods show that the exposure levels are

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[63] Hess D., et al, 1996 Use of inhaled nitric oxide in patients with acute respiratory distress syndrome. *Respiratory Care*, 41(5): 424-446

significantly less than the levels recommended by the Safe Work Australia Workplace Exposure Standards for Airborne Contaminants.

Point of clarification

The TGA Delegate's Summary states that 'The sponsor has no plans [sic] make a similar application with USA or Canada.' The sponsor would like to clarify the registration plan for these two regions:

USA: Due to recent US legislation exploring the use of real world data in FDA applications, the sponsor is planning to submit a meeting request to the FDA to discuss the appropriate use of such data to expand the currently approved INOmax indication to include the cardiac surgery indication.

Canada: The sponsor plans make a submission to Health Canada in Q4 2019 in order to expand the currently approved INOmax indication to include the cardiac surgery indication.

Conclusion

The Delegate's Overview states 'interpretation of the data and the contribution of each study to the overall understanding of the place of inhaled nitric oxide in peri-and post-operative cardiac surgical management takes into account decades of use off-label, and to some extent extrapolation from knowledge in the paediatric data. Some reassurance of the similarity of the effects on the pulmonary vasculature has been demonstrated including a consistent reduction in mean pulmonary arterial pressure and pulmonary vascular resistance across broad patient groups. Data are less robust to demonstrate direct improvements in right ventricular function although it could be argued that a reduction in pulmonary vascular resistance should result in improved right ventricular ejection fraction.'

The Delegate concludes 'Overall, and on balance, taking into consideration the evidence presented in the submission notwithstanding its limitations, decades of use internationally either approved or off-label in adults, and the proposal that use of inhaled nitric oxide is restricted to situations directly supervised by specialists experienced in managing the complexities of patient in the peri- and postoperative surgical environment, the preliminary conclusion is favourable for inhaled nitric oxide for the proposed use'.

The sponsor has presented the above justifications to support:

- retention of the wording of the indication as proposed by the sponsor; and
- minimum and maximum dosing recommendations in line with published data and worldwide clinical experience in the adult population.

Advisory Committee Considerations[64]

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

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[64] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

The ACM, taking into account the submitted evidence of efficacy and safety, agreed that INOmax medicinal gas containing nitric oxide 800 ppm for inhalation, starting dose for adults (over 17 years) of 10 ppm inhaled gas and increasing up to 20 ppm if required, has an overall positive benefit-risk profile for the indication:

> *to selectively decrease pulmonary arterial pressure in patients with perioperative pulmonary hypertension in conjunction with heart surgery.*

In providing this advice the ACM noted that:

- The two currently approved indications for INOmax are:

  - *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 to17 years in conjunction with heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation.*

- The sponsor is seeking to expand the peri and post-operative indication to an adult setting as follows: '*as part of the treatment of peri- and post-operative pulmonary hypertension in conjunction with heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation*'.

- The requested extension of indication also includes a proposed higher dosing in adults, up to 40 ppm, as opposed to the currently approved 20 ppm limit in paediatric use.

- In 2017, a similar product, Vasokinox, was registered with the following indication '*to selectively decrease pulmonary arterial pressure in patients with perioperative pulmonary hypertension in conjunction with heart surgery*'. Dosage up to 20ppm is approved for this product.

- Evidence supplied by the sponsor was not considered to show any benefit in higher doses up to 40 ppm of nitric oxide and, additionally, higher doses would result in an increased risk of adverse outcomes. Accordingly, the ACM was of the view that the upper limit for INOmax dosing should be restricted to 20 ppm, consistent with the maximum dosage for Vasokinox.

- As the evidence supplied by the sponsor was not considered to show consistent significant improvements in oxygenation or right ventricular function, the ACM was of the view that reference to these outcomes be removed from the proposed indication.

Proposed conditions of registration

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

Specific advice

1. Has sufficient evidence been provided to support the claim of treatment of pulmonary hypertension in adult patients undergoing cardiac surgery, or should the indication be limited to haemodynamic effects?

The ACM was of the view that there was not sufficient evidence provided to support a specific reference to improvements to right ventricular function and oxygenation and suggested that the indication be limited to decreasing pulmonary arterial pressure, consistent with the approved indication for Vasokinox.

The ACM also noted that, while evidence for the use of nitric oxide in adults is sparse generally, there is already significant off-label use occurring, and so approved indications

with increased associated pharmacovigilance would provide an opportunity to gather better data about real-world outcomes.

2. Has sufficient evidence been provided to support the proposed maximum 40 ppm dosing in adults? Should adult dosing commence at 10 ppm?

The ACM was of the view that sufficient evidence had not been provided to support increased dosing to 40 ppm for adults and therefore the approved upper limit should be maintained at 20 ppm. The ACM agreed 10 ppm was an appropriate starting dose for use in adults.

3. 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.

The ACM noted that the PI for INOmax currently describes the use of methylene blue as a reversal agent for elevated methaemoglobinaemia at levels of 2.5 % and 5 %. The Committee considered that this may be problematic for several reasons:

- methylene blue can negatively interact with other medications likely to be in use in these settings, such as phosphodiesterase inhibitors, which could result in a worse patient outcome than elevated methaemoglobinaemia

- the levels of methaemaglobinaemia described are not particularly high and would in practice more likely be managed through titration of nitric oxide dosing, rather than with a reversal agent

- elevated methaemoglobinaemia (for example, 10 % or above) should more accurately be considered a failure of treatment and/or monitoring and alternative treatment for the pulmonary hypertension should be considered.

The ACM therefore advised that the PI relating to use of methylene blue should be revised or removed.

The ACM 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, the registration of INOmax nitric oxide 800 ppm medicinal gas for inhalation was approved for:

- *to selectively decrease pulmonary arterial pressure in patients with perioperative pulmonary hypertension in conjunction with heart surgery.*

The full indications are:

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.*

- *to selectively decrease pulmonary arterial pressure in patients with perioperative pulmonary hypertension in conjunction with heart surgery.*

Specific conditions of registration applying to these goods

The following is the proposed condition of registration for nitric oxide:

- The INOmax Australian RMP (version 4, dated 23 October 2018, data lock point 31 January 2018) included with this submission, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

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>.

Therapeutic Goods Administration