Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Nitric oxide

Proprietary Product Name: VasoKINOX

Sponsor: Air Liquide Healthcare Pty Ltd

January 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

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

Contents

Common abbreviations

Abbreviation	Meaning
ACPM	Australian Committee on Prescription Medicines
ACPM	Advisory Committee on Prescription Medicines
ADEC	Australian Drug Evaluation Committee
ALSI	Air Liquide Santé International
ARDS	Acute Respiratory Distress Syndrome
ASA	Australian Specific Annex
cGMP	Cyclic guanosine monophosphate
CHD	Congenital heart disease
CMI	Consumer Medicines Information
CPB	Cardiopulmonary bypass surgery
CVP	Central venous pressure
ECMO	Extracorporeal membrane oxygenation
EEG	Electroencephalogram
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FiO_2	Fraction of inspired oxygen
GTN	Glyceryl trinitrate
Hb	Haemoglobin
HV	Healthy volunteer
ICU	Intensive care unit
iNO	Inhaled nitric oxide
IQR	Interquartile range
IV	Intravenous

Abbreviation	Meaning
kPa	Kilopascal
LVAD	Left ventricular assist device
M(S)AP	Mean (systemic) arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
metHb	Methaemoglobin
MHRE	Maximum Human Recommended Exposure
Mil	Milrinone
mmHg	Millimetres of mercury
mPAP	Mean pulmonary artery pressure
N_2	Nitrogen (gas)
NO	Nitric oxide
NOAEL	No observable adverse event level
NOEL	No observable effect level
PaO_2	Partial pressure of oxygen
PaO_2:FiO_2	Ratio of partial pressure arterial oxygen and fraction of inspired oxygen
PAP	Pulmonary arterial pressure
PCWP	Capillary wedge pressure
PD	Pharmacodynamic
PDE	Phosphodiesterase
PGE1	Prostaglandin E1
Ph.Eur.	European Pharmacopoeia
PHT	Pulmonary hypertension
PHTC	Pulmonary hypertensive crisis
PHTC	Pulmonary hypertensive crises
PI	Product information

Abbreviation	Meaning
PK	Pharmacokinetic
PND	Postnatal Day
PPHN	Persistent pulmonary hypertension of the newborn
ppm	Parts per million
PSUR	Periodic Safety Update Report
PVR	Pulmonary vascular resistance
PVRI	Pulmonary vascular resistance index
QS	Quantum statis
RCH	Royal Children's Hospital (Melbourne)
RMP	Risk Management Plan
RVEF	Right ventricular ejection fraction
SAE	Serious adverse event
SAP	Systemic arterial pressure
SBP	Systemic blood pressure
sGC	Soluble guanylate cyclase
SPC	Summary of Product Characteristics
TAU	Temporary Authorisation for Use
TGA	Therapeutic Goods Administration
TPG	Transpulmonary pressure gradient
UK	United Kingdom
$\dot{V}/\dot{Q}$	Ventilation-perfusion
VF	Ventricular fibrillation

I. Introduction to product submission

Submission details

Type of submission:	Major variation; Extension of indications and new strength
Decision:	Approved
Date of decision:	18 March 2016
Date of entry onto ARTG	16 January 2017
Active ingredient:	Nitric oxide
Product name:	VasoKINOX
Sponsor's name and address:	Air Liquide Australia Limited 380 St. Kilda Road Royal Domain Centre Melbourne, Victoria 3004
Dose form:	Medical gas
Strength:	450 ppm mol/mol
Container:	Compressed gas aluminium cylinder
Pack sizes:	5; 11; and 20 L
Approved therapeutic use:	*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*
Route of administration:	Inhalation
Dosage:	See Product Information for details
ARTG number :	235184

Product background

This AusPAR describes the application by Air Liquide Australia Limited (the sponsor)[1] to extend the indications for nitric oxide and register a new strength of nitric oxide as VasoKINOX, nitric oxide gas in cylinders containing 450 parts per million (ppm) mol/mol. The initial proposed indication was as follows:

1 Subsequent to registration the sponsor for VasoKINOX has changed to Air Liquide Healthcare Pty Ltd Locked Bag 1008 Rosebery NSW 1445

'*VasoKINOX is indicated in conjunction with ventilatory support and other appropriate active substances for the treatment of perioperative pulmonary hypertension in adults and newborn infants, infants and toddlers, children and adolescents, ages 0-17 years in conjunction to heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation by increasing the pulmonary flow.*'

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

After diffusing into the blood, NO is scavenged by haemoglobin with the resulting oxidation of haem ferrous iron to the ferric form, rapid chemical inactivation of NO and the formation of methaemoglobin.

Pulmonary hypertension is defined as a mean pulmonary artery pressure (mPAP) > 25 mmHg, a normal capillary wedge pressure (PCWP) and increased pulmonary vascular resistance (PVR). It has been argued that pulmonary hypertension is present if the ratio of mPAP to mean systemic arterial pressure (MAP) is > 0.4, or > 0.5 for children with congenital cardiovascular disease undergoing surgical repair.[2] Pulmonary hypertensive crises (PHTCs) are life-threatening events characterised by a rapid increase in PVR to the point where pulmonary arterial pressure (PAP) exceeds the systemic blood pressure (SBP). The resulting right heart failure leads to a decrease in pulmonary blood flow, decreased cardiac output, hypoxia and biventricular failure. Without treatment these crises result in rapid cardiovascular collapse and death.

Regulatory status

VasoKINOX is not currently registered in Australia; however nitric oxide (by a different sponsor) is currently registered as a medicinal gas in cylinders containing 800 ppm.

Nitric oxide has been previously registered (in Australia), the current ARTG entry for nitric oxide is as follows:

Table 1: Registration details for nitric oxide at the time of the submission

Drug	Formulation	Indications
Nitric Oxide (INOmax)	Medicinal gas 800ppm	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. as part of the treatment of peri- and post-operative pulmonary hypertension in newborn infants, infants and toddlers, children and adolescents, ages 0-17 years in conjunction with heart surgery, in order to selectively

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

Drug	Formulation	Indications
		decrease pulmonary arterial pressure and improve right ventricular function and oxygenation.

At the time period when TGA considered this application, a similar application had been approved in a number of member states of the European Union (EU). The indication in a number of EU member states is:

> *'VasoKINOX is indicated in conjunction with ventilator support and other appropriate active substances 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.*
> *Perioperative pulmonary hypertension in adults and newborn infants, infants and toddlers, children and adolescents, ages 0-17 years in conjunction to heart surgery, in order to selectively decrease pulmonary arterial pressure and improve left ventricular function and oxygenation by increasing the pulmonary flow.'*

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 Timeline

Table 2: Registration timeline

Description	Date
Submission dossier accepted and 1st round evaluation commenced	31 March 2015
1st round evaluation completed	11 September 2015
Sponsor provides responses on questions raised in 1st round evaluation	31 October 2015
2nd round evaluation completed	30 November 2015
Delegate's overall risk-benefit assessment and request for Advisory Committee advice	4 January 2016
Sponsor's pre-Advisory Committee meeting response	18 January 2016
Advisory Committee meeting	26 February 2016
Registration decision	18 March 2016
Entry onto ARTG	16 January 2017
Number of TGA working days from submission dossier	197

Description	
acceptance to registration decision *	

* Target timeframe for standard applications: 220 working days

III. Quality findings

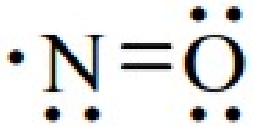
Introduction

The proposed medicinal gas, VasoKINOX, is a blend of NO gas with nitrogen gas, equivalent to 450 ppm (0.0450 mol) in nitrogen (quantum statis (QS) to 100 mol) held under pressure at 200 bar (20,000 kPa) in aluminium alloy cylinders with stainless steel residual pressure valves.

Drug substance (active ingredient)

NO is a colourless gas, which turns brown upon decomposition when exposed to air. At 20°C and at a pressure of 101 kPa, 1 volume of NO dissolves in 21 volumes of water. NO is manufactured through the reaction of sulfuric acid (diluted at 55%) with a sodium nitrite 40% solution. The slightly exothermic reaction is carried out at ambient temperature, at a pressure that is close to atmospheric pressure.

Figure 1. Chemical structure of nitric oxide



Nitric oxide is the subject of a harmonised British Pharmacopoeia (BP)/European Pharmacopoeia (Ph.Eur.) monograph and is the compliant drug substance specification.

Drug product

VasoKINOX is a colourless medicinal gas for inhalation containing 450 ppm mol/mol of NO in nitrogen contained within aluminium alloy cylinders with stainless steel valves. The gas cylinders are white with a 'Turkish blue' shoulder.

The manufacturing process involves two major steps: the preparation of an intermediate product and the dilution of the intermediate product with nitrogen to obtain the finished product.

The finished product is appropriately controlled using the finished product specifications applicable to medicinal gas.

A shelf-life of 3 years when stored at temperatures between -10°C and 50°C is recommended for the proposed drug product.

Chemistry and quality control aspects are considered acceptable.

Biopharmaceutics

Biopharmaceutical evaluation was not required for this submission.

Quality summary and conclusions

Registration is recommended with respect to chemistry and quality control aspects.

IV. Nonclinical findings

Background

The sponsor provided a large body of published literature that has been previously evaluated (by the TGA), did not provide any new information, was not directly relevant to the current application, or was of inadequate quality. All submitted material was evaluated however none of the material has been summarised.

Pharmacology

Primary pharmacology

No new information has been provided by the sponsor. In brief NO is an endogenous endothelial-derived vasodilator. NO is rapidly scavenged by haemoglobin (Hb) on diffusing into the blood with the resulting oxidation of haem Fe^{2+} to Fe^{3+}, rapid chemical inactivation of NO and the formation of methaemoglobin. Accordingly the pharmacological effects of inhaled NO are mostly limited to the pulmonary arterial vasculature.

NO rapidly diffuses across the alveolar-capillary membrane into the subjacent smooth muscle of pulmonary vessels. NO is a soluble guanylate cyclase (sGC) receptor agonist. sGC mediates many of the biological effects of NO and is responsible for subsequent downstream signalling via raised cGMP. This results in vascular smooth muscle relaxation via several mechanisms. cGMP acts locally due to its hydrolysis to GMP by cyclic nucleotide phosphodiesterases (PDE) or by its export from the cell. PDE5 is the most important enzyme that terminates the effects of cGMP (and thus the effects of NO) in smooth muscle. NO also acts as a bronchodilator and has anti-inflammatory and anti-proliferative effect.

Intrapulmonary ventilation perfusion (V/Q) distribution is a major determinant of the efficiency of transpulmonary oxygenation and determines arterial blood partial pressure of oxygen (PaO_2). In the normal lung, a low oxygen tension constricts the vascular bed in hypoxic regions and redistributes blood flow toward lung regions with better ventilation and a higher intra-alveolar partial pressure of oxygen. Inhaled NO enhances this mechanism by increasing blood flow to well ventilated lung areas that, in some diseases, have an elevated vasomotor tone.

Secondary pharmacodynamics and safety pharmacology

No new information has been provided by the sponsor.

Pharmacokinetics

No new information has been provided by the sponsor.

Toxicology

Acute toxicity

No new information has been provided by the sponsor.

Repeat dose toxicity and paediatric use

To support the use of VasoKINOX in the neonatal population, the sponsor has supplied a preliminary, subacute inhalation dose ranging study in 4 week old rats, a preliminary repeat exposure inhalation dose ranging study in neonatal rats (Postnatal Day (PND) 2 to 21) and a formal repeat exposure inhalation exposure study in rats (PND 1 to 29). A test apparatus feasibility study (Study No. ALQ 003) was also submitted. This study has been evaluated but is not summarised because it contained no data on the effects of NO exposure.

All submitted studies were methodologically limited. Limited clinical chemistry, clinical observations, clinical investigations, investigation of lung inflammation and limited or no anatomic pathology was performed. Accordingly the nonclinical repeat dose toxicology database presented by the sponsor is incomplete and preliminary. Furthermore, potentially critical pages of some of the study reports are missing. Accordingly the overall quality of the submitted data set is uncertain and potentially unreliable.

It should be noted that the data from neonatal animals is summarised in this section rather than in the sections pertaining to post-natal development because the human target population is 0 to 17 years of age.

Relative exposure

Relative exposure calculations have not been performed because: the relative inaccuracy of mathematically extrapolating whole body exposures in neonatal rats to anesthetised humans aged 0 to 17 years of age, lack of relevant respiratory physiological data for neonatal rats; and lastly, the lack of pharmacokinetic/toxicokinetic data.

Major toxicities

The studies submitted by the sponsor demonstrated a no observable effect level (NOEL) for methaemoglobin formation of approximately 20 ppm, 6 hours/day nose only for 7 consecutive days in adult rats. With exposures of approximately ≤ 100 ppm 6 hours/day nose only for 7 consecutive days the NOAEL methaemoglobin levels did not exceed around 1.5% and were not physiologically adverse. Exposure at approximately 400 ppm was rapidly fatal with clear evidence of severe methaemoglobinaemia.

Whole body inhalation exposure of neonatal rats over the PND 1 to 29 stage of development at levels approximately ≤ 100 ppm was not associated with physiologically adverse methaemoglobin (metHb) formation (metHb levels around ≤ 1%). However, this exposure resulted in a reduced body weight and weight gain over PND 1 to 90 period (particularly the PND 4 to 29 period) that exceeded a 10% reduction in some cases. Most notably adequate compensatory growth did not occur following the cessation of NO exposure after PND 29. Accordingly the NOAEL for NO exposure in neonatal rats was 10 ppm, whole body exposure, 6 hours/day, PND 1 to 29 (consecutive); due to reduced body weight without compensatory growth over the PND 1 to 90 period (particularly the PND 4 to 29 period).

Most notably the sponsor did not adequately evaluate the potentially adverse effects of inhaled NO on the respiratory tract in any of the submitted rodent studies and did not monitor the level of NO_2 in the dosing systems. This is of particular concern give that up to 5 ppm NO_2 has been detected during clinical administration of NO.[3] NO is a highly reactive gas that spontaneously oxidises in air to NO_2, a well-known respiratory toxicant. Increased airway reactivity has been reported in humans at exposures as low as 1.5 ppm NO_2. Other toxic effects observed following inhalation of NO_2 (≤ 5 ppm) include altered surfactant chemistry and metabolism, epithelial hyperplasia of the terminal bronchioles, increased

[3] Schedin U et al. Formation of nitrogen dioxide from nitric oxide and their measurement in clinically relevant circumstances. *Br. J. Anaesth*. 1999; 82, 182–192.

cellularity of the alveoli in rats, and diffuse inflammation. At higher doses, the major toxicological effect of NO_2 is pulmonary oedema. In rats, histopathological changes and increased lung weight have been reported following inhalation of 25 to 50 ppm NO_2 for 30 minutes. Additionally, NO also reacts with water within the respiratory tract to produce nitrous acid, another known airway toxicant.

Genotoxicity

The sponsor has supplied a bacterial reverse mutation study, an in vitro mammalian cell forward mutation assay and an in vivo rat micronucleus assay. Nitric oxide displayed clear metabolic activation-independent and metabolic activation-dependent mutagenic potential in the bacterial reverse mutation assay (strains TA100 (base pair substitution) and TA1535 (base pair substitution)) and mutagenic potential in the mammalian cell forward mutation assay. However no mutagenic potential was apparent in the higher tier, nose-only inhalation exposure and, rat bone marrow micronucleus assay.

Critically, it should be noted that validity of the rat micronucleus study fundamentally depends on exposure of bone marrow erythroblasts to the test article. Given that inhaled NO is rapidly scavenged by erythrocyte haemoglobin within the pulmonary circulation it is highly doubtful that any bone marrow erythroblast exposure has occurred. Furthermore, the study report did not provide any toxicokinetic data demonstrating bone marrow exposure to the test article. Accordingly the results of the in vivo rat bone marrow micronucleus study are regarded as falsely negative.

NO and/or its metabolites and/or its reaction products are regarded as directly DNA interacting mutagens. The sponsor has provided no new information on the mutagenic mode of action of NO.

Carcinogenicity

No new information has been provided by the sponsor.

Reproductive toxicity

See repeat-dose toxicity above.

Pregnancy classification

The sponsor has proposed pregnancy category B2.[4] This is considered adequate and is consistent with the currently approved alternative product.

Impurities

The drug substance fulfils the requirements of the Ph.Eur. 1550 monograph.

Nonclinical summary and conclusions

With a few exceptions, the majority of the submitted nonclinical data is unreliable. There are insufficient nonclinical data to support the requested extension of indication/major variation. The decision regarding the requested extensions of indication/major variation needs to be based largely on clinical data.

[4] TGA Pregnancy Category B2: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

It is reasonable to expect that VasoKINOX administered at 2 to 40 ppm will not induce physiologically adverse methaemoglobinaemia in normal animals in the absence of co-exposure to agents known to oxidise haem.

The clinical Delegate should note that the extension of indication for VasoKINOX includes increasing the maximum exposure to 40 ppm. Notably, the maximum concentration for the approved alternative product is 20 ppm. The submitted nonclinical data demonstrated that subacute repeated daily exposure to ≤ 100 ppm NO (6 h/day) in rats did not result in physiologically adverse methaemoglobinaemia. However, only a limited range of toxicological endpoints were examined. In particular, detailed evaluation of respiratory/pulmonary inflammation (for example, bronchoalveolar lavage evaluations, a more complete range of tissue inflammation biomarkers) was not performed. Therefore, there is insufficient nonclinical data to support increasing the maximum exposure to 40 ppm. A maximum recommended human exposure concentration of 40 ppm may have to be justified on clinical grounds.

The clinical relevance of the deleterious effects of pre-weaning exposure to NO on weight gain during the pre-weaning to adolescent/early adulthood stages of development in rats are uncertain. However, it is very notable that the effects were long-lasting and that adequate post-exposure compensatory growth did not occur.

The relevant nonclinical sections of the Australian Specific Annex (ASA) to the EU-Risk Management Plan (RMP) and the Australian Annex 3 RMP for VasoKINOX have been evaluated. No changes are recommended.

Nonclinical summary and conclusions following sponsor's response to original nonclinical evaluation findings

- The sponsor submitted a response to the nonclinical evaluation report. The sponsor's response has made claims of errors of fact or omission in the original nonclinical report, has provided a series of general comments, and has made a series of additional points.
- As identified in the original nonclinical evaluation, the critical difference identified in the initial application between the inhaled NO product currently available in the Australian market and VasoKINOX was the proposed maximum human recommended exposure (MHRE). Current products registered on the Australian market have a MHRE of 20ppm. VasoKINOX has a proposed MHRE of 40 ppm.
- As identified in the original nonclinical evaluation, the key nonclinical safety concern is the potential for induction of airway and pulmonary inflammation and other adverse effects following exposure to 40 ppm of NO, particularly when there is a maximal duration of exposure of 7 days. Neither the sponsor's nonclinical studies, nor the sponsor's response, have systematically addressed these concerns. On the contrary, the published literature submitted by the sponsor provides clear evidence of adverse effects in the respiratory tract at exposure levels of 40 ppm, particularly (but not exclusively) when nitric oxide is co-administered with oxygen. Co-administration of nitric oxide and oxygen is a likely scenario during peri-surgical environment (the intended clinical use of VasoKINOX).
- Critically, the original nonclinical evaluation did not recommend rejection. The original nonclinical evaluation noted that if the sponsor desired a MHRE of 40 ppm, this would have to be clinically justified. There is insufficient nonclinical data to support a MHRE of 40 ppm (which is twice the MHRE of existing products in the Australian marketplace). This review has not resulted in a change in this key outcome of the nonclinical evaluation of VasoKINOX.

V. Clinical findings

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

Introduction

Clinical rationale

NO relaxes vascular smooth muscle by activating guanylate cyclase and increasing intracellular levels of cGMP, which then leads to vasodilation and increased oxygenation. Inhaled NO (iNO) produces selective pulmonary vasodilation. NO is a medical gas, classified in the pharmacotherapeutic group as 'Other respiratory system products', ATC code: R07 AX01.[5] iNO is delivered to the patient via mechanical ventilation after dilution with an oxygen/air mixture using an approved (CE marked) NO delivery system.

The objective of this literature based submission was to document the efficacy and safety of iNO (VasoKINOX) in the treatment of perioperative pulmonary hypertension (PHT) experienced in conjunction with cardiac surgery in children and adults.

Children with many forms of congenital heart disease (CHD) are prone to developing postoperative PHT. Furthermore, the surgical correction of CHD requires cardiopulmonary bypass (CPB), which can further increase PHT in the perioperative period and promote the occurrence of acute, life threatening PHT crises.[6] Postoperative PHT is associated with significant delay in postoperative recovery and significant morbidity and even mortality.[7,8,9,10,11] According to more recent studies, PHT still accounts for approximately 8% of postoperative deaths.[12,13] The sponsors claim that in Australia, iNO is considered the standard of care for PHT in patients recovering from cardiac surgery, especially in paediatric population.[14] According to the Australian and New Zealand Paediatric Intensive Care database, 1,816 children in Australia and New Zealand were treated with iNO for PHT related to cardiac disease between 2000 and 2012. Of these, 32.9% were neonates, 36.7% were aged 1 to 12 months, 18.0% were aged 1 to 4 years, 5.2% were aged 5 to 9 years, 4.9% were aged 10 to 14 years, and 2.3% were aged 15 to 17 years. At the Royal Children's Hospital (RCH) in Melbourne, 585 children aged from newborn infants to 16 years of age have received a total of approximately 48,000 hours of iNO treatment since 2005. The use of iNO in postoperative PHT in the paediatric

[5] The Anatomical Therapeutic Chemical (ATC) Classification System is used for the classification of active ingredients of drugs according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. It is controlled by the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC), and was first published in 1976.
[6] Hopkins R. et al., Pulmonary hypertensive crises following surgery for congenital heart defects in young children. *Eur J Cardiothorac Surg* 1991; 5: 628-634.
[7] Berghetti M. et al., Continuous low dose inhaled nitric oxide for treatment of severe pulmonary hypertension after cardiac surgery in paediatric patients. *Br Heart J* 1995; 73: 65-68.
[8] Hiramatsu T. et al., Time course of endothelin-1 and nitrate anion levels after cardiopulmonary bypass in congenital heart defects. *Ann Thorac Surg* 1997; 63: 648-652.
[9] Duke T. et Al., Altered activation of the L-arginine nitric oxide pathway during and after cardiopulmonary bypass. *Perfusion* 1997; 12: 405-410.
[10] Wessel D. et al., Use of inhaled nitric oxide and acetylcholine in the evaluation of pulmonary hypertension and endothelial function after cardiopulmonary bypass. *Circulation* 1993; 88: 2128-2138.
[11] Wheller, J. et al., Diagnosis and management of postoperative pulmonary hypertensive crisis. *Circulation* 1979; 60: 1640-1644.
[12] Lindberg L. et al., How common is severe pulmonary hypertension after pediatric cardiac surgery? *J Thorac Cardiovasc Surg* 2002; 123:1155-1163.
[13] Ma M. et al., Causes of death after congenital heart surgery. *Ann Thorac Surg* 2007; 84:1438-1445.
[14] Checchia P. et al., Review of inhaled nitric oxide in the paediatric cardiac surgery setting. *Pediatr Cardio*, 2012; 33: 493-505.

population with CHD has been widely studied and published. The publications retrieved in the literature search in this submission were provided as evidence to support the proposed indication.

The causes of postoperative PHT in adults are diverse, but the treatment always aims at reducing PVR to prevent or treat right ventricular failure. In adult patients with preoperative PHT, CPB may increase PAP by several mechanisms: release of vasoactive pro-inflammatory mediators, pulmonary arterial vasoconstriction secondary to the administration of protamine, acidosis, hypercapnia, and hypoxaemia. In addition, the production of endogenous NO by the pulmonary vascular endothelium is inhibited by CPB. There is a loss of endothelium-dependent relaxation with acetylcholine, while the reactivity of the pulmonary vessels to the inhalation of exogenous NO is conserved.[10] The administration of iNO to a patient with postoperative PHT leads to a significant drop in PAP and in PVR without a systemic effect. However, iNO has no effect in the absence of an elevation in PVR. Many studies have compared iNO after cardiac surgery to other intravenous vasodilators, including prostaglandin E1 (PGE1), nitroglycerin, and PDE3 and PDE5 inhibitors for the treatment of PHT. Unlike intravenous vasodilators, iNO has a selective effect on pulmonary resistance and does not reduce systemic arterial pressure (SAP), which can adversely affect renal perfusion. Between 2010 and 2012, adult patients in Australian intensive care units (ICU) received approximately 100,000 hours of iNO treatment for a variety of conditions, including PHT, right ventricular dysfunction, after cardiac surgery, after transplantation (lung and heart), arterial hypoxaemia, and acute respiratory distress syndrome (ARDS). The use of iNO in adults is similar to its use in children and infants with similar safety, specificity, and functionality. Inhaled prostacyclin is also used in adults with good effect, although this option involves a more complicated method of delivery and the possibility of systemic hypotension when used at higher doses. The use of iNO in PHT after cardiac surgery in adults has been widely studied and published, and the publications retrieved in the literature search in this submission were provided as evidence to support the indication.

Inhaled NO, in conjunction with ventilatory support and other appropriate treatments, induces a selective pulmonary anti-hypertensive effect. The absence of systemic effects enables SAP, and particularly coronary perfusion pressure, to be maintained. The decrease in PVR without a decrease in coronary perfusion pressure should permit an improvement in right ventricular function. By being a rapid onset, direct pulmonary vasodilator, iNO works quickly and specifically to decrease acute pulmonary hypertension and allow rapid ventricular recovery. The immediate, selective, and reversible effect of iNO makes it very convenient for use in perioperative PHT.

Guidance

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

- EMEA/CHMP/EWP/356954/2008: Guideline on the Clinical Investigations of Medicinal Products for the Treatment of Pulmonary Arterial Hypertension
- EMEA/CHMP/EWP/147013/2004: Clinical Investigation of Medicinal Products in the Paediatric Population
- EMEA/536810/2008: Guideline on the Investigation of Medicinal Products in the Term and Preterm Neonate
- CHMP/EWP/83561/2005: Guideline on Clinical Trials in Small Populations
- CHMP/CHMP/EWP/147013/2044 Corr: Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population

- EMEA/536810/2008: Guideline on the Investigation of Medicinal Products in the Term and Preterm Neonate

Contents of the clinical dossier

- 4 Phase III clinical studies:
  - Study ALS-1-97-P-301: One study matching that of the proposed indication for this submission - a prospective, multicentre, double blind, parallel-group, randomised, placebo controlled study testing iNO for the 'prevention' of postoperative PHT after surgery for congenital heart disease (CHD) in children;
  - Study CT04009 (in newborns with hypoxic respiratory failure);
  - Study ALS-94 30 (in adults with ARDS); and
  - Study ALS-1-98-A-301 (for the prevention of pulmonary oedema after pulmonary thromboendarterectomy for chronic cor pulmonale in adults).
  - 56 evaluable publications (including two versions of the meta-analysis), 24 met the inclusion criteria for both efficacy and safety, 3 met the criteria for efficacy only, and 29 met the criteria for safety only. Of the 56 included publications, 37 involved paediatric patients and 19 involved adult patients.
- 98 other papers were cited in the submission are review-type articles or background information rather than reports of specific studies.
- A Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

Paediatric data

The submission included paediatric pharmacokinetic, pharmacodynamic, efficacy and safety data.

Good clinical practice

A declaration by the Qualified Person of Air Liquide Santé France confirming that the drug substance nitric oxide is manufactured in accordance with the Good Manufacturing Practices for starting materials was provided.

Pharmacokinetics

Studies providing pharmacokinetic data

The company has not performed any new pharmacokinetic (PK) studies on iNO for this application. However, the information on clinical pharmacology of iNO was derived from available literature.

Evaluator's conclusions on pharmacokinetics

No new PK studies on iNO were conducted for this application. The selected publications cover the evaluation of absorption, lung distribution, metabolism and excretion after NO inhalation. The studies were conducted in both healthy volunteers (HV) and adult patients with severe heart failure, with iNO doses ranging from 20 to 100 ppm.

Inhaled NO is well absorbed, diffuses into ventilated areas of the lungs, crosses the alveolar-capillary membrane and reaches the arteriolar pulmonary vasculature. NO

conversion to metHb and to nitrate is the major metabolic pathway. Contrary to other pulmonary vasodilators, iNO has little systemic effect because of its short half-life (6 to 10 seconds) related to its inactivation by binding to Hb to form metHb. NO reacts with oxygen and water to form nitrogen dioxide and nitrites, which react with oxyhaemoglobin to produce metHb and nitrates which are the principal metabolites of NO are found in the systemic circulation.

Nitrates are eliminated mainly in urine whereas metHb is metabolised in several hours into Hb by endogenic reductases. The nitrates excreted in urine represent over 70% of the inhaled nitric oxide dosage.

According to EU guidelines adopted by the TGA, bioequivalence studies are not required for medicinal gases that are intended to be inhaled. Therefore, it is not necessary to demonstrate therapeutic equivalence between the various sources of NO used within the supporting clinical data.

The sources of iNO within the published literature were delivered via inhalation route of administration using the same or similar doses of iNO in ppm, regardless of initial strength of NO. All clinical data are therefore considered as relevant whatever the source of the molecule NO. No clinical drug interactions studies were conducted for this submission.

Although no new studies were conducted by the sponsors, this is not a limitation of the submission as the PK characteristics are quite well-characterised in various published studies.

Pharmacodynamics

Studies providing pharmacodynamic data

The pharmacodynamics (PD) of nitric oxide is well characterised and no new studies were submitted in the current dossier. However, many publications were provided in the current submission which have been evaluated and summarised (please see Attachment 2 for further details).

Evaluator's conclusions on pharmacodynamics

Inhaled NO induces selective pulmonary arterial vasodilation which is rapid, sustained throughout the time of inhalation, and quickly reversible when inhalation is stopped. The studies presented above showed that iNO can reverse the pulmonary vasoconstriction induced by hypoxia in HVs as well as in adults with ARDS.[15,16] Dilatation of pulmonary vessels produced by inhaling NO during hypoxia was not accompanied by systemic vasodilation. This effect appears within a few minutes following the initiation of iNO treatment.

With regard to the dose/concentration-response relationships, the studies report a dose-dependent improvement of pulmonary circulation and arterial oxygenation. In the considered studies, a significant effect on arterial oxygenation and/or PAP was reported for iNO concentrations ranging from less than 1 ppm to 100 ppm. In adult and paediatric patients with ADRS or acute respiratory failure, the maximum effect of iNO on arterial oxygenation and PAP seems to be obtained at concentrations of 2 to 10 ppm. In neonatal

[15] Frostell C et al., Inhaled nitric oxide selectively reverses human hypoxic pulmonary vasoconstriction without causing systemic vasodilation. *Anestesiology* 1993; 87: 427-435
[16] Rossaint R et al., Inhaled nitric oxide for the adult respiratory distress syndrome. *N Engl J Med* 1993; 328: 399-405.

patients with ADRS and PPHN, the maximum effective dose has been reported to be of 10 to 20 ppm.

The PD studies submitted in the dossier involved only HVs or patients with ARDS which is not the proposed indication for this submission. Interpretation was limited by lack of dose response or other specific PD studies in the target patient population with perioperative pulmonary hypertension in conjunction to heart surgery. However, almost all published studies discussed under 'Efficacy' in the clinical evaluation report had haemodynamic and oxygenation parameters as their efficacy endpoints (please see Section 7 (clinical efficacy) of Attachment 2 for further details).

Dosage selection for the pivotal studies

There were no specific dose ranging studies for the proposed indication.

Efficacy

Studies providing efficacy data

The sponsor conducted 4 studies, but only one Phase III study (Study ALS-1-97-P-301) was considered 'pivotal' by the sponsors. The other 3 studies were for other indications and only provided safety data.

Numerous studies have been published in the literature, both in paediatric and in adult populations for the proposed indication. However, the sponsor did not sponsor/conduct any of these published studies.

Comment: Publication bias was minimised by the use of a systematic review of the literature; all published studies that met the pre-defined inclusion criteria were included regardless of their results or language. However, it is possible that publication bias (where studies with a 'positive result' are more likely to be published) may have had a positive influence on the overall outcomes reported in this submission. The potential for selection bias was minimised by the inclusion of only randomised studies reporting efficacy outcomes.

For the full evaluation of the clinical data and publications provided in support of this submission for efficacy please see Attachment 2.

Evaluator's conclusions on efficacy for treatment of peri-operative PHT in paediatric patients

The only study conducted by sponsor for the proposed indication was ALS-1-97-P-301 in 219 infants (mean age of 4 to 5 months) at risk of developing PHT following corrective cardiac surgery. However, the 5 ppm dose of iNO used was found to be suboptimal and this study failed to provide any evidence to support efficacy of iNO for proposed indication due to limitations outlined in the evaluator's comments (please see Section 7 of Attachment 2).

In the paediatric population, 15 published studies (14 publications, including 2 versions of 1 meta-analysis, and 1 abstract) were selected which evaluated the effectiveness of iNO at doses ranging from 5 to 80 ppm in a population of newborns or children (ages 1 day to 20 years), who had pre or post-operative PHT. Efficacy was mainly evaluated by the reduction in PHT, reduction in PVR, and the improvement of oxygenation, without modification of cardiac output.

In most of the studies, the patients had PHT at inclusion, in general defined as a PAP: SAP ratio > 0.50 (> 0.66 in Goldman 1995, > 0.7 in Kirbas 2012), PAP > 25 mmHg (Morris 2000), or transpulmonary pressure gradient (TPG) > 10 mmHg (Cai, Ann Thor Surg, 2008 and Cai, Artificial Organs, 2008).[17,18,19,20,21] In addition, in some studies, the patients were hyperventilated before randomisation and so the severity of the PHT differed between the studies.

Four randomised controlled studies compared iNO with N_2 (Russell 1998; Miller 2000), hyperventilation (Morris 2000), or conventional therapy (not specified) (Day 2000) and these were labelled as 'pivotal' by the sponsor.[22] However, only one of them (Miller, 2000) was considered 'pivotal' by the evaluator due to limitations of the other studies. In infants at high risk of PHT crisis after cardiac surgery, use of iNO can lessen the occurrence of crisis and shorten the postoperative course (Miller, 2000). One meta-analysis (Bizzarro 2005, 2014) of these four studies was also included but it was difficult to draw valid conclusions from this meta-analysis given concerns regarding methodological quality, sample size, and heterogeneity.[23,24]

Five randomised controlled studies compared iNO with other active drugs, specifically, IV prostacyclin (Goldman 1995), IV sildenafil (Stocker 2003), and aerosolised iloprost (Gorenflo 2010; Loukanov 2011; Kirbas 2012).[25,26,27] Three randomised studies compared iNO with Milrinone (Mil) infusion and with the combination of iNO and Mil (Khazin 2004; Cai, Ann Thorac Surg 2008; Cai, Artif Organs 2008).[28] One conference abstract reported a comparison of iNO plus aerosolised iloprost with iloprost alone (Harimurti 2012).[29] The heterogeneity of the control groups in these studies precludes direct comparison.

In most studies, iNO administration started in the early postoperative period, usually immediately after CPB termination. In some studies, iNO administration was started at later times, including several hours after CPB termination (Stocker 2003) and after admission to the ICU (Morris 2000). Some studies did not specify the timing of iNO administration (Day 2000; Cai, Ann Thor Surg 2008; Cai, Artificial Organs 2008; Harimurti

[17] Goldman, A., et al., Nitric oxide is superior to prostacyclin for pulmonary hypertension after cardiac operations. *Ann Thorac Surg* 1995; 60: 300-305; and discussion 306.
[18] Kirbas A, et al., Comparison of inhaled nitric oxide and aerosolized iloprost in pulmonary hypertension in children with congenital heart surgery. *Cardiology Journal* 2012; 19: 387-394
[19] Morris K, et al. Comparison of hyperventilation and inhaled nitric oxide for pulmonary hypertension after repair of congenital heart disease. *Crit Care Med* 2000; 28: 2974-298.
[20] Cai J, et al. Nitric oxide and milrinone: combined effect on pulmonary circulation after Fontan-type procedure: a prospective, randomized study. *Ann Thorac Surg* 2008; 86 :882-888
[21] Cai J, et al. Nitric oxide in conjunction with milrinone better stabilized pulmonary hemodynamics after Fontan procedure. *Artif Organs* 2008; 32: 864-869
[22] Miller O, et al. Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: a randomised double-blind study. Lancet 2000; 356: 1464-1469
[23] Bizzarro, M et al. Inhaled nitric oxide for the postoperative management of pulmonary hypertension in infants and children with congenital heart disease. *Cochrane Database of Systematic Reviews* 2005(4):CD005055.
[24] Bizzarro, M et al., Inhaled nitric oxide for the postoperative management of pulmonary hypertension in infants and children with congenital heart disease. *Cochrane Database of Systematic Reviews* 2014(7):CD005055.
[25] Stocker, C et al. Intravenous sildenafil and inhaled nitric oxide: a randomised trial in infants after cardiac surgery. *Intensive Care Med* 2003; 29: 1996-2003.
[26] Gorenflo, M et al. Peri-operative pulmonary hypertension in paediatric patients: current strategies in children with congenital heart disease. *Cardiology* 2010;116: 10-17.
[27] Loukanov, T., et al. Comparison of inhaled nitric oxide with aerosolized iloprost for treatment of pulmonary hypertension in children after cardiopulmonary bypass surgery. Clin Res Cardiol, 2011;100(7): 595-602.
[28] Khazin, V et al, Milrinone and nitric oxide: combined effect on pulmonary artery pressures after cardiopulmonary bypass in children. *J Cardiothorac Vasc Anesth* 2004;18: 156-159.
[29] Harimurti, G.M et al. Subsequent nitric oxide with inhaled iloprost versus inhaled iloprost alone in pulmonary hypertension following cardiac surgery in children with congenital heart disease. *Cardiology in the Young* 2012;22: S15.

2012).[30] Inhaled NO doses ranged from 5 to 80 ppm and in most studies, the dose of iNO was 20 ppm. In some studies (Morris 2000; Cai, Ann Thor Surg 2008; Cai, Artificial Organs 2008), the dose of iNO was increased as part of the study procedures. Haemodynamic parameters were usually recorded after 10 to 20 minutes of iNO inhalation. In some studies, continuous administration and haemodynamic measurements were performed for several days (Miller 2000; Loukanov 2011; Kirbas 2012).

The premedication and ventilation provided to the patients throughout the perioperative period and before randomisation seemed to be similar between groups in all the studies.

In most studies, the main endpoint was the change from baseline in PAP and the PAP: SAP ratio. Changes from baseline in PVR, cardiac index, and blood gas measurements were also provided in many of the studies. The number of PHT crises was the primary endpoint in the Miller 2000, Day 2000, Gorenflo 2010, and Loukanov 2011 studies.[22,26,27,30]

The statistical methods used differed among the studies. In some studies, the analysis was only descriptive, whereas in other studies, within group and/or between groups statistical tests were performed.

The heterogeneity in terms of inclusion criteria, controls used, endpoints, and the limited sample size in these studies does not allow a global analysis of the data. However, the main efficacy results obtained are summarised below.

Pulmonary arterial pressure

In the studies that reported changes in PAP (Russell 1998; Day 2000; Morris 2000; Khazin 2004; Goldman 1995; Stocker 2003; Loukanov 2011; Kirbas 2012; Harimurti 2012), iNO was effective in reducing PAP by approximately 10% to 30% in paediatric patients with PHT after cardiac surgery.[17,18,19,27,28,29,30,31] Treatment with iNO appeared to be more effective than N_2, prostacyclin 20 ng/kg/min, and equally effective as conventional therapy, hyperventilation, sildenafil, and aerosolised iloprost. Combination of iNO with Mil produced a greater reduction in PAP than either iNO or Mil alone. Only iNO selectively dilated the pulmonary vasculature; all other active comparators also dilated the systemic vasculature, reducing SAP.

Vascular resistance

In the studies that reported changes in vascular resistance (Morris 2000; Stocker 2003), iNO reduced the pulmonary vascular resistance index (PVRI) by approximately 15% to 25% and had no significant effect on SVRI in paediatric patients with PHT after cardiac surgery.[19,25] No difference in the reduction of PVRI was seen between iNO and hyperventilation or sildenafil. Both the publications by Cai (2008) showed that the combined use of iNO and Mil provided additive benefits as compared with iNO or Mil alone for patients with elevated PVR after Fontan procedure.[20,21] The combination produced a greater decrease in TPG and central venous pressure as well as a greater improvement in arterial oxygen saturation. Besides improving haemodynamics and oxygenation, the combination may offer unique advantage in minimising the potential side effects related to longer exposure period. However, rebound PHT during iNO withdrawal was a concern in both studies.

Oxygenation

In the studies that reported changes in oxygenation (Day 2000; Cai, Ann Thorac Surg 2008; Cai, Artif Organs 2008; Goldman 1995; Stocker 2003), PaO_2 or the ratio of partial pressure arterial oxygen and fraction of inspired oxygen (PaO_2:FiO_2) ratio was improved

[30] Day, R.W., et al. Randomized controlled study of inhaled nitric oxide after operation for congenital heart disease. *Ann Thorac Surg* 2000; 69: 1907-1912; discussion 1913.
[31] Russell, I.A., et al. The effects of inhaled nitric oxide on postoperative pulmonary hypertension in infants and children undergoing surgical repair of congenital heart disease. *Anesth Analg* 1998; 87: 46-51.

only with iNO.[17,20,21,25,30] No improvement in oxygenation was seen with prostacyclin, Mil, or sildenafil, despite their effects on PAP. Conventional therapy also improved oxygenation, although not significantly.

PHT crises

In the studies that reported PHT crisis (Miller 2000; Day 2000; Gorenflo 2010; Loukanov 2011), iNO reduced the number of PHT crisis compared with nitrogen, but not compared with conventional treatment or iloprost.[22, 26, 27, 30]

Cardiac function

In both studies that reported cardiac index (Morris 2000; Stocker 2003), iNO did not affect this parameter, whereas hyperventilation significantly reduced cardiac index.[19,25]

Given the limited sample size and the low level of detail in the publications, the comparison of results in sub-populations was not possible. Nevertheless, the Russell (1998) study showed significant efficacy of iNO in reducing PAP only in patients who emerged from CPB with PHT (and not in those without PHT).[31] In the Day (2000) study, the presence of lung disease had no significant effect on measurements at baseline (before treatment) or at 1-hour post treatment with iNO or conventional therapy.[30] However, interpretation was limited due to very small sample size in subgroups.

The main limitations of the submission were:

- Although 1000 infants and children were evaluated in the submitted paediatric studies, majority of studies included infants with mean age < 1 year; studies in toddlers, children and adolescents were few with inconsistent results.
- Study ALS-1-97-P-301 in 219 infants (mean age of 4 to 5 months) at risk of developing PHT following corrective cardiac surgery showed that the 5 ppm dose of iNO used in this study was found to be suboptimal. However, the sponsor has stated that this study was not considered or claimed to be a pivotal study and was provided for evaluation to demonstrate the safety of inhaled nitric oxide in the paediatric population.
- Four randomised controlled studies compared iNO with N_2 (Russell 1998; Miller 2000), hyperventilation (Morris 2000), or conventional therapy (not specified) (Day 2000) and these were labelled as 'pivotal' by the sponsor.[19,22,30,31] However, only one of them (Miller, 2000) was considered 'pivotal' by the evaluators due to limitations of the other studies (discussion available in Attachment 2, Section 7).
- The meta-analysis (Bizzarro 2005; 2014) of the four main randomised studies failed to show any significant changes in MPAP, MAP, PVRI, HR or oxygenation compared to control groups although it was difficult to draw valid conclusions from this meta-analysis given concerns regarding methodologic quality, sample size, and heterogeneity.[23,24]
- In the studies that reported PHT crises (Miller 2000; Day 2000; Gorenflo 2010; Loukanov 2011), iNO reduced the number of PHT crises compared with N_2, but not compared with conventional treatment or iloprost.[22,26,27,30]
- Clinical outcomes such as morbidity and mortality were not adequately evaluated. The only study with primary objective of evaluating impact of iNO treatment on survival was a single arm uncontrolled study in 24 children (Sharma, 2001) which showed equivocal results.[32] However, there were no controlled studies evaluating effects of iNO on mortality.
- Effects of iNO on long term mortality and neurodevelopment were not evaluated.

[32] Sharma, R et al. Does inhaled nitric oxide improve survival in operated congenital disease with severe pulmonary hypertension*? Indian Heart J* 2001; 53: 48-55.

Evaluator's conclusions on efficacy for treatment of peri-operative PHT in adult patients

There were 12 main published studies submitted to provide evidence of efficacy of iNO for the proposed indication in adult patients after various cardiac surgeries. The definition of PHT based on PVR and/or mean PAP differed among the studies. In most studies, the patients had postoperative severe PHT, defined as mean PAP ≥ 30 mmHg and/or PVR ≥ 300 dyn sec^{-1} cm^{-5} (Schmid 1999), mean PAP ≥ 25 mmHg (Argenziano 1998; Knothe 1996; Winterhalter 2008; Khan 2009; Matamis 2012), systolic PAP > 60 mmHg (Fernandes 2011), and PVR > 250 dyn sec ^{1} cm^{-5} with accompanying systolic PAP > 45 mmHg or mean PAP > 25 mmHg (Fattouch 2006).[33,34,35,36,37,38,39,40] In the Solina (2000, 2001) studies, the patients had preoperative PHT (defined as PVR > 125 dyn sec^{-1} cm^{-5}).[41,42] In the majority of studies, the diagnosis of PHT was made preoperatively as an inclusion criterion (Solina 2000, Solina 2001, Knothe 1996, Fernandes 2011, Schmid 1999, Fattouch 2005, Fattouch 2006, Winterhalter 2008; Matamis 2012).[35,36,38,39,40,41,42] The presence of postoperative PHT was confirmed in the immediate postoperative period in the Winterhalter (2008) study.[36] In the Argenziano (1998) study, PHT was documented in patients after left ventricular assist device (LVAD) insertion, and in the Khan (2009) study, after heart or lung transplantation.[34,37] The type of surgery with CPB differed among the studies. The haemodynamic effect of iNO was documented in patients after cardiac surgery, including arterial grafts, venous grafts, and valve repair/replacement (Solina 2001, Solina 2000, Knothe 1996, Fernandes 2011, Fattouch 2006, Fattouch 2005, Winterhalter 2008, Schmid 1999; Matamis 2012), after LVAD insertion (Argenziano 1998);[33,35,36,38,39,40] or after heart or lung transplantation (Rajek 2000, Khan 2009).[37,43]

The selected main studies were randomised and controlled versus inhaled N_2 (Argenziano 1998);[34] conventional treatment (Knothe 1996);[35] oxygen (Fernandes 2011);[39] IV Mil (Solina 2000);[41] IV PGE1 (Schmid 1999; Rajek 2000);[33,43] IV nitroprusside or NTG (Schmid 1999; Fattouch 2005; Fattouch 2006);[33,40] inhaled iloprost (Winterhalter 2008; Khan 2009);[36,37] inhaled prostacyclin (Fattouch 2005; Fattouch 2006);[40] or oral sildenafil (Matamis 2012).[38] One study (Solina 2001) compared different doses of iNO with Mil.[41] The heterogeneity of the control groups in these studies precludes direct comparison. The

[33] Schmid, E et al. Inhaled nitric oxide versus intravenous vasodilators in severe pulmonary hypertension after cardiac surgery. *Anesth Analg* 1999; 89: 1108-1115.
[34] Argenziano, M., et al. Randomized, double-blind trial of inhaled nitric oxide in LVAD recipients with pulmonary hypertension. *Ann Thorac S*urg, 1998; 65: 340-345.
[35] Knothe, C., et al. [NO inhalation in heart surgery procedures: relevance for right heart function?]. *Anaesthesist* 1996; 45: 240-248.
[36] Winterhalter, M., et al. Comparison of inhaled iloprost and nitric oxide in patients with pulmonary hypertension during weaning from cardiopulmonary bypass in cardiac surgery: a prospective randomized trial. *J Cardiothorac Vasc Anesth* 2008; 22: 406-413.
[37] Khan, T.A., et al. A prospective, randomized, crossover pilot study of inhaled nitric oxide versus inhaled prostacyclin in heart transplant and lung transplant recipients. *J Thorac Cardiovasc Surg* 2009; 138: 1417
[38] Matamis, D., et al. Inhaled NO and sildenafil combination in cardiac surgery patients with out-of-proportion pulmonary hypertension: acute effects on postoperative gas exchange and hemodynamics. *Circulation: Heart Failure* 2012; 5: 47-53.
[39] Fernandes, J.L., et al. Comparison of inhaled nitric oxide versus oxygen on hemodynamics in patients with mitral stenosis and severe pulmonary hypertension after mitral valve surgery. *Am J Cardiol* 2011; 107: 1040-1045.
[40] Fattouch, K., et al. Treatment of pulmonary hypertension in patients undergoing cardiac surgery with cardiopulmonary bypass: a randomized, prospective, double-blind study. *J Cardiovasc Med* (Hagerstown), 2006; 7: 119-123.
[41] Solina, A et al. A comparison of inhaled nitric oxide and milrinone for the treatment of pulmonary hypertension in adult cardiac surgery patients. *J Cardiothorac Vasc Anesth* 2000; 14: 12-17.
[42] Solina, A.R., et al. Dose response to nitric oxide in adult cardiac surgery patients. *J Clin Anesth,* 2001; 13: 281-286.
[43] Rajek, A., et al. Inhaled nitric oxide reduces pulmonary vascular resistance more than Prostaglandin E1 during heart transplantation. *Anesth Analg* 2000; 90: 523-530.

premedication and ventilation provided to the patients throughout the perioperative period and before randomisation seemed to be similar between groups in all the studies.

In adults, inhaled NO doses ranged from 4 to 40 ppm. In most of the studies, the dose of iNO was 20 ppm. The time of administration in cardiac surgery patients in most studies was at weaning from CPB. The duration of administration ranged from 15 to 20 minutes in acute haemodynamic studies to several hours (up to the arrival in the ICU or later). The doses of iNO used in the included publications support the recommended dosage of 2 to 20 ppm. In adults, the dose may be increased up to 40 ppm if the lower dose has not provided sufficient clinical effects.

The endpoints were similar in each study, including haemodynamic (changes from baseline in PAP, SAP, cardiac index), vascular parameters (changes from baseline in PVR), and right ventricular ejection fraction (RVEF) in most of the studies. The statistical methods used were different between trials. In some trials, the analysis was only descriptive, while in other trials between-groups statistical tests were performed.

The sponsor designated 3 of the 12 published studies as pivotal (Argenziano, 1998; Knothe, 1996 and Fernandes, 2011);[34,35,39] but the evaluator does not consider these studies as pivotal due to limitations. The heterogeneity in terms of inclusion criteria, controls used, endpoints, and the limited sample size in these studies does not allow a global analysis of the data. Furthermore, the methods used to collect haemodynamic and vascular parameters were not always described, and different methods (pulmonary arterial catheters or echocardiography) may have affected the results obtained. However, the main efficacy results obtained are summarised below.

Pulmonary arterial pressure

In the studies that reported changes in PAP (Argenziano 1998; Knothe 1996; Fernandes 2011; Fattouch 2005; Fattouch 2006; Solina 2000; Winterhalter 2008; Rajek 2000; Schmid 1999; Khan 2009; Matamis 2012), iNO was effective in reducing PAP by approximately 15% to 40% in adult patients with PHT after cardiac surgery.[33,34,35,36,37,38,39,40,42,43] Treatment with iNO appeared to be more effective at reducing PAP than N_2 (in patients undergoing LVAD insertion), nitroprusside, and NTG, and at least as effective as conventional therapy, oxygen, Mil, prostacyclin, PGE1, and sildenafil. In all these studies, only iNO selectively dilated the pulmonary vasculature; the other active comparators also dilated the systemic vasculature, reducing SAP. The only active comparator reported to be more effective than iNO in reducing PAP was iloprost (Winterhalter 2008).[36] Although SAP was reduced by both agents in this study, iNO had greater pulmonary selectivity than iloprost.

Vascular resistance

In the studies that reported changes in vascular resistance (Solina 2001; Knothe 1996; Fernandes 2011; Fattouch 2005; Fattouch 2006; Solina 2000; Winterhalter 2008; Rajek 2000; Schmid 1999; Matamis 2012), iNO reduced the PVR by approximately 35% to 65% and had no significant effect on SVR (where reported) in adult patients with PHT after cardiac surgery.[33,35,36,38,39,40,42,43] Treatment with iNO appeared to be more effective at reducing PVR than oxygen, nitroprusside, and NTG, at least as effective as PGE1 and sildenafil, and equally effective as Mil and conventional treatment. The only active comparator reported to be more effective than iNO in reducing PVR was iloprost (Winterhalter 2008);[36] however, iloprost also significantly reduced SVR, whereas iNO did not. In all these studies, only iNO selectively reduced pulmonary resistance; the other active comparators also reduced systemic resistance.

Cardiac function

All the studies reported changes in at least one cardiac function parameter, i.e., cardiac index, cardiac output, RVEF, and/or LVAD flow index (Solina 2001; Argenziano 1998;

Knothe 1996; Fernandes 2011; Fattouch 2005; Fattouch 2006; Solina 2000; Winterhalter 2008; Rajek 2000; Schmid 1999; Khan 2009; Matamis 2012).[33,34,35,36,37,38,39,40,41,42,43] In all studies, iNO treatment maintained or improved cardiac function. In most studies, the effects of iNO on cardiac function were not significantly different from those of the comparator treatments. However, the increase in cardiac index after iNO was significantly greater than after oxygen,[39] and the increase in LVAD flow index after iNO was greater than after N_2.[34] In contrast, the increase in cardiac output after iNO was significantly lower than after iloprost.[36]

Overall, the efficacy of iNO was assessed in 12 randomised, controlled published studies involving 398 adults presenting with PHT after or immediately before cardiac surgery. All the studies showed consistent evidence of the efficacy of iNO in postoperative PHT and also demonstrated its pulmonary selectivity. The efficacy of iNO in this indication is largely recognized in the medical community. The other nonrandomised studies submitted did not provide additional evidence for efficacy of iNO in adults.

However, interpretation of evidence to support proposed indication of iNO for treatment of perioperative PHT in adult patients was limited by the following:

- lack of any large, controlled randomised studies by the sponsors;
- heterogeneity of submitted published studies (in terms of inclusion criteria, controls used, endpoints, and the limited sample size); and
- effect on clinical outcomes including morbidity and mortality was not adequately evaluated.

Safety

Studies providing safety data

The following studies provided evaluable safety data:

1. Clinical studies sponsored by the sponsor. Only 1 study (ALS-1-97-P-301) was conducted for the proposed indication (in children only); the other 3 studies were for other indications:
    a. Study CT04009, in 192 newborns with hypoxic respiratory failure.
    b. Study ALS-94-30, in 203 adults with ARDS.
    c. Study ALS-1-98-A-301, for the prevention of pulmonary oedema after pulmonary thromboendarterectomy for chronic cor pulmonale in 57 adults.
2. Safety data from publications on the use of iNO in the treatment of perioperative PHT in adult and paediatric patients.
3. Post-marketing data of Kinox and VasoKINOX: Prescription tracking and drug safety monitoring in the context of a compassionate use program (referred to as Temporary Authorisation for Use (TAU)) of Kinox in France from 1996 to 2001 and cumulative safety data from periodic safety update reports (PSURs) of Nitric Oxide Air Liquide since January 2002.

For the full clinical evaluation of safety please see Attachment 2.

Patient exposure

In the pivotal study for the proposed indication (Study ALS-1-97-P-301) 106 patients were randomised to the iNO treatment group. The study treatment was administered until the occurrence of the first pulmonary hypertensive episode of sufficient severity to require

treatment or until extubation; however the specific duration of treatment was not reported.

For the other 3 pivotal studies for indications different to that proposed in this submission, in Study CT04009 95 newborns were randomised to receive at least 2 h of iNO; in Study ALS-94-30, 98 adults were randomised to receive 10 ppm iNO for up to 28 days; and in Study ALS-1-98-A-301, 27 adults were randomised to receive 5 ppm iNO for 4 h.

Excluding the patients in the meta-analysis, there were 1,235 children and 462 adults involved in the included publications. However, as many as 46 adults may have been included in more than one publication. Of the total number of patients involved, approximately 844 children and 276 adults received iNO.[44]

Safety issues with the potential for major regulatory impact

Adverse events or safety issues of special interest included withdrawal failure or rebound PHT; raised metHb and/or NO_2 concentrations; left ventricular dysfunction; effects on renal function; neurodevelopmental changes; and pulmonary oedema. Full evaluation and discussion of these can be found in Attachment 2.

Post-marketing data

Periodic safety update reports

The list of PSURs provided in this submission was provided. The adverse reactions were coded with Medical Dictionary for Regulatory Activities (MedDRA) versions from 11.0 to 17.0 due to continuous updates of MedDRA versions.

On average, a patient receives 5 m^3 of nitric oxide 225 ppm or 2.5 m^3 of NO 450 ppm. In total, 143,000 m^3 of nitric oxide 225 ppm and 225,600 m^3 of nitric oxide 450 ppm have been distributed to hospitals since the first marketing authorisation. The estimated number of patients exposed to nitric oxide since the first marketing authorisation is 118,800.

During the period from 25 January 2002 to 23 June 2014, 76 adverse events were reported in spontaneous individual case safety reports in countries where the sponsor has marketing authorisation for iNO, including reports from healthcare professionals, consumers, scientific literature, and Competent Authorities. No serious adverse events have been reported from non-interventional post marketing surveillance or other solicited sources.

The available post marketing data confirm the safety profile of iNO. Nine cases of methaemoglobinaemia, a listed reaction, were reported in the period of January 2002 to June 2014.

For the full evaluation of the post-marketing information please see Attachment 2.

Temporary authorisation for use

Kinox was first authorised in France under a compassionate use program between February 1996 and January 2002. Air Liquide collected safety information during this period; no unexpected AEs associated with iNO were identified.

[44] Note: the exact number cannot be determined.

Evaluator's conclusions on safety

Although the safety profile of iNO is well characterised because of its extensive use in children and adults for more than two decades in different clinical conditions (including in the treatment of perioperative PHT), the safety database in this submission is limited because the reporting of safety in publications is heterogeneous and incomplete.

In the present submission, the clinical safety of iNO has been evaluated based on:

1. Clinical studies sponsored by the sponsor (ALSI);
2. Safety data from publications on the use of iNO in the treatment of perioperative PHT in adult and paediatric patients; and
3. Published safety studies in other indications.

A total of four clinical studies were sponsored by ALSI; one clinical study was conducted within the indication in paediatric patients, and three were conducted in other indications (one in newborns with hypoxic respiratory failure, one in adults with ARDS, and one in the prevention of pulmonary oedema after pulmonary thromboendarterectomy for chronic cor pulmonale in adults).

The safety evaluation focussed on deaths and other serious adverse events (SAE) in the pivotal study in 209 neonates. A total of 9 deaths occurred during the study, including 4 within the first 48 hours and 5 during the observation period (up to 30 days). Among those 9 deaths, 3 occurred in the iNO group and 6 in the N_2 group. None of the reported deaths were considered related to the study drugs.

In Study CT04009, there was no significant difference in the number of deaths or AEs between the iNO group and the conventional treatment control group in newborns with hypoxic respiratory failure.

Limited safety information is provided in the two other studies conducted by the sponsor that compared iNO with placebo in adults. Adverse events were not reported. No significant difference was seen in the number of deaths between groups.

Adverse events were not reported in the majority of publications; the available AE information is included in the summary of AE data from published studies (see Tables 32 and 33 of Attachment 2 for details). No death attributed to iNO treatment was reported in any publication. A total of 59 (of 1,275) paediatric patients and 9 (of 515) adult patients in the included publications died. SAEs were not reported systematically in studies not conducted by ALSI or in published studies.

In the Macrae ALSI study, the metHb levels were monitored after 30 minutes, 3, 6, 12, and 24 hours, and every 12 hours thereafter.[45] The metHb level increased significantly with time, but there was no significant difference between the two groups. Information on metHb and NO2 levels was reported in many, but not all, publications. Rare cases of metHb or NO_2 levels exceeding the upper permitted limit were reported.

Haemodynamic, blood gas, and respiratory parameters were evaluated as primary and secondary efficacy endpoints for each individual study conducted by the sponsor. No effect on SAP was observed in patients receiving iNO due to the selectivity of iNO on pulmonary resistance.

Safety of iNO based on intrinsic or extrinsic factors was not evaluated. No specific drug interactions studies were conducted. There is limited information on use of iNO in pregnant or lactating women. In the submitted studies, iNO was administered at doses up

[45] Macrae, D., Air Liquide Santé study ALS-1-97-P-301. Evaluation of the use of inhaled nitric oxide for the prevention of pulmonary hypertension following congenital heart surgery in children. European iNO clinical trial group Air Liquide Santé, Study report 2006

to 80 ppm and no specific toxicities were observed. iNO does not have any potential for drug abuse.

Withdrawal failure or rebound PHT was a concern associated with administration of iNO. In most publications, the weaning period was described as progressive and uneventful. However, some studies reported an increase in PAP, that is, rebound PHT with weaning (in a total of 53 patients), particularly when iNO was stopped abruptly.

Post-marketing data and safety information from the compassionate use program in France have confirmed the safety profile of iNO. Nine cases of methaemoglobinaemia (which is a listed adverse drug reaction) were reported over the period January 2002 to June 2014. No new event that was likely to modify the evaluation of the safety profile was observed during the period under consideration.

First Round Benefit-Risk Assessment

First round assessment of benefits

The benefits of VasoKINOX in the proposed usage are:

- Selective pulmonary vasodilation resulting in significant decrease in PAP and PVR
- Short-acting, rapidly reversible action
- Does not affect systemic circulation and does not cause decreased SAP
- Improved oxygenation and right ventricular function were observed in the paediatric studies. However, adult studies did not show consistent improvement in oxygenation and right ventricular function following iNO treatment.

First round assessment of risks

The risks of VasoKINOX in the proposed usage are:

- Withdrawal failure with risk of rebound PHT
- Methaemoglobinemia and increase in NO_2
- Potential risk of increased bleeding
- Lack of pivotal controlled studies conducted by sponsors; efficacy and safety based predominantly on published studies which showed inconsistent results
- The majority of patients in paediatric studies included infants; very few toddlers, children and adolescents were included in the paediatric studies
- Long term effects on mortality, neurodevelopmental toxicity, mutagenesis not known
- Risk of off-label use in ARDS
- Risk of pulmonary oedema in adults.

First round assessment of benefit-risk balance

Although 1000 infants and children were evaluated in the submitted paediatric studies, the majority of studies included infants with mean age < 1 year; studies in toddlers, children and adolescents were few with inconsistent results. In the paediatric population, inhaled NO doses ranged from 5 to 80 ppm with the proposed 20 ppm dose used in most studies. In the majority of studies, iNO administration started in the early postoperative period, although administration was later in some studies.

In the published paediatric studies that reported changes in PAP, iNO was effective in reducing PAP by approximately 10% to 30% in paediatric patients with PHT after cardiac surgery. Treatment with iNO appeared to be more effective than N_2, prostacyclin 20 ng/kg/min, and equally effective as conventional therapy, hyperventilation, sildenafil, and aerosolised iloprost. Combination of iNO with Mil produced a greater reduction in PAP than either iNO or Mil alone. Only iNO selectively dilated the pulmonary vasculature; all other active comparators also dilated the systemic vasculature, reducing SAP. In the studies that reported changes in vascular resistance, iNO reduced the PVRI by approximately 15% to 25% and had no significant effect on SVRI. No difference in the reduction of PVRI was seen between iNO and hyperventilation or sildenafil. The combined use of iNO and Mil provided additive benefits as compared with iNO or Mil alone for patients with elevated PVR after Fontan procedure (Cai, 2008). In the studies that reported changes in oxygenation, PaO_2 or the PaO_2:FiO_2 ratio was improved only with iNO. No improvement in oxygenation was seen with prostacyclin, Mil, or sildenafil, despite their effects on PAP. In the studies that reported PHT crises (Miller 2000; Day 2000; Gorenflo 2010; Loukanov 2011), iNO reduced the number of PHT crises compared with N_2, but not compared with conventional treatment or iloprost.[22,26,27,30] In the 2 studies that reported cardiac index (Morris 2000; Stocker 2003), iNO did not affect this parameter, whereas hyperventilation significantly reduced cardiac index.[19,25]

Due to pulmonary selectivity of iNO in postoperative PHT and the absence of systemic effects, in contrast with most comparators, permits the maintenance of SAP, and particularly coronary perfusion pressure, and therefore could allow an improvement in right ventricular function although this was not evaluated in majority of the studies.

Given the limited sample size and the low level of detail in the publications, the comparison of results in sub-populations was not possible.

The sponsors claim that the use of iNO in the treatment of postoperative PHT in newborns, infants, children, and adolescents in the context of cardiac surgery has become the standard therapy (Checchia, 2012), including in Australia.[14]

Based on submitted data, there is evidence to suggest that iNO may provide a therapeutic option for treatment of perioperative PHT in newborns/infants with CHD; however, there is limited evidence to support use in toddlers, children and adolescents. Furthermore, effect of iNO on clinical outcomes such as morbidity/mortality and neurodevelopment were not adequately evaluated.

Twelve randomised, controlled published studies involving 398 adults presenting with PHT after or immediately before cardiac surgery provided evidence to support use of iNO for perioperative PHT in adults. In adults, inhaled NO doses ranged from 4 to 40 ppm. In most of the studies, the dose of iNO was 20 ppm. The time of administration in cardiac surgery patients in most studies was at weaning from CPB. The duration of administration ranged from 15 to 20 minutes in acute haemodynamic studies to several hours (up to the arrival in the ICU or later).

All the published adult studies showed consistent evidence of the efficacy of iNO in postoperative PHT and also demonstrated its pulmonary selectivity. However, the data in adult studies in the current submission were limited by the lack of large, controlled randomised studies, relatively low number of patients in the individual published studies, heterogeneity of the trials and lack of evaluation of clinical outcomes.

The safety data are supported by clinical trials (in neonates only) and publications and by extensive post-marketing data. In general, these data are insufficiently detailed to retrieve maximal safety information, partly because of the context of iNO administration (that is, emergency situations, ICU, or operating rooms). Results of studies consistently demonstrated that within the recommended dosage a selective pulmonary vasodilatation is obtained without reaching clinically significant increase of methaemoglobin and NO_2

level. However, rebound PHT on withdrawal of iNO remains a concern. To avoid the risk of rebound, iNO treatment should not be stopped abruptly. Once iNO has been started with beneficial effects, reasonable attempts to wean patients off iNO should be made every 12 to 24 hours using a weaning protocol. Drug safety monitoring during the compassionate use program and by way the periodic safety reports did not raise any additional safety concerns. Overall, the main safety concerns associated with iNO, metHb and rebound PHT, can be readily avoided or minimised with appropriate dosing of iNO, monitoring, and management.

Inhaled nitric oxide is approved by TGA and also by FDA for the treatment of term and near-term (> 34 weeks) neonates with hypoxic respiratory failure, in conjunction with ventilatory support and other appropriate agents, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation (ECMO).[46] The approval was based on results from several double blind, randomised, placebo controlled, multicentre trials. The Neonatal Inhaled Nitric Oxide Study Group trial documented that iNO reduced the need for ECMO without increasing neurodevelopmental, behavioural, or medical abnormalities at 2 years of age.

Inhaled nitric oxide is well established and widely accepted for use in acute vasodilator testing in adults with PAH due to its selective effect on the pulmonary vasculature and lack of systemic haemodynamic effects (such as hypotension) that can occur with some other forms of vasodilators.[47,48]

Clinical trials evaluating the use of inhaled nitric oxide for numerous indications are ongoing.

The potential therapeutic role of inhaled nitric oxide in adults remains uncertain at this time and FDA approved indications are restricted to paediatric practice.

Increased morbidity and mortality is generally associated with PHT in paediatric and adult patients undergoing cardiac surgery. Inhaled NO, acting as a selective pulmonary vasodilator may provide a useful therapeutic option in these seriously ill patients. However, there is inadequate data on whether these short-term improvements in haemodynamic parameters are translated into beneficial effects on clinical outcomes such as morbidity and mortality.

First Round Recommendation Regarding Authorisation

It is recommended that VasoKINOX be rejected for the proposed indication:

[46] Hypoxic respiratory failure in neonates born at or near term may be caused by such conditions as primary persistent pulmonary hypertension, respiratory distress syndrome, aspiration syndromes, pneumonia or sepsis, and congenital diaphragmatic hernia. According to the American Academy of Paediatrics, conventional therapies, which have not been validated by randomised controlled trials, include administration of high concentrations of oxygen, hyperventilation, high-frequency ventilation, the induction of alkalosis, neuromuscular blockade, and sedation.

[47] Vasodilator testing is performed to determine whether the patient might derive clinical benefit from calcium channel blocker therapy (such as nifedipine). During the vasoreactivity trial, inhaled NO is administered after baseline haemodynamic parameters are measured. Haemodynamic measurements are repeated after inhalation of NO for five to ten minutes at doses between 10 and 80 parts per million. The ability of vasoreactivity testing with inhaled NO to predict nifedipine-induced vasodilation of the pulmonary vasculature has been confirmed in several small studies. Ricciardi et al (1998) demonstrated that vasodilation of the pulmonary vasculature induced by inhaled NO at a dose of 80 ppm predicted an acute haemodynamic response to nifedipine with a sensitivity, specificity, and predictive accuracy of 88, 100, and 94 percent, respectively.

[48] Scientific Rationale – Update May 2010 file:///C:/Users/Me/Downloads/InhaledNitricOxideTherapy.pdf

'*VasoKINOX indicated in conjunction with ventilatory support and other appropriate active substances for the treatment of perioperative pulmonary hypertension in adults and newborn infants, infants and toddlers, children and adolescents, ages 0-17 years in conjunction to heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation by increasing the pulmonary flow.*'

The main reasons for rejection at this stage are:

- Although 1000 infants and children were evaluated in the submitted paediatric studies, the majority of studies included infants with mean age < 1 year; studies in toddlers, children and adolescents were few with inconsistent results.
- Lack of adequate randomised, controlled clinical trials in adults.
- Although reduction in pulmonary arterial pressure was shown in most of the paediatric and adult studies, effects on right ventricular function and oxygenation were not evaluated in many studies and did not show consistent results.

Although the proposed indication does not make claims for effects on morbidity/mortality, it is important to evaluate effects on clinical outcomes following short-term improvements in haemodynamic parameters following administration of iNO to patients in conjunction with cardiac surgery; there was inadequate data regarding this in the submitted data.

Clinical Questions

For details of the clinical questions and sponsor's responses please see Attachment 2.

Second Round Evaluation of clinical data submitted in response to questions

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

Second Round Benefit-Risk Assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of VasoKINOX in the proposed usage are unchanged from those identified in the first round assessment of benefits.

Second round assessment of risks

After consideration of the responses to clinical questions and evaluation of additional data provided by the sponsors in their response to the TGA's requests for information, the risks of VasoKINOX in the proposed usage are:

- Withdrawal failure with risk of rebound PHT
- Methaemoglobinaemia and increase in NO
- Potential risk of increased bleeding
- Risk of off-label use in ARDS

- Risk of pulmonary oedema in adults.

However, the proposed product information (PI) and Australian RMP have included adequate measures to minimise the risks associated with iNO when used for the proposed indication.

Second round assessment of benefit-risk balance

The benefit-risk balance of VasoKINOX for the modified proposed indication:

> *'VasoKINOX is indicated in conjunction with ventilatory support and other appropriate active substances for the treatment of perioperative pulmonary hypertension in adults and newborn infants, infants and toddlers, children and adolescents, aged 0-17 years in conjunction to heart surgery'*

is unfavourable, but would become favourable if the changes recommended in the following section are adopted.

Second round recommendation regarding authorisation

It is recommended that the application to register VasoKINOX for the following indication be rejected:

> *'VasoKINOX is indicated in conjunction with ventilatory support and other appropriate active substances for the treatment of perioperative pulmonary hypertension in adults and newborn infants, infants and toddlers, children and adolescents, aged 0-17 years in conjunction to heart surgery.'*

It should be noted that according to the ARTG the TGA has recently approved (30 July 2015) an extension of indication to the Australian alternative approved nitric oxide product for the same indication in the paediatric age group of 0 to 17 years.

> '*Interpretation of results from adult studies was limited by study design, heterogeneous patient population, sample size and lack of evaluation of clinical outcome. Although iNO may be beneficial in some adults with perioperative pulmonary hypertension such as those with pulmonary hypertension and right ventricular dysfunction, there is not enough data based on submitted studies to determine which subgroups of the adult patient population could benefit from iNO.'*

Due to lack of adequate evidence to support use in adults, a modified indication (which excludes adults) may be approved:

> *'VasoKINOX is indicated in conjunction with ventilatory support and other appropriate active substances for the treatment of perioperative pulmonary hypertension in newborn infants, infants and toddlers, children and adolescents, aged 0-17 years in conjunction to heart surgery.'*[49]

[49] Note; the approved indication following completion of evaluation process differs from this recommendation and is located in summary and outcome sections of document.

VI. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan, EU-RMP, Australian Specific Annex version 01 dated 5 March 2015 which was reviewed by the RMP evaluator.[50].

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown below in Table 3.

Table 3: Sponsor's summary of the ongoing safety concerns

Summary	Ongoing safety concerns
Important identified risks	Rebound phenomenon Risks associated to the medical device Methaemoglobinaemia Inhibition of platelet aggregation Inflammatory reaction and lesions to airway
Important potential risks	None
Important missing information	None

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance for all the safety concerns. No additional pharmacovigilance is considered necessary by the sponsor.

RMP evaluator's comment

The sponsor's plan is acceptable.

Risk minimisation activities

Routine risk minimisation has been proposed to mitigate all the safety concerns. Educational material for healthcare professionals is also been proposed to help mitigate all the safety concerns.

RMP evaluator comment

The sponsor has advised in the Australian Specific Annex (ASA) that the educational material presented in Annex 2 of the EU-RMP will be provided to healthcare professionals. The sponsor should confirm whether the content of the educational material distributed in Australia will be identical to that in Annex 2 of the EU-RMP.

In regard to the proposed routine risk minimisation activities, the draft PI and Consumer Medicines Information (CMI) documents appear to be consistent with those approved for

[50] The final version of the RMP that was approved was VasoKINOX EU-Risk Management Plan (EU-RMP), version 3.3 dated 10 April 2015(data lock point 13 January 2014) with Australian Specific Annex version 02 dated 3 November 2015

INOmax by the TGA and the Summary of Product Characteristics (SPC) approved in the UK. Therefore, they are considered acceptable in the context of RMP.

Reconciliation of issues outlined in the RMP report

Table 4 summarises the TGA's first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA and the TGA's evaluation of the sponsor's responses.

Table 4: Reconciliation of issues outlines in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
1. The following safety concerns have been found to be associated with nitric oxide inhalation: a. Pulmonary oedema and worsening of left ventricular dysfunction in patients with left ventricular dysfunction and patients with elevated baseline pulmonary capillary pressure (important identified risk); b. Airway injury from NO_2 (important potential risk); c. Bleeding and thrombocytopenia (important potentials risk). The evaluator has noted that warnings against these safety issues have been included in the draft PI. Nonetheless, they should be added in the ASA.	[Information redacted]	The evaluator has noted that the addition of the following safety concerns: Pulmonary oedema in patients with pre-existing left ventricular dysfunction; · NO_2 formation; · Inhibition of platelet aggregation and increased bleeding time. It is also noted that airway injury and toxicity have been discussed under the risk of NO_2 formation. The sponsor's response is satisfactory.
2. The sponsor has advised in the EU-RMP that pregnant and breastfeeding women have not been studied. The sponsor also states in the draft PI that 'the safety in premature infants less than 34 weeks of gestation has not been established'. These should be added as 'missing information' in the ASA.	[Information redacted]	The evaluator has noted the addition of 'use during pregnancy and lactation' in the RMP as missing information. The sponsor's response is acceptable.
3. It should be noted that educational materials to healthcare professionals are considered additional risk minimisation. It should be detailed in the ASA as such.	[Information redacted]	The evaluator has noted the inclusion of the content of pocket guide in 'Table 1: Comparison of Risk minimisation activities in the EU and Australia' in the updated ASA. The sponsor's response is acceptable.
4. The sponsor has advised in the ASA that the	[Information redacted]	The evaluator has noted the inclusion of the draft Pocket

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
educational material presented in Annex 2 of the EU-RMP will be provided to healthcare professionals. The sponsor should confirm whether the content of the educational material distributed in Australia will be identical to that in Annex 2 of the EU-RMP.		guide in Annex 1 of the updated ASA. The sponsor's justification to the differences between the content of the pocket guide in the EU and Australia is reasonable, therefore, this is acceptable.

Summary of recommendations

There are no outstanding issues in relation to the RMP for this submission.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Suggested wording for conditions of registration

RMP

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

The suggested wording is:

> Implement EU-RMP version 3.3 dated 10 April 2015 (data lock point 13 January 2014) with Australian Specific Annex version 02 dated 3 November 2015 and any future updates as a condition of registration.

VII. Overall conclusion and risk/benefit assessment

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

Quality

The pharmaceutical chemistry evaluator has no objections to approval of this submission.

NO is a colourless gas manufactured through the reaction of sulfuric acid (diluted to 55%) with a 40% sodium nitrite solution. VasoKINOX is a blend of nitric oxide 0.0450 mol and nitrogen 0.99955 mol held under pressure at 20,000 kPa (200 bar). It is presented as compressed gas in cylinders with a white painted body and turkish blue painted shoulder. The stability data support a shelf life of three years when stored at temperatures from -10°C to 50°C.

Nonclinical

The nonclinical evaluator noted that no new nonclinical information about the primary pharmacology, secondary pharmacodynamics, pharmacokinetics and single dose toxicity of nitric oxide was provided in the submission. The evaluator considered the majority of

the submitted nonclinical data to be unreliable but noted NO is a highly reactive gas that spontaneously oxidises in air to form nitrogen dioxide in the dosing systems. Nitrogen dioxide is a respiratory toxin and causes increased airway reactivity and pulmonary oedema. It also reacts with water within the respiratory tract to produce nitrous acid, also an airway toxin. The mutagenic potential of NO was demonstrated in mutation assays and in vitro mammalian cell models, and chromosome aberrations were seen in Chinese hamster ovary cells and gene mutations were seen in rat lung cells in vivo.

The evaluator noted the submitted nonclinical data demonstrated that subacute repeated daily exposure to ≤ 100 ppm NO (6 hours/day) in rats did not result in physiologically adverse methaemoglobinaemia but was concerned that an incomplete range of toxicological endpoints were examined. In particular, detailed evaluation of respiratory/pulmonary inflammation (for example bronchoalveolar lavage evaluations, a more complete range of tissue inflammation biomarkers) was not performed.

The nonclinical evaluator's major concern was the maximum dose proposed by the sponsor. The evaluator noted the maximum recommended exposure for the alternative approved nitric oxide is 20 ppm, and sought nonclinical data from the submission in support of the sponsor's proposed maximum dose of 40 ppm. The nonclinical evaluator expressed particular concern about adverse effects in the respiratory tract at exposure levels of 40 ppm in various models. The evaluator also noted toxic effects of 20 ppm in a hyperoxic environment (fraction of inspired oxygen (FiO_2) 0.95), and there was concern about renal tubular epithelial apoptosis in piglets exposed to 40 ppm iNO for 30 hours.

The evaluator considered that the sponsor's data showed a concentration of 20 ppm is as equally efficacious as 40 ppm. The evaluator concluded that there were insufficient nonclinical data to support an increase in maximum exposure to 40 ppm based on the nonclinical data and that this dose would require clinical justification.

Clinical

Pharmacology

The sponsor provided information from published literature to describe the pharmacokinetics of inhaled NO (iNO), a summary of which follows:

- 55% of radiolabelled iNO reached the alveoli and 90% of the alveolar NO was absorbed.
- Once absorbed it rapidly binds to deoxygenated or oxygenated Hb with higher affinity than oxygen or carbon monoxide.
- iNO has a half-life of 6 to 10 seconds.
- The binding of NO to oxyHb forms nitrosylated Hb that rearranges to metHb with the release of nitrates. Exposure to 25 ppm for 1 hour resulted in an increase in metHb from 7 to 13 μM, and no change in nitrosohaemogloblin.
- Absorbed NO was detected as NO_3, which had a plasma half-life of 6 to 7 hours, clearance was. About 70% was found in the urine in the form of nitrates, mostly in the first 24 hours.

The PD studies in the submission were conducted in HVs or patients with ARDS and showed:

- In the arteriolar pulmonary vasculature NO produces vasodilation through the activation of guanylate cyclase and generation of cyclic guanosine monophosphate (cGMP) and the subsequent activation of cGMP dependent kinase protein. It has a

rapid onset and offset of action. It has a selective action on the pulmonary circulation because of its very short plasma half-life and its effects are localised to well ventilated areas of lung, improving intrapulmonary shunting.

- Dose related (range 1 to 100 ppm) increases in PaO_2 and dose related reductions in PVR and PAP were reported in the ARDS studies, although maximal improvement in PaO_2 was seen in patients given 10 ppm. In a study of 9 neonates and 8 children with ARDS the optimal dose in neonates was 20 ppm and in children 10 ppm.

Additional PD information was included in efficacy studies supporting the indication as it is included in the discussion of those studies.

No specific drug interaction studies were included in the submission. Interactions are predicted with drugs known to induce metHb formation (for example, alkyl nitrates, sulphamides, prilocaine) and drugs that act as NO donors (sodium nitroprusside or glyceryl trinitrate).

Efficacy

The sponsor provided four clinical studies in the submission; however three studies were not of direct relevance to the proposed indication (for newborns with hypoxic respiratory failure, adults with ARDS, and for the prevention of pulmonary oedema after pulmonary thrombarterectomy for chronic cor pulmonale in adults). Evidence from 27 evaluable publications (including two versions of the same meta-analysis) was presented in support of the efficacy of iNO in management of pulmonary hypertension in the peri- and post-operative setting in patients undergoing cardiac surgery.

Efficacy in children

Efficacy in children was supported by four studies considered of most relevance by the evaluator.

Miller (2000)

Miller (2000) [22] reported a prospective, randomised, double blind study of the efficacy of iNO 10 ppm versus placebo in 124 infants (median age 3 months (interquartile range (IQR): 1 to 5 months)) with large ventricular, atrioventricular septal defects, truncus arteriosus or total anomalous pulmonary venous drainage with high pulmonary flow, pressure or both, undergoing corrective surgery for congenital heart disease administered iNO or nitrogen (placebo) for up to 7 days.[22] Randomisation was stratified by diagnosed Down's syndrome and occurred prior to surgery. A sample size of 136 patients was required to provide 80% power to detect a 50% reduction in the number of pulmonary hypertensive crises (PHTC) events with a two-sided significance level of 0.05. Clinically important pulmonary hypertension (PAP/SAP > 0.5 with haemodynamic instability or > 0.75 at any time) was managed by a standardised protocol of sedation and muscle relaxation, IPPV, vasopressors, and vasodilators, and additional open label iNO if required. Patients were well matched for demographic characteristics type of cardiac lesion and baseline haemodynamics. There were no withdrawals during the study. The study was discontinued prematurely because of logistical reasons (both the principal research fellow and the principal investigator were due to leave the country in which the study was conducted) and a blinded evaluation of the data by the data safety monitoring committee that determined there was a statistically significant difference of the primary endpoint with the lower number of subjects.

The primary endpoint was the number of PHTCs in the treatment period, which lasted for up to 7 days. Infants who received iNO had significantly fewer PHTCs (median 4 events (IQR 0 to 12)) than infants receiving nitrogen placebo (median 7 events PHTCs (IQR 1 to 19); unadjusted relative risk 0·66 (95% CI 0.59 to 0.74) p < 0·001; adjusted for dispersion 0·65 (0.43 to 0·99), p = 0.045).

The iNO patients reached extubation criteria significantly sooner (80 h (IQR 38 to 121) versus 122 h 63 to 164), p = 0.019). Most (82%) of the infants in the study weaned off the study gas in < 7 days, and the remainder (6 in the iNO group and 15 in the placebo group) weaned at 7 days per protocol. The iNO patients spent less time overall on study gas (87h (IQR 43 to 125) versus 117 h (67 to 168), p = 0.023). The PVRI measured every 12 hours during study-gas administration was also significantly lower in the iNO group (p < 0·001).

Russell (1998)

Russell (1998)[31] (n = 40 studies in 39 children, 3 sets of measurements excluded) conducted a double blind placebo controlled study of the measurements of mPAP in children undergoing cardiac surgery for congenital heart defects with pre-operative pulmonary hypertension given inhaled iNO 80 ppm or placebo at FiO_2 of 0.9.[31] Measurements were taken at baseline, after 1, 10 and 20 minutes of study gas and 1 minute after the discontinuation of study gas. A significant haemodynamic effect for iNO over 20 min compared to placebo, was seen in the subset of the study population consisting of 13 subjects with elevated PAP, (5 received iNO). MPAP was reduced by 19% (range 80 to 35% at 20 minutes) with iNO (p = 0.008) and increased by 9% with placebo. Oxygenation was not changed during the study period.

Morris (2000)

Morris (2000)[19] conducted a small randomised, controlled, open label crossover study (n = 12) of children aged 0.1 to 17.7 years to compare the haemodynamic effects of iNO (5 ppm for 15 minutes then 40 ppm for 15 minutes) with hyperventilation induced alkalosis (HV) to a pH of 7.5 in children recovering from biventricular repair and CPB.[19] After the randomised treatment each group received a combination of iNO and HV. Subjects received treatments for 30 minutes in random order with a 30 minutes washout between treatments. All children received sedation and muscle relaxation, inotropes and other medications as indicated. Eight of the 12 patients received sodium nitroprusside at baseline. No significant changes were observed in PVRI and mPAP with both treatments, relative to baseline, but some improvement could have been due to recovery from CPB with time. There was a decrease in PAP/SAP with iNO compared with baseline but this was not different from HV.

Day (2000)

The open label study by Day (2000)[30] of patients after biventricular repair or heart transplantation with a PAP > 50% of SAP after successful removal from CPB (n = 40 samples from 38 patients) compared the efficacy of iNO 20 ppm with conventional therapy (determined by the treating clinician, using a variety of regimens).[30] The median age in control subjects was 6 months (range 1 day to 3 years) and in the iNO subjects 7 months (range 1 day to 20 years). The baseline PAP was 47 ± 2 mmHg and in the iNO group 52 ± 3 mmHg. The difference did not reach statistical significance but equalled the size of the treatment effect in the iNO group. The primary endpoint, PHTC, occurred in 4 control patients and in 3 iNO patients, a difference that was not statistically significant. There were no statistical differences between treatments for the major secondary endpoints of changes in haemodynamic parameters, but the trends were favourable. SPAP in the control group started relatively low and increased after an hour, whereas sPAP in the iNO group started relatively high and decreased by approximately 10%. The changes in ratio of systolic pulmonary and systemic arterial pressures were greater with iNO than with conventional therapy, and this comparison approached statistical significance (p = 0.066).

Study ALS-1-97-P-301

Study ALS-1-97-P-301 was a randomised, double blind, placebo controlled, parallel design study in 219 children aged 0 to 5 years undergoing corrective procedures for high flow (VSD, AVSD, TGA-VSA truncus arteriosus, AP window) or with obstructed pulmonary

venous return (mitral stenosis, obstructed TAPVD) and at risk of developing PH following surgery to investigate the prophylactic use of low concentrations of iNO (5 ppm) versus N_2 placebo gas in the post–operative ICU setting. The main exclusion criteria were the need for iNO in the operating room, iNO use in the preceding 6 months, known metHb reductase deficiency, platelet count < 50,000/known platelet disorder/coagulopathy or severe left-sided univentricular heart failure. Patients were of mean age 4.5 and 5.5 months in the iNO and placebo groups respectively. Across the study the mean weight was 4.7 kg (2 to 12 kg) and height 58.8 cm (43 to 88 cm). The study was powered to detect a 20% difference in pulmonary hypertensive events between the two treatment groups with 250 evaluable patients. The sample size was not achieved because the study was terminated early due to recruitment difficulties. Events were counted for 48 hours in the high flow lesion group and 4 days in the obstructed lesion group.

The primary endpoint was the percentage patients alive at 48 hours without an episode of pulmonary hypertension warranting additional treatment (12.3% and 12.4% in the iNO and placebo groups, respectively, p = 0.7). The secondary endpoints of mean duration of gas inhalation, mean duration of inhalation and mean duration of stay in ICU were all shorter in the placebo group. There were 3 deaths in the placebo group (one after an episode of PHT) and one death in the iNO group (after an episode of PHT).

Other efficacy studies in children

The remaining 8 efficacy studies in children compared iNO to active alternatives. These studies were not specifically powered to demonstrate differences between iNO and the active alternative.

Cai (2008)

The study by Cai (2008)[20] (n = 46), was an open label, parallel group study in which iNO at a starting dose of 10 ppm and continued for at least 24 hours was compared to intravenous milrinone 0.5 mcg kg^{-1} min^{-1} and a combination of the two treatments in children with pulmonary hypertension after a Fontan procedure.[20] In a 3 group, open label design, each agent was compared to the other agent and to the combination of both agents. Inhaled NO was significantly superior to milrinone for the study's main measure of PVR, and TPG. An improvement in oxygenation was shown in all groups, but greatest in the groups using iNO.

Goldman (1995)

Goldman (1995)[17] (n = 13), was a small, brief, open label crossover study, which showed that iNO 20 ppm was significantly superior to intravenous prostacyclin 20 ng/kg/min in the short-term (10 minute) treatment of severe pulmonary hypertension in paediatric subjects after cardiac surgery.[17] MPAP was reduced by 33% during iNO treatment (95% CI: -24% to -51%), compared to a reduction of 15% during prostacyclin treatment (95% Cl: -4% to -38%; p < 0.01).

Kirbas (2012)

Kirbas (2012)[18] (n = 16), was a small, open label study in paediatric cardiac surgery patients found no difference between the efficacy of iNO 20 ppm (n = 8) and aerosolised iloprost (n = 8) in the treatment of pulmonary hypertension.[18] Favourable reductions in PAP and in PAP/SAP ratio were observed in both groups.

Loukanov (2011)

Loukanov (2011)[27] (n = 15), was a small, open label pilot study comparing iNO 10 ppm and aerosolised iloprost 0.5 µg/kg every 2 h in infants aged 77 to 257 days, 73% of whom had trisomy 21. [27] Similar efficacy between iNO and iloprost to prevent PHTCs was suggested but the study was not adequately powered to demonstrate equivalence. Trends

in MPAP were weakly in favour of iNO. The study by Gorenflo (2010) was thought by the evaluator to be based on the same data as the study by Loukanov.

Stocker (2003)

Stocker (2003)[25] (evaluable n = 15), compared iNO 20 ppm and intravenous sildenafil 0.35 mg/kg in a small, open label crossover study in infant cardiac surgery patients, showing that the two drugs were similar in their ability to lower mPAP and PVRI.[25] In the iNO-first group, mPAP had fallen after 20 min of therapy, reducing by 1.4 ± 0.4 mmHg (by 7.8 ± 2.1%; p = 0.008). The subsequent addition of sildenafil did not further lower PA pressure. In the sildenafil first group, mPAP had also fallen by 20 min; the reduction seen with sildenafil was numerically greater than that seen in the iNO first group when expressed as a percentage of baseline, but the fall was not statistically significant (reduction of 10 ± 4.1%; p = 0.055). The subsequent addition of iNO produced a further fall in mPAP. The authors noted that iNO had greater pulmonary selectivity.

Efficacy in adults

Efficacy in adults was supported in 6 publications considered important by the sponsor:

Argenizano (1998)

Argenizano (1998)[34] published a single centre, double blind, randomised controlled trial in 11 adults receiving a left ventricular assist device (LVAD) for advanced heart failure with significant PHT after weaning from CPB.[34] Patients received a 15 minute trial of either iNO at 20 ppm or N_2. Non-responders were given the alternative treatment in a blinded manner and responders continued the assigned treatment until arrival in ICU where the study gas was weaned. All patients initially assigned N_2 crossed over to iNO. In the 6 patients initially assigned iNO PAP decreased from 35 ± 6 mmHg to 24 ± 4 mmHg (p = 0.02) and in the 5 patients that switched to iNO PAP decreased from 31 ± 4 mmHg to 22 ± 3 mmHg (p = 0.002). LVAD flow index increased from 1.9 ± 0.2 to 2.7 ± 0.3 L min^{-1} m^2 and 2.0 ± 0.2 to 2.5 ± 0.2 L min^{-1} m^2 in the initial iNO and crossover groups, respectively.

Knothe (1996)

Knothe (1996)[35] was a randomised study to investigate the effect of iNO 30 ppm compared with conventional treatment in 10 patients undergoing valve replacement surgery requiring ECMO support, with a PAP > 25 mm Hg 10 minutes after returning to conventional ventilation.[35] Treatment with iNO for 20 minutes significantly reduced PAP and PVR, with half the effects seen in the first 3 minutes and the remainder in the first 10 minutes. PaO2 (FiO_2 = 1.0) decreased by a small amount in the iNO and conventional therapy groups (377 ± 60.7 to 317 ± 65.9 mmHg, and 341 ± 118.1 to 315 ± 132.0 mmHg, respectively). SVR increased in both groups, statistically significantly in the iNO group, without a difference in CI, central venous pressure (CVP) or PCWP.

Fernandes (2011)

Fernandes (2011)[39] was a single centre study in 29 adults with severe PH (systolic PAP >60 mmHg) compared iNO (10 ppm starting immediately before weaning from CPB, n=14) with oxygen (n = 15).[39] Baseline characteristics were similar between the patients, although the iNO group was an average of 4 years older. The primary endpoints were change in CI and PVR from baseline to 48 hours. CI improved from baseline in both groups at 24 hours but was sustained at 48 hours in the iNO group with a mean increase of 1.58 L/min/m^2 (95% CI 1.0 to 2.16, p < 0.0001) versus 0.4L/min/m^2 (95% CI 0.01 to 0.81L/min/m^2, p = 0.06) in the oxygen group. PVR reductions were significant at 24 and 48 hours for the iNO group only (34%, p < 0.005). Secondary endpoints were changes in sPAP, PCWP, postoperative complications (renal insufficiency, reintubation, sepsis, cardiogenic shock and need for re-operation), total ICU stay was shorter (2.0 (IQR 0.25) days versus 3.0 (IQR 7.0) days), and number of systemic vasoactive drugs was smaller in

the iNO group in particular 14% versus 40% noradrenaline, and 29% and 60% Mil. There were fewer predefined complications in the iNO group 29% versus 60%.

Solina (2001)

Solina (2001)[41] was a dose response study comparing iNO 10ppm (n = 11), 20 ppm (n = 12), 30 ppm (n = 12) and 40 ppm (n = 12) with Mil 0.5 µg/kg/min (n = 15) in adult cardiac surgery patients aged 66 to 73 years with preoperative PHT, from the separation from CPB to the arrival of the patient in ICU.[41] The patient had similar baseline characteristics except for less fentanyl use in the 30 ppm group and more valve replacement surgeries in the Mil and 20 ppm groups. Percentage reductions of PVR were 38% (10 ppm), 50% (20 ppm), 44% (30 ppm), 36% (40 ppm) and 58% (Mil), and were not statistically significantly different between the groups (p = 0.86). Other haemodynamic variables were also not statistically significantly different between the groups.

Fattouch (2005)

Fattouch (2005)[40] was a single centre, three way crossover study investigating iNO 20 ppm, inhaled prostacylin and IV nitroprusside (control) use in 58 patients admitted to ICU after mitral stenosis repair.[40] Study medication was given for 30 minutes with a 15 minute washout-out between treatments. There were reductions in PVR (45%/50%/45%), TPG (62%/64%/44%) and mPAP (19%/20%/21%) in the iNO/prostacyclin/nitroprusside groups. Cardiac output and stroke volume were not significantly changed in the iNO group and were increased in the prostacyclin group.

Solina (2000)

Solina (2000)[42] was a single centre, open label, randomised study comparing intravenous milrinone, iNO 20 ppm and iNO 40 ppm in 45 adults with preoperative PHT undergoing cardiac surgery with CPB.[42] After the administration of anaesthesia the mPAP and PVR were significantly greater in the iNO 20ppm group but other baseline characteristics were similar. After initiation of treatment there were no differences in PVR, SVR or CI. At arrival in ICU, the iNO 20 ppm group had a significantly higher MAP, and the iNO 40 ppm group had a higher RVEF (30%/33%/40% for the Mil and iNO 20 ppm and iNO 40 ppm groups respectively, $p < 0.05$)). The Mil group required more phenylephrine support than the iNO groups (p = 0.01).

Winterhalter (2008)

Winterhalter (2008)[36] was a single centre, randomised parallel group study comparing 30 minutes of iloprost (20 µg in 2 mL of NaCl) (n = 23) and iNO 20 ppm (n = 23) in adult patients, mean age 68 to 69 years, with PHT during weaning from CPB after cardiac surgery.[36] Both therapies significantly reduced mPAP and PVR and significant increased cardiac output ($p < 0.0001$). Iloprost had a greater reduction in PVR (p = 0.013) and mPAP (p = 0.0006) but iNO increased PaO_2 whereas iloprost reduced it (not statistically significant). Iloprost significantly increased heart rate and reduced SVR. The inotropic support required was similar in both groups and both weaned from CPB.

Rajek (2000)

Rajek (2000)[43] was a randomised, double blind study that compared intravenous PGE1 (n = 34) and iNO (n = 34) for the treatment of PH in adult patients undergoing orthoptic heart transplant for ischaemic or idiopathic dilated cardiomyopathy.[43] Both treatments started 10 minutes before weaning from CPB 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. Both treatments were stopped 6 hours postoperatively. Patients were switched to alternative treatments if the PAP was consistently elevated on maximal treatment with the allocated therapy. Immediately after weaning from CPB iNO reduced PVR by about half and PGE1 by 10%, PAP was reduced by 30% by iNO and 16% by PGE1. At 6 hours after surgery, PVR and PAP were similar but PGE1 increased the ratio of PVR to SVR by about 30% while iNO reduced

the ratio by about 20%. CO, HR, mSAP, RAP and PCWP did not differ between the groups. Six patients were switched from the PGE1 group because of high PVR and right ventricular failure. Weaning from CPB was successful in all iNO patients. At 6 hours the PVR was the same in both groups but the PGE1 patients needed more inotropic support. Although most patients weaned from their allocated therapy 6 hours post-operatively 6 patients in the iNO groups needed a slower wean (over a maximum of 48 hours).

Other studies

The following studies were also included in the submission and were considered by the evaluator to be of relevance.

Schmid (1999)

Schmid (1999)[33] was a single centre, prospective, randomised, crossover study comparing iNO 40 ppm, intravenous PGE1 0.1 µg/kg/min and glyceryl trinitrate (GTN) 3 to 5 µg/kg/min in 14 adults aged 25 to 76 years, 24 hours after undergoing cardiac surgery (mostly mitral valve replacement).[33] Each treatment was administered for 20 minutes followed by a wash-out period of 20 minutes. Each treatment resulted in reductions in PAP and PVR. PGE1 and GTN significantly reduced SAP and SVR (serious hypotension occurred in 3 GTN and 2 PGE1 patients), iNO and PGE1 increased cardiac index, and PGE1 increased RVEF. At study completion all patients were given PGE1. All were discharged from hospital and long-term follow up revealed one death each from gastric cancer (3 months after discharge) and unknown cause (9 months after discharge).

Fattouch (2006)

Fattouch (2006)[40] reported additional details of the study reported by Fattouch 2005 (see above), including 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 nitroprusside group.[40] Compared to prostacyclin iNO increased in PaO_2 but had a lesser reduction in PVR and PAP, but unlike iNO, prostacyclin reduced SVR and increased HR and cardiac output.

Khan (2009)

Khan (2009)[37] was a prospective, crossover study comparing iNO 20 ppm and inhaled prostacyclin (20 µg/mL) in 25 adult patients (aged 59 ± 2 years) undergoing heart or lung transplant.[37] 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. There were no significant differences between the groups 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 PHT or RV dysfunction.

Matamis (2012)

Matamis (2012)[38] compared iNO 10 ppm and oral sildenafil (100 mg) alone or in combination in 20 adult patients with PHT after cardiac surgery for valve replacement.[38] Treatment was either iNO for 90 minutes with sildenafil administered after 30 minutes, or oral sildenafil followed after 60 minutes by 30 minutes of iNO. Both sildenafil and iNO significantly reduced mPAP and PVRI. Sildenafil also decreased SAP and SVRI when given initially or after iNO. Sildenafil alone but not iNO alone reduced the PaO_2: FiO_2 ratio, but this was not reversed by the addition of iNO. The combination therapy regardless of the order of administration reduced PAP and PVRI greater than monotherapy. CI was not significantly changed by either treatment.

Safety

Safety information from 53 publications, clinical studies submitted by the sponsor, and post-market data for KINOX and VasoKINOX have been considered. In Study ALS-1-97-P-301 the focus of the sponsor's safety reporting was death and SAEs. Among the 219 children there were 9 deaths occurring during the study including 4 deaths within the first 48 hours and 5 during the observation period. Of those 3 were exposed to iNO, and none were considered related to iNO. Of the 19 SAEs, one, a PHTC at the end of the iNO administration was reported possibly related to iNO. No statistically significant differences in methaemoglobinaemia were reported in the placebo and nitrogen groups, with maximum levels of 7.4% and 1.7% in the nitrogen and iNO groups, respectively at 48 hours.

The publications provided a limited account of the safety of NO, focussing on deaths, SAEs, and adverse events of specific interest, and the adverse events gleaned from the publications cannot be considered a comprehensive account of adverse effects that may be seen with the use of NO. Overall 1,235 children and 462 adults, including 46 adults that may have appeared in more than one study, were exposed to study medication and of those 844 children and 276 adults were exposed to iNO.

Deaths occurred in 61 children and 11 adults exposed to study medications, all attributed to disease progression, complications of surgery or unrelated causes rather than iNO. SAEs were not systematically reported in the publications.

The following is a summary of adverse effects identified in the submission:

- Rebound pulmonary hypertension (especially with abrupt discontinuation or rapid weaning of iNO) can result in bradycardia and circulatory collapse. Cardiac arrest (ventricular fibrillation (VF)) was reported by Argenziano after abrupt disruption of NO supply in an adult patient.[34]
- Methaemoglobinaemia, a recognised adverse effect with iNO was monitored for in the clinical trials, publications and in the post-market safety information. The highest reported dose was in a case study (Syed, 2013) with metHb levels of 56.4% with iNO 20 ppm. The highest in a clinical trial was 8% (Goldman, 1995) with a 20 ppm dose, and decreased to 4% when the dose was reduced to 15 ppm.[17] The sponsor has recommended dose adjustment if metHb is > 2.5%.
- Nitrogen dioxide levels were inconsistently reported in publications, and levels were generally below 5 ppm, however levels of 8.4 ppm in a child and 6.4 ppm in an adult were reported. At 2 ppm in humans pulmonary toxicities are observed and the sponsor has recommended an alert threshold of 1 ppm for NO_2, which is higher than the alternative approved nitric oxide recommendation of 0.5 ppm.
- Use in pregnancy: 11 women exposed to iNO 5 to 80 ppm had no reported increase in maternal metHb levels, but there is no information on foetal methaemoglobinaemia from clinical trials.
- Electroencephalogram (EEG) abnormalities in 11 patients from a retrospective case review showed background slowing, low-voltage activity, with a suppression burst pattern in two patients and sharp waves in another 2 patients. The abnormalities were non-specific and reversible, and causality with iNO was not established. Nitric oxide is rapidly inactivated in Hb so possible mechanisms are unclear.
- Patients with heart failure due to left ventricular dysfunction were shown to have a 23% increase in mean PCWP associated with a 31% decrease in PVR after 10 minutes of iNO 80 ppm. Pulmonary oedema has been reported in patients with left ventricular dysfunction.

- A plausible mechanism for reduced platelet function arising from the action of iNO on guanylate cyclase, supported by animal studies, did not emerge as a safety signal in the submission but may not have been sought as an outcome.
- A review undertaken by the sponsor did not establish a causal link between iNO and impaired renal function in adult patients.
- No safety signals were detected in a long-term follow-up study of neonates given iNO for PPHN (Walsh et al).[51]

Clinical evaluator's recommendation

The clinical evaluator recommended approval of VasoKINOX for use in children but considered there to be insufficient evidence in support of its use in adults and proposed a modification of the sponsor's indication as follows:

> *VasoKINOX is indicated with ventilatory support and other appropriate active substances for the treatment of perioperative pulmonary hypertension in newborn infants, infants and toddlers, children and adolescents aged 0 to 17 years in conjunction to cardiac surgery.*

Risk management plan

The TGA has accepted EU-RMP version 3.3 dated 10 April 2015 (data lock point 13 January 2014) with Australian Specific Annex version 02 dated 3 November 2015. There were no outstanding matters for consideration.

Risk-benefit analysis

Delegate's considerations

Efficacy

The sponsor has requested an indication that includes patients of all ages with pulmonary hypertension in the context of cardiac surgery. The evidence in support of this request is dominated by published literature, with studies that are heterogeneous in terms of study design, comparator, dosage regimen and measured endpoints.

For the paediatric population, most of the evidence comes from younger children. This is clinically relevant because the correction of major congenital abnormalities often begins in infancy. Four key studies support the indication in children, of which the study by Miller is considered pivotal and measured clinical (number of PHTCs) and haemodynamic endpoints.[22] The study was conducted in a clinical setting and for durations of treatment for which iNO is likely to be used. The outcomes need to be considered in the context of its early termination for logistical reasons. The majority of the remainder of the efficacy studies are small and heterogeneous in design and dosing, and there are methodological concerns with some. However, the effect of iNO on haemodynamic parameters was well demonstrated and some studies demonstrated clinical endpoints such as a reduction in the number of PHTCs. The sponsor's study excluded patients with more severe disease (requiring treatment in the operating suite) and used suboptimal doses of iNO as prophylaxis rather than treatment. It lacked adequate power to detect a statistically significant difference for the primary endpoint and was terminated early because of

[51] Walsh, M et al., Two year neurodevelopmental outcomes of ventilated preterm infants treated with inhaled nitric oxide. *J Pediatr* 2010; 156: 556-561

recruitment difficulties. Its support for the proposed indication is limited but it does suggest that 5 ppm is an insufficient dose for efficacy.

The evidence to support the use in adults is sparser than that provided for the use in children. The duration of exposure to determine efficacy for most studies was short. Most of these studies had methodological issues, and all had small patient numbers. The doses ranged from 4 to 40 ppm. Most studies had haemodynamic endpoints but few had other clinical endpoints. Whilst Fernandes measured endpoints such as postoperative complications, total ICU stay and number of additional vasoactive drugs required the outcome data are based on 14 patients.[39]

Evidence has been provided of the haemodynamic effects and can be summarised as a reduction in PVR, mPAP and increased oxygenation (when reported). Pulmonary selectivity for the haemodynamic effects has been demonstrated in a number of studies. Although there are many years of post-market experience internationally with the use of iNO for this indication, this is can be only considered somewhat supportive of the use of iNO. Overall, the evidence is considered just sufficient to support an indication for use in the paediatric population. It is not clear that the sponsor has presented sufficient evidence to support the efficacy of iNO in the adult population. The ACPM is requested to comment.

Safety and RMP

Safety information was limited in the published studies. The safety information from the sponsor's study is limited by the use of doses lower than those proposed for the use in children or adults, and was focussed on deaths and SAEs.

Among the studies and publications in the submission the safety concerns of methaemoglobinaemia and nitrogen dioxide toxicity were identified, and the safety consequences of sudden interruption of therapy including cardiac arrest were reported, but none of the studies was large enough to detect uncommon or rare events and none of sufficient duration, or with sufficient long term follow-up, to determine the longer term consequences of use in this indication. Some reassurance of the long term consequences of exposure in the neonatal period for persistent pulmonary hypertension of the newborn was provided in the study by Walsh.[51]

The sponsor has proposed the use of VasoKINOX be limited to cardiothoracic units that have received adequate training in the use of a nitric oxide delivery system, and should be prescribed and supervised by a physician experienced in cardiothoracic anaesthesia and intensive care. This restriction appears appropriate given the likely clinical scenarios for its use and the risks associated.

The safety of 40 ppm was questioned by the nonclinical evaluator, who was concerned about the local alveolar effects of concentrations of NO at or above 40 ppm, and at 20 ppm in a hyperoxic environment. The absence of methaemoglobinaemia with doses of 40 ppm does not remove the concern about the local pulmonary toxicity of NO. In the presence of high concentrations of oxygen animal models showed lung abnormalities with 20 and 40 ppm NO, and while high concentrations of oxygen alone have been shown to cause pulmonary toxicity in juvenile animals, not all studies were conducted using high fractions of inspired oxygen. There are limited clinical data to support the use of doses greater than 20 ppm in adults. Among the 6 studies suggested by the sponsor as the main adult studies only 27 of the 274 exposed patients received 40 ppm, and the actual duration of exposure is unclear from the information provided. The additional study by Schmid added 14 extra patients exposed for 20 minutes.[33] The robust clinical data required to address the nonclinical evaluator's concerns about iNO doses higher than 20 ppm is lacking in the submission.

An acceptable RMP has been provided.

Dose

The sponsor has proposed a starting dose of 10 ppm and a maximum dose of 20 ppm in the paediatric population and in adults a maximum dose of 40 ppm. Doses of 4 ppm to 80 ppm were included in the publications. A starting dose of 10 ppm up to a maximum dose of 20 ppm is supported. As noted above the evidence was not sufficiently robust to mitigate the concerns of the nonclinical evaluator about doses greater than 20 ppm. A subgroup of patients in whom the benefits outweigh the risks of potential toxicity at these doses was not identified in the submission. The ACPM is requested to comment.

Indication

The clinical evaluator has recommended an amended indication as follows:

> *'VasoKINOX is indicated with ventilatory support and other appropriate active substances for the treatment of perioperative pulmonary hypertension in newborn infants, infants and toddlers, children and adolescents aged 0–17 years in conjunction to cardiac surgery.'*

The ACPM will be requested to provide advice regarding the adequacy of the submission to support an indication in adults.

Data deficiencies

The following were the major data deficiencies in this submission:

- This was a predominantly literature based submission. The publications were of varying ages, the studies of variable quality and varied detail.
- The most studied population were children less than 5 years and the information for older children (especially those aged 12 to 17) and adults was limited.
- The individual studies were of insufficient size to detect rare or uncommon adverse events and the safety information in many of the publications was limited.

Conditions of registration

The following were proposed as conditions of regarding:

Implement EU-RMP version 3.3 dated 10 April 2015 (data lock point 13 January 2014) with Australian Specific Annex version 02 dated 3 November 2015 as agreed with the TGA and any future updates.

Additional conditions may be imposed following consideration of the submission by the ACPM.

Questions for the sponsor

The sponsor was requested to respond to the following questions in the pre-ACPM response:

1. For the ACPM, please provide a brief summary of the clinical evidence that supports the use of iNO in adults in the context of cardiac surgery.
2. For the ACPM, please provide a brief summary of the clinical evidence that supports nitric oxide doses greater 20 and less than 40 ppm.
3. A continuous supply of iNO is crucial during the period the treatment is prescribed. Please explain how the delivery system allows uninterrupted supply in the event of ventilator failure or if BVM ventilation is required.
4. The sponsor states in the PI that 24 hour technical support is available. Please provide a brief description of the support. Is it only provided for hospital staff using the sponsor's device with the sponsor's nitric oxide cylinders?

5. As noted by the clinical evaluator the quality of the published safety data does not allow a global analysis of AEs. Please justify the frequencies reported for the AEs in the Tabulated list of adverse reactions.
6. Please identify the clinical trials in which thrombocytopenia is listed as a common adverse effect.
7. The majority of studies did not report a change in systolic blood pressure or did not report the systolic blood pressure. Please describe the evidence for including hypotension as a common adverse reaction.
8. Please discuss the reasons an alert threshold should be set at 1 ppm for NO2 when the PI includes an instruction to reassess the delivery system if a level of > 0.5 ppm is detected.

Proposed action

The Delegate has no reason to say, at this time, that the application for VasoKINOX should not be approved for registration for use in the paediatric population. However, the Delegate is not in a position to say, at this time, that the application for use in the adult population should be approved for registration.

The Delegate's suggested indication is a follows:

> *'VasoKINOX is indicated in conjunction with ventilator support and other appropriate active substances for the treatment of perioperative pulmonary hypertension in newborn infants, infants and toddlers, children and adolescents, ages 0 to 17 years in conjunction to heart surgery.'*

Request for ACPM advice

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

1. Is there sufficient evidence to support the claims about changes in haemodynamic parameters proposed for the indication?
2. The sponsor has requested indications for the use in children and adults with pulmonary hypertension in the context of cardiac surgery.
    a) Has the sponsor provided sufficient evidence to support the use of nitric oxide in adults?
    b) If so, has the sponsor provided adequate evidence to support the efficacy and safety of nitric oxide concentrations greater than 20 ppm in adults?

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

The sponsor submitted its response to the TGA's 'Request for ACPM's Advice' addressing the matters raised by the delegate for ACPM consideration. The sponsor firmly believed that this information will assist the ACPM considering the summary of issues raised by the Delegate and provides information regarding the advice sought from the committee and will permit the committee to recommend approval for VasoKINOX in all proposed indications. Sponsor's comments on evaluations and Delegate's request for advice [Information redacted].

Advisory Committee Considerations

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

VasoKINOX gas in cylinders containing 450 ppm mol/mol of nitric oxide has an overall positive benefit–risk profile for the (amended) indication:

> *'VasoKINOX is indicated in conjunction with ventilator support and other appropriate active substances for the treatment of perioperative pulmonary hypertension in conjunction with heart surgery, in order to selectively decrease pulmonary arterial pressure'*

In making this recommendation the ACPM:

- noted the difficultly of expecting better quality clinical trials data in this challenging group of critically ill patients
- considered evidence in support of efficacy and safety for the proposed 20 ppm maximum dose in children was adequate
- considered the evidence in support of a maximum dose of 40 ppm for adult patients was inadequate to support safety and efficacy.

Proposed conditions of registration

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

Specific Advice

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

1. *Is there sufficient evidence to support the claims about changes in haemodynamic parameters proposed for the indication?*

The ACPM advised that, by the nature of the submission (a mixture of small studies and some literature studies), data were provided on only very small numbers of patients in each group detailed in the sponsor's proposed indication.

It should be noted that showing a haemodynamic benefit does not mean a clinically important patient benefit. There are several small studies that showed no meaningful benefit. The numbers are too small to support any of the specific claims in the sponsor's proposed indication. This also included the specific age groups nominated, particularly the adolescents.

2. *The sponsor has requested indications for the use in children and adults with pulmonary hypertension in the context of cardiac surgery.*
    a. *Has the sponsor provided sufficient evidence to support the use of nitric oxide (NO) in adults?*

The committee was of the view that the use of nitric oxide in the treatment of perioperative pulmonary hypertension is not universally considered 'standard care' and there are alternative selective pulmonary vasodilators such as inhaled prostaglandins.

Despite this, NO has a history of two decades of use for the treatment of pulmonary hypertension in ventilated patients in ICU; in neonates (PPHN) and with both cardiac and non-cardiac surgery in children and adults. It has significant 'off-label' use in adults and some evidence of both safety and efficacy from submitted trials. In addition, there is large post-marketing safety data (n = 600,000) providing reassurance on safety in general.

The ACPM noted the sponsor's amended indication proposed in the pre-ACPM response to restrict use in adults undergoing cardiac surgery to those having mitral valve surgery, heart transplantation, left ventricular assist device implantation.

The ACPM was of the view that there were insufficient numbers of patients in the studies submitted in these individual surgeries to support such a specific indication.

b. If so, has the sponsor provided adequate evidence to support the efficacy and safety of nitric oxide concentrations greater than 20 ppm in adults?

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 INOmax).

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.

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

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of VasoKINOX nitric oxide 450 ppm mol/mol medicinal gas for inhalation supplied via compressed gas cylinders, indicated for:

> *'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.'*

Specific conditions of registration applying to these goods

The VasoKINOX EU-Risk Management Plan (EU-RMP), version 3.3 dated 10 April 2015(data lock point 13 January 2014) with Australian Specific Annex version 02 dated 3 November 2015, included with submission PM-2014-04327-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

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

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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