EU Risk Management Plan for

Nitric Oxide (NO)
INOmax®

RMP version to be assessed as part of this application:

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Summary of significant changes in this RMP:	Alignment to Guidance on the format of the risk management plan (RMP) in the EU - in integrated format (Rev. 2.0.1). Safety concerns: Addition of Important Identified risk, following Pharmacovigilance Risk Assessment Committee (PRAC) recommendation on signals (EMA/PRAC/537837/2024): - *Risk of pulmonary oedema in patients with PVOD*
Details of the currently approved RMP:	
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Approved with procedure:	EMEA/H/C/000337/II/051
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Approved by:	Name Carola López EU-QPPV	Date and signature The content of this RMP has been reviewed and approved by the MAH's QPPV. The electronic signature is available on file.

Reviewed by:	Name Peter Kalin Global QPPV and Safety Physician Linde GmbH	Date and signature The content of this RMP has been reviewed and approved by the MAH's QPPV. The electronic signature is available on file.

Table of Contents

List of Tables

Abbreviations

ACT	activated clotting time
ADR	adverse drug reaction
AE	adverse event
aPTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
ASD	atrial septal defect
ATC	anatomical therapeutic chemical
AVSD	atrioventricular septal defect
BPD	bronchopulmonary dysplasia
CABG	coronary artery bypass graft
cAMP	cyclic adenosine 3',5'-monophosphate
CDH	congenital diaphragmatic hernia
cGMP	cyclic guanosine 3',5'-monophosphate
CHMP	committee for medicinal products for human use
CMDh	coordination group for mutual recognition and decentralised procedures - human
CPB	cardio pulmonary bypass
DIC	disseminated intravascular coagulation
DLP	data lock point
DNA	deoxyribonucleic acid
DSB	double-strand breaks
ECC	extracorporeal circulation
ECMO	extracorporeal membrane oxygenation
EEA	European economic area
EMA	European Medicines Agency
EU	European Union
EURD	European Union reference date
FDA	Food and Drug Administration (US)
FiO_2	fraction of inspired oxygen
FUM	follow-up measure
HCP	healthcare professional
HFOV	high frequency oscillation ventilation
IBD	international birth date
IFU	instruction for use
iNO	inhaled nitric oxide
IVH	intraventricular haemorrhage
kg	killogram
LHC AB	Linde Healthcare AB
LVAD	left ventricular assist device
MA	marketing authorization
MAH	marketing authorization holder
MAS	meconium aspiration syndrome
MetHb	methaemoglobin
ml	millilitre

N_2	nitrogen
NO	nitric oxide
NO_2	nitrogen dioxide
NODS	nitric oxide delivery system
PAH	pulmonary artery hypertension
PaO_2	partial pressure of arterial oxygen
PAP	pulmonary artery pressure
PCWP	pulmonary capillary wedge pressure
PGE	prostaglandin E
PGI	prostaglandin I (prostacyclin)
PH	pulmonary hypertension
PIL	package information leaflet
PPHN	persistent pulmonary hypertension in the newborn
ppm	parts per million
PRAC	pharmacovigilance risk assessment committee
PSMF	Pharmacovigilance system master file
PSUR	periodic safety update report
PT	prothrombin time
PVR	pulmonary vascular resistance
QPPV	qualified person for pharmacovigilance
RMP	risk management plan
ROP	retinopathy of prematurity
RoW	rest of the world
RV	right ventricular
SD	standard deviation
sGC	cytosolic guanylate cyclase
SmPC	summary of product characteristics
TAPVD	total anomalous pulmonary venous connection
TEG	thromboelastogram
UK	United Kingdom
USA	United States of America
V/Q	ventilation/perfusion
VSD	ventricular septal defect

Part I: Product(s) Overview

Table 1 Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Nitric oxide (NO) Chemical name: NO The CAS number: 10102-43-9 IUPAC name: Nitric oxide Other non-proprietary names: Nitric oxide (USAN, BAN) Nitrogen monoxide Nitrogen(II) oxide
Pharmacotherapeutic group(s) (ATC Code)	Other respiratory system products (R07 AX)
Marketing Authorisation Holder	Linde Healthcare AB (LHC AB)
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	INOmax
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Medicinal gas
	NO Despite its structural simplicity NO has a wide and complex biological action. NO is a compound produced by many cells and a potent endogenous mediator with a role in blood pressure control as well as in neurotransmission and immune function. When inhaled as a gas at low concentrations NO relaxes the vascular smooth muscles and produces pulmonary vasodilatation. Thus, inhaled nitric oxide (iNO) has been shown to reverse pulmonary vasoconstriction due to a variety of causes. Studies in animals support that iNO exerts its activity mainly by vasodilatation in ventilated lung regions, thus improving ventilation perfusion (V/Q) matching and reducing pulmonary artery pressure (PAP) and subsequent pulmonary vascular resistance (PVR). When administered to newborns with severe respiratory distress, it improves V/Q matching and therefore improving oxygenation. It also decreases PAP, reduces pulmonary artery hypertension (PAH). The effects associated to low clinical parts per million (ppm) dose of iNO is selective, due to the rapid uptake by the haemoglobin. There are no significant systemic effects associated to the clinical use of INOmax. The primary mode of action by which inhaled NO relaxes pulmonary vasculature (relaxation of smooth muscle) is by binding to the haeme moiety of cytosolic guanylate cyclase (sGC) to synthesize cyclic guanosine 3',5'-monophosphate (cGMP).

	The increased cellular levels of cGMP subsequently activates cGMP-dependent protein kinase, which results in vasodilatation.
Hyperlink to the Product Information	See the Product Information for medicinal NO, INOmax, in Module 1.3.1
Indication(s) in the EEA	Current: Medicinal NO, INOmax, in conjunction with ventilatory support and other appropriate active substances, is indicated: • for the treatment of newborn infants ≥ 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation (ECMO). • as part of the treatment of peri- and post-operative pulmonary hypertension in adults and newborn infants, infants and toddlers, children and adolescents, ages 0-17 years in conjunction to heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation.
	Proposed: Not applicable
Dosage in the EEA	Current: • Persistent Pulmonary Hypertension in the Newborn (PPHN): The maximum recommended dose of INOmax is 20 ppm and this dose should not be exceeded. Starting as soon as possible and within 4-24 hours of therapy, the dose should be weaned to 5 ppm providing that arterial oxygenation is adequate at this lower dose. Inhaled nitric oxide therapy should be maintained at 5 ppm until there is improvement in the neonate's oxygenation such that the FiO_2 (fraction of inspired oxygen) reaches < 0.60. Treatment can be maintained up to 96 hours or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from INOmax therapy. The duration of therapy is variable, but typically less than four days. • Pulmonary hypertension associated with heart surgery: Newborn infants, infants and toddlers, children and adolescents, ages 0-17 years: the starting dose of inhaled nitric oxide is 10 ppm of inhaled gas. The dose may be increased up to 20 ppm if the lower dose has not provided sufficient clinical effects. The lowest effective dose should be administered and the dose should be weaned down to 5 ppm provided that the PAP and systemic arterial oxygenation remain adequate at this lower dose. Clinical data supporting the suggested dose in the age range 12-17 years is limited.

	Adults: the starting dose of inhaled nitric oxide is 20 ppm of inhaled gas. The dose may be increased up to 40 ppm if the lower dose has not provided sufficient clinical effects. The lowest effective dose should be administered and the dose should be weaned down to 5 ppm provided that the PAP and systemic arterial oxygenation remain adequate at this lower dose. The effects of iNO are rapid, decrease in PAP and improved oxygenation is seen within 5-20 minutes. In case of insufficient response, the dose may be titrated after a minimum of 10 minutes. Consideration should be given to discontinuation of treatment if no beneficial physiological effects are apparent after a 30-minute trial of therapy. Treatment may be initiated at any time point in the peri-operative course to lower pulmonary pressure. In clinical studies treatment was often initiated before separation from Cardio Pulmonary Bypass (CPB) in order to facilitate the weaning from extracorporeal circulation (ECC). iNO has been given for time periods up to 7 days in the peri-operative setting, but common treatment times are 24-48 hours.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Medicinal gas for inhalation, compressed. 400 ppm mol/mol NO in N_2. 800 ppm mol/mol NO in N_2.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

a) Persistent Pulmonary Hypertension in the Newborn

The product is indicated for the treatment of newborn infants ≥ 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension (PH), in order to improve oxygenation and to reduce the need for ECMO.

b) Pulmonary hypertension associated with heart surgery

The product is indicated as part of the treatment of peri- and post-operative PH 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 RV function and oxygenation.

- ## Incidence and prevalence

a) Persistent Pulmonary Hypertension in the Newborn (PPHN)

PPHN is a well-known complication during the neonatal period, which is manifested by elevated PAP and PVR. PPHN occurs as a primary developmental defect or as a condition secondary to other diseases such as meconium aspiration syndrome (MAS), pneumonia, sepsis, hyaline membrane disease, congenital diaphragmatic hernia (CDH), and pulmonary hypoplasia. In these states, PVR may be high, secondary to right-to-left shunting of blood through the patent ductus arteriosus and foramen ovale.

The overall incidence of PPHN ranges from 2–4 per 1,000 live births, but the proportion of all newborns with associated with respiratory failure accompanied can be as high as 10%. Newborns diagnosed with PPHN are typically full-term or late preterm infants with no significant congenital anomalies and exhibiting severe respiratory failure within hours after birth, requiring intubation and mechanical ventilation. In this group, the incidence of PPHN can reach 5.4 per 1000 live births, with mortality rates varying between 4% and 33%. Recent studies show that PPHN is increasingly observed in premature infants, primarily due to the underdeveloped pulmonary vasculature, resulting in PPHN being frequently a neonatal emergency in the neonatal intensive care unit. PPHN-related in-hospital mortality rates associated with PPHN ranges from 3.0%–57.9%, with the highest rates reported in Asia and the lowest in the United States of America (USA) and the United Kingdom (UK)[1].

In neonates with PPHN and respiratory failure, INOmax can reduce the PAP and improve oxygenation, as indicated by significant increases in the partial pressure of arterial oxygen (PaO_2).

b) Pulmonary hypertension associated with heart surgery

Cardiac surgery is performed primarily in middle aged adults and elderly individuals but is also not uncommonly performed in the paediatric population born with heart malformations. Traditionally, cardiac surgical procedures have occurred under CPB; however, off - pump and minimally invasive techniques are alternatives in certain procedures depending on patient characteristics[2]. As a result, patients undergoing heart surgery are becoming older and present with more complex cardiac disease and subsequently the risk for right heart failure and PAP in conjunction to weaning from cardio-pulmonary by-pass is increasing[3].

In high income countries, an average total cardiac surgical volume of 123.2 per 100,000 population per year was performed (range, 27.3 in South Korea to 271.5 in the USA) for 24 countries with available data[4]. Table 2 Part SI.1 summarises annual volumes:

Table 2 Part SI.1. Annual Cardiac Surgical Volumes per 100,000 Population

	Procedural volume per 100,000 population per year

Surgical procedure	Average	Range
All cardiac surgery	123.2	27.3-271.5
Coronary artery bypass grafting	36.7	7.7-64.5
Valve surgery	30.8	12.7-55.2
Congenital heart surgery	7.9	1.2-18.2

Indication for surgery is to improve cardiac performance/cardiac function and patients scheduled for heart surgery having compromised cardiac reserve. In patients undergoing heart surgery, an increase in PAP due to pulmonary vasoconstriction is not infrequently seen, especially associated to the weaning from heart-lung machine. Classical manoeuvres to reduce pulmonary artery hypertension include optimising oxygenation, correction of acidosis, sedation and potentially relaxation. Selective vasodilators are needed to reduce PAP and the risk of acute cardiac failure especially during weaning from CPB.

iNO is a mainstay therapy for the management of pulmonary arterial hypertension and RV failure associated with weaning from CPB following heart and heart/lung transplant. iNO has been shown to reduce PVR, selectively and reverse acute increases in PAP and pulmonary artery hypertension increasing RV ejection fraction and thereby improve pulmonary circulation and oxygenation, without causing any reduction in systemic pressure. Intravenous NO-donors such as nitroglycerin or nitroprusside in contrast reduce PAP but also commonly have effects, reduces systemic pressure thus jeopardising tissue perfusion[5-7].

Some degree of cardiac failure is most frequently seen among patients scheduled for cardiac surgery. The prevalence of acute heart failure in patients undergoing heart surgery is obviously high taking in consideration that more than 60% have chronic heart failure. 1.5- to 2.5 % of these patients require perioperative aortic balloon pumping assistance to prevent cardio-circulatory collapse. Despite mortality in relation with cardiac surgery has been decreased around the world, it may vary between 1-7% depending on the underlying condition and type of surgery[8]. INOmax is thus commonly used in conjunction to surgical correction of congenital heart disease and in conjunction with adult heart surgery.

Severe postoperative PH has been described to occur following 2% of cardiac procedures, and is associated with high morbidity and mortality[9].

INOmax has been shown effective in reducing PH and improving RV function in conjunction to heart surgery in children as well as adults. It is commonly used also in heart transplant in order to improve RV function, facilitate circulation and graft function[10].

- **Demographics of the population in the authorised indication - age, gender, racial and/or ethnic origin and risk factors for the disease**

The product can be used regardless of gender, racial and/or ethnic origin.

Elevated PVR and resultant pulmonary arterial hypertension is a common postoperative complication after congenital heart surgery. PAH can acutely elevate RV afterload with resultant RV dysfunction and may cause low cardiac output syndrome and potentially cardiac arrest in the postoperative period. Several factors contribute to its development, including CPB, which is associated with a systemic inflammatory response syndrome, involving mediators, such as interleukin 6, interleukin 10, tumour necrosis factor α, P-selectin and E-selectin, leptin, soluble

intercellular adhesion molecule and vascular cell adhesion molecule, and fractalkine[11]. Mitral valve procedures and more complex congenital heart disease corrections requiring prolonged period on CPB increases the risk for pulmonary artery hypertension during the postoperative course[12].

PH is also commonly seen preoperatively in infants with congenital heart lesions and is associated with pulmonary overcirculation, such as truncus arteriosus or atrioventricular canal. In addition, children undergoing cavopulmonary connections for single ventricle lesions require low PVR for surgical success. iNO can attenuate PH in at-risk postoperative patients, reduce the number of PH crises, and shorten time on mechanical ventilation[11,12].

Patient factors that contribute to PH include cardiac physiology, comorbid conditions, and some genetic syndromes.

The cardiac physiologies most at risk for development of PAH are those associated with:

1. Increased pressure load to the pulmonary arterial system;
2. Impaired egress of blood from the pulmonary arterial tree, mitral valve stenosis, or restrictive atrial communication in cases of hypoplastic left heart syndrome;
3. Pre-existing PH (e.g., restrictive cardiomyopathy) in heart transplant patients.

Comorbid conditions, such as CDH, and some genetic syndromes, in particular Down syndrome, can also be risk factors for develop of PAH. Prevention is the initial approach to postoperative PH. iNO is thus indicated pre- as well as post-operatively in children undergoing correction for congenital heart disease in order to prevent and/or treat elevated pulmonary pressure and impaired RV function. In the entire perioperative period the use of iNO decreases vascular tone and is an effective agent in the treatment of PH. As a selective pulmonary vasodilator, iNO reduces PVR and may benefit those patients with PH. iNO represent a beneficial approach for patients with significant RV dysfunction and/or PH electively reducing PAP without compromising the systemic blood pressure[11].

- **The main existing treatment options**

Alternative pulmonary vasodilators include intravenous nitroglycerin, sodium nitroprusside, prostaglandins (PGE_1, PGI_2) and phosphodiesterase inhibitors, which are known to dilate both the pulmonary and systemic circulations. These agents produce non-selective with an obvious risk for impaired systemic blood pressure[11,13-16]. Results published from a study conducted to compare nebulization of iloprost (a synthetic analogue of PGI_2) to inhaled NO in the management of children with secondary PH who underwent congenital cardiac surgery, showed that both iNO and aerosolized iloprost are effective to selectively reduce pulmonary arterial pressure without effects on the systemic circulation[17]. Neither NO nor inhaled iloprost caused a significant change in the arterial tension and central venous pressure values, whereas they caused an increase in the heart rate and cardiac output values and a decrease in the pulmonary arterial pressure and ratio of PAP to systemic artery pressure values. No serious adverse events (AEs) and mortality was detected in either group.

- **Natural history of the indicated condition in the untreated population, including mortality and morbidity**

Hypoxic respiratory failure (as result of PPHN) is a serious and potentially fatal diagnosis that carries a high risk of associated neurological complications (for mortality rates please refer to Incidence and prevalence). Thus, intensive care is most commonly required. Intensive care of the

newborn is associated high risk for cerebral haemorrhage, pulmonary haemorrhage, retinopathy and enterocolitis.

iNO is indicated for the treatment of newborn infants ≥ 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of PH, in order to improve oxygenation and to reduce the need for ECMO, which was the only treatment available before iNO was approved[18] . iNO has been demonstrated to improve oxygenation and reduce the need for ECMO.

In Europe and in certain regions in the rest of the world, inhaled NO is also indicated as part of the treatment of peri- and post-operative PH 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 RV function and oxygenation. iNO is frequently used peri-operatively, to prevent or treat PH crises, improve oxygenation, and increase cardiac output[12].

- ## Important co-morbidities

The primary therapeutic action of NO is the relaxation of both vascular and non-vascular smooth muscle, with a selective vasodilatation of the pulmonary vasculature by binding to the haeme moiety of sGC, activating guanylate cyclase and increasing intracellular levels of cGMP, which then leads to vasodilation.

- **Hypoxemia in newborn patients with persistent pulmonary hypertension:** In newborn patients with PPHN, the PVR is high, which results in hypoxemia secondary to right-to-left shunting of blood through the patent ductus arteriosus and foramen ovale. The efficacy of INOmax has been investigated by means of the trials NINOS and CINRGI in term and near-term newborns with hypoxic respiratory failure resulting from a variety of aetiologies (see above). The treatment of term- and preterm neonates with INOmax (initial concentration of 20 ppm) together with oxygen reduce the occurrence of the composite endpoint death and/or initiation of ECMO showing a significant advantage for the nitric oxide treated patients.

  In hypoxic preterm infants (gestational age <29 weeks) the treated with INOmax in a dose of 5 ppm or nitrogen did not show improvement in alive without bronchopulmonary dysplasia (BPD). No difference in the incidence of intraventricular haemorrhage (IVH) or death was however observed in this study.

  Hypoxic respiratory failure is a serious and potentially fatal condition that carries a high risk of associated complications. Newborn with severe respiratory failure commonly need intensive care and oxygen supplementation. Pulmonary haemorrhage, intracranial bleeding or retinopathy of prematurity are principally related to intensive care of the newborn. Altogether INOmax can improve oxygenation in neonates with PPHN, as indicated by significant increases in PaO_2.

  a) Pulmonary Haemorrhage

  Pulmonary haemorrhage is not infrequently seen in preterm neonates especially in conjunction to intensive care including assisted ventilation. Previous information sent within the first RMP (e.g.: INOT27 study) as well as the follow up an evaluation of the literature show that occurrence of pulmonary haemorrhage is similar in patients treated with iNO as

in non-treated (control) preterm neonates. For this reason, pulmonary haemorrhage is not considered a potential risk and therefore not further included in the RMP.

b) Intracranial Bleeding

Cerebral bleedings are not uncommon events in the neonatal patient population. Premature neonates are more vulnerable than term neonates and a number of specific factors (prematurity, hypoxia, acidosis, frequent intensive care handling and medications, etc.) may contribute to the occurrence of cerebral bleeding. The cumulative evaluation of cerebral bleed (studies and literature) does not provide any clear association to iNO therapy. For this reason, cerebral bleed is not further considered a potential risk and therefore not included in the RMP.

c) Retinopathy of Prematurity (ROP)

ROP was identified based on a publication by van Sorge[19]. The authors of this publication reported that the use of iNO in pre-term neonates is a risk factor for the development of ROP. However, other risk factors known to be associated with the development of ROP should be considered, including maternal preeclampsia, low birth weight, presence of pulmonary haemorrhage, duration of ventilation support, and repeated episodes of hyperoxia and hypoxia.

The US-Marketing Auhorisation Holder (MAH) (IKARIA in those days) Global Safety Database containing both post market AEs and serious AEs reports was queried to identify all reported cases of ROP, and the evaluation of data indicated that ROP is not a risk associated with the use of INOmax. Thus, a signal was closed and refuted. ROP is monitored via routine pharmacovigilance.

- **Patients suffering of cardiac impairment/diseases**

  INOmax increase the PaO_2 by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from lung regions with low V/Q ratios toward regions with normal ratios. When inhaled, NO exerts its effects on the respiratory and cardiopulmonary system. Therefore, further relevant co-morbidities are cardiac impairment/disease and different degrees of severity of this condition including impairment of other vital functions. These relevant co-morbidities were well studied.

  In patients suffering of cardiac impairment/disease, an increase in PAH due to pulmonary vaso-constriction is frequently seen, also as a complication during weaning from CPB following heart and heart/lung transplant during the intervention. It is also commonly used after surgical correction of congenital heart disease in both adults and children and in conjunction with adult heart surgery. The most important co-morbidity is complex heart disease. Other co-morbidities may be of very heterogeneous nature taking in consideration of age and aetiology of the heart disease.

  iNO has been shown to selectively reduce PVR and reduce the increased PAP. This may increase the RV ejection fraction. These effects in turn lead to improved blood circulation and oxygenation in the pulmonary circulation.

  Additional information to incidence, prevalence and mortality is available above in this section.

Part II: Module SII - Non-clinical part of the safety specification

1. Safety Specification

A review of pre-clinical data throughout the life-cycle for INOmax is here summarised. In basic original marketing application, the methaemoglobin (MetHb) formation and subsequent toxicology was identified as main pre-clinical safety signal. NO_2 formation and potential effect on haemostasis was also addressed. NO_2 levels were not always specified, mainly in the older studies.

The pharmacology of iNO relevant to its use is centred upon NO's selective properties of causing vasodilatation of hypertensive pulmonary vasculature. Its mechanism of action through generation of c-GMP in smooth muscle cells has been extensively reviewed[20-22]. Inhaled NO enters the circulation, but red blood cells prevent systemic vasodilatation, by forming MetHb. The nitric oxide reaching the pulmonary circulation may also have effects of passing platelets.

The non-clinical efficacy and safety documentation supporting the original MA application for PPHN was based on studies published in the literature and company sponsored studies of which the majority of them were safety studies. These data were assessed in an Expert Report written by Dr. Heywood[23]. To support a marketing renewal of INOmax in 2006, an Expert Statement focusing on information on the pharmacology and toxicology of NO published between the years of 2000 and 2005 inclusive were submitted[24]. The conclusion draw by Dr. Heywood in his assessment was that literature reports (2000-2006) "on inhaled NO are not considered to raise any new safety signals for NO as used in its licensed indication at doses of 5-20 ppm".

No relevant new safety signals were identified in non-clinical *in-vivo* or *in-vitro* studies since its renewal in 2006.

A 2-year rat carcinogenicity and chronic toxicity study with iNO (see below) as well as a 6-month safety and pharmacology study in sheep have been finalized since the marketing renewal providing significant reassurance regarding the safety of the 20 ppm dose of iNO. The 2-year rat study was assessed by the Committee for Medicinal Products for Human Use (CHMP) in association with a Follow-Up Measure (FUM) and a requested Type II variation to change the product label under section 5.3 of the Summary of product characteristics (SmPC) (FUM 013 and variation EMEA/H/C/337/II/0017). As a result, the SmPC was updated to provide information that uterine adenocarcinoma in the 2-year rat carcinogenicity study was tentatively considered treatment related. However, within the procedure EMEA/H/C/00337/II/0036 approved by the CHMP in November 2013 and by the European commission in January 2014, the re-valuation and analysis of the data showed that the finding of a single uterine adenocarcinoma in the high dose NO treatment is insufficient evidence to consider it tentatively related to treatment and the most likely explanation is that it is a spontaneous lesion. Thus, the SmPC was updated to reflect the absence of a test article related effect on uterine adenocarcinomas in the 2-year rat study (N005243) (See also section 3.3 Carcinogenicity).

Furthermore, literature searches were conducted periodically by the US-MAH (IKARIA in those days) utilizing Medline and Embase databases. A free-text search was performed in these databases using the terms "inhaled nitric oxide" or "nitric oxide inhalation" or "nitric oxide administration". Searches were limited to "animals", and no review articles were identified.

The literature review indicated that iNO was well-tolerated in various animal disease models using sheep, rabbits, rats, and mice. Taken together, no new clinically relevant safety signals were identified for iNO in these animal studies.

2. Pharmacokinetics

Linde Healthcare AB is currently not conducting non-clinical studies with nitric oxide.

iNO is administered by inhalation and rapidly taken up by the haemoglobin, forming MetHb. Nitric oxide is a reactive species and thus reacts with oxygen forming NO_2. There is a subsequent transformation into peroxynitrite, and elimination by renal excretion.

3. Toxicology

3.1 Single and repeat-dose toxicity

Linde Healthcare AB is currently not conducting non-clinical studies with nitric oxide.

For the original MA for PPHN Single dose toxicity studies in mice, rats and dogs were reported. The data was mainly from published literature. Repeat dose toxicity Studies were conducted in the mouse, rat and rabbit. The mouse and rabbit data came solely from published literature. Nitric oxide pre-clinical results are that acute toxicity is primarily related to the formation of MetHb and subsequent decrease in oxygen and oxygen delivery.

Acute toxicity was evaluated in Sprague Dawley rats (5 animals/sex/group) as part of a 7-day range-finding study after iNO exposure by nose-only for 6 hours per day for 1, 3, or 7 days with iNO concentrations of 80, 200, 300, 400, or 500 ppm (Study Nos. SC940063, RDR-0149DS, and RDR-0151DS). In addition, information on acute toxicity is also available from the 28-day study in Sprague Dawley rats (15 animals/sex/group) with iNO after exposure by nose-only for 6 hours per day with iNO concentrations of 40, 80, 160, 200, or 250 ppm (Study Nos. SC940064, RDR-0150DS, and RDR-0152DS).

In the 7-day rat study, mortality was noted at 300 ppm and higher, starting on day 1. Survivors in the 300 ppm dose group had pale or blue-tinted skin. In the early death animals, brown discoloration of the lungs was noted at necropsy without any correlating microscopic changes. MetHb levels were increased in all iNO dose groups, with animals in the 80 ppm iNO dose group having a minimal increase in MetHb on Day 7 and animals in the 200 ppm dose groups and above significant increases in MetHb, starting on Day 1.

In the 28-day rat study, mortality was noted at 200 ppm and higher, with 1/15 female death at 200 ppm on Day 2 of the study. Clinical signs similar to those noted in the 7-day rat study were observed at the higher dose groups.

No separate acute toxicology studies were performed in non-rodents. However, tolerability of iNO in non-rodents can be derived from the two cardiovascular safety pharmacology studies in dogs and a 6-month sheep study. Anesthetized dogs were exposed for 6 hours to iNO concentrations of 0, 80, 160, 320, or 640 ppm. At 640 ppm, 1 out of 3 animals died within 4 hours after exposure to iNO (Study No. SC940065). No adverse in-life findings were noted at lower concentrations, although cardiovascular parameters were affected. In the second cardiovascular safety pharmacology study, conscious dogs were exposed for 4 hours to iNO concentrations of 40, 80, 160, or 320 ppm and no adverse in-life findings were observed (Study No. RDR-0087-DS). As in rats, a dose-related increase in MetHb was noted in both dog studies.

The dose-limiting toxicity from iNO in both rats and dogs at higher concentrations of iNO was considered anoxia due to methaemoglobinemia.

A series of repeat-dose toxicity studies were conducted in rats (one 7-day, nose-only, GLP; one 28-day, nose-only, GLP; one 2-year, whole body, GLP) and in sheep (6 months, nasal cannula, non-GLP) [Study Nos. SC940063, RDR-0149DS, RDR-0151DS, SC940064, RDR-0150DS, RDR-0152DS, N005243, and ABRAB1].

The 28-day toxicology study was performed in Sprague Dawley rats (15 animals/sex/group) with iNO after exposure by nose-only for 6 hours per day with iNO concentrations of 40, 80, 160, 200, or 250 ppm (Study Nos. SC940064, RDR-0150DS, and RDR-0152DS). A 28-day recovery period was included (5 animals/sex/group). In this 28-day rat study, lethality was observed after single, 6-hour exposures at concentrations primarily $\geq$ 250 ppm iNO with 1 animal dying after a single 6-hour exposure of 200 ppm. Clinical observations included respiratory distress, lethargy, blue-tinted skin, and ataxia. In the early death animals, brown discoloration of the lungs was noted at necropsy without any correlating microscopic changes. Exposures of up to 160 ppm were tolerated with findings limited to animals appearing pale and elevated MetHb levels. At $\geq$ 200 ppm, findings were similar to those reported above after a single exposure. Based on the increase in MetHb at 160 ppm and higher, the NOAEL in the 28-day rat study was 80 ppm and the maximum tolerated dose 160 ppm.

The only dose-limiting toxicity observed in rats exposed to iNO was MetHb formation, which at high concentrations led to hypoxia and death.

There were no findings attributed to iNO exposure in a 2-year study in rats at daily 20-hour exposures of 5, 10, or 20 ppm (see 3.3 Carcinogenicity).

In the 6-month non-GLP repeat-dose efficacy and safety study in sheep (ABRAB1), iNO was well-tolerated and did not result in adverse findings at doses of 0.23 mg/kg per hour, the highest dose employed.

Although early studies in the literature attributed a number of adverse findings in the lung to iNO exposure, there were no respiratory tract (including nasal passage) abnormalities identified on routine microscopic evaluation of hematoxylin and eosin sections at any of the concentrations evaluated (even those associated with lethality in the Sponsor conducted studies where exposure to NO_2 was tightly controlled and monitored). When the lungs from animals exposed to 200 ppm iNO 6 hours/day for 1, 7, and 28 days were examined by electron microscopy, findings were limited to increased incidence and severity of interstitial oedema that was most pronounced after a single exposure and was similar to controls at 28 days. Therefore, it is likely that the formation of NO_2 may have played a role in the literature reported adverse findings and that iNO does not adversely affect respiratory tissues.

A safety and pharmacology study was conducted in female sheep to evaluate long-term administration of iNO. Five female sheep per group were administered placebo or test article 18 hours/day for 6 months via nasal cannula. Three animals per group were sacrificed after 6 months and 2 animals per group after a 1-month recovery period. For all iNO groups, the same calculated dose (0.23 mg/kg per hour) was attained by varying the pulsed volumes/breath and using different cylinder concentrations. Doses employed were placebo (N_2 gas), 400 (20 mL pulses/breath), 800 (10 mL pulses/breath), or 2000 ppm iNO (4 mL pulses/breath) and were all well-tolerated. The only test article-related effect noted in all iNO groups was an increase in MetHb, which did not result in any adverse findings. No test article-related effects were noted on all other clinical

pathology parameters, airway mechanics, gross pathology, and histopathological evaluations. Thus, the NOAEL in the 6-month sheep study was 0.23 mg/kg per hour (see also Table 3 Part SII.1).

Table 3 Part SII.1: Doses in repeat-dose toxicology and pharmacology studies, expressed as lung burden, and exposure margins

Species (Study Nos.)	**Duration, dose**	**Lung burden (mg iNO/gram lung/day)[a]**	**Exposure Margin[b]**
Rat (N005243)	2 years, 20 ppm (NOAEL)	3.4	5.5
Sheep (ABRAB1)	6 months, 0.23 mg/kg/hr (NOAEL)	0.43	0.70

NOAEL = no-observed-adverse-effect-level.

a) Part per million (ppm) concentration in the rat toxicity study was converted to lung burden based on a respiratory rate of 290 L per day (ICH Q3C(R2)) and the mean lung weight obtained at terminal necropsy.

b) Lung burden at 20 ppm iNO for a preterm infant calculated as 0.617 mg/g/day based on an average birth weight of 0.790 kg (studies INOT25, INOT27, BALLR1), a respiratory rate using Bide RW, 2000 (RMV (L) = 0.499* W0.809), and a lung weight of 3% of the birth weight based on preterm infant data by De Paepe ,2005.

3.2 Genotoxicity /Mutagenicity

There have been no studies identified in the recent literature that contribute to the assessment of genotoxic risk beyond that already performed. A few studies were found addressing certain aspects of NO genotoxicity. In a study by Li and co-workers it was for example demonstrated that DNA double-strand breaks (DSB), mutagenesis (TK1 mutations), and protective cellular responses were observed in human blastoid TK6 cells and p53 null NH32 cells at or above concentrations equivalent to the NO cytotoxicity threshold[25]. DNA recombinational repair was higher in NH32 than in TK6 cells at similar cell viability. Together with observations of a lower degree of DSB's but a higher mutation frequency in NH32 cells this suggested that recombinational repair contribute to resistance to NO toxicity and a potential increased risk for mutations. In another study using chicken B-lymphoma cell clones with different DNA deficient repair pathways, it was shown that cells deficient in DNA polymerase zeta were especially sensitive to the chromosomal damaging effect of NO donors[26]. Since this polymerase is error prone, it was suggested that NO-induced DNA repair likely contribute to the accumulation of single base substitutions.

Investigations in human gingival fibroblasts, showed that nitroprusside, an NO donor, induced DNA damage and partially prevented apoptosis induced by staurosporine[27]. It was further demonstrated that inhibition of apoptosis was related to the modulation of caspase-1 activation.

The biological relevance of the above findings as well as earlier demonstrations of the genotoxic activity of NO is addressed by the conduct of a conventional inhalation carcinogenicity study in rats (see 3.3 Carcinogenicity).

3.3 Carcinogenicity

The carcinogenic potential of inhaled NO has been investigated in a two-year study in rats (N005243). This study has been earlier presented by the Applicant in association with a follow-up measure (FUM 013) and a subsequent Type II variation application (EMEA/H/C/337/II/0017).

In the study, male and female F344/CrlBR (F344) rats (50/sex/group) were exposed by whole-body inhalation to NO at target concentrations of 0 (filtered air control), 5, 10, or 20 ppm NO for 20 hr/day, 7 days/week for up to 105 weeks. The purpose of the study was to determine the chronic toxicity and carcinogenic potential of NO exposures in F344 rats.

A full histopathology peer-review was conducted by the US-MAH (IKARIA in those days) on the 2-year inhalation toxicology and carcinogenicity study with nitric oxide in F344 rats. This evaluation confirmed the absence of a carcinogenic effect by nitric oxide, also in the uterus (report N005243, amended in May 2013).

In summary, the original 2-year rat study report concluded that no clear evidence of a toxic effect on the respiratory tract or other organs was noted as determined using clinical and ophthalmoscopic observations, examination of tissues at necropsy, organ and body weight changes, clinical pathology, and histopathologic examination of tissues. The same conclusion was reached after the recently conducted full histopathology peer-review.

Also, a 2-year bioassay in mice with iNO reported in the literature did not show evidence of a carcinogenic effect[28].

4. Reproductive and developmental toxicity

There is no formal investigational program on reproductive and developmental toxicity done by LHC AB, the MAH. There have been no investigations published on NO since the renewal of the marketing authorization (MA) that can be classified as reproductive and development toxicity studies. No effects were seen on the reproductive organs after life-long treatment in rats with up to 20 ppm of NO (see 3.3 Carcinogenicity) demonstrating the absence of a direct toxic effect on male and female reproductive organs of iNO. The absence of standard fertility and embryo-foetal development studies is considered acceptable owing to the seriousness of the indication where the heart surgery procedure as such and associated medical treatments would incur a significant risk to for example a pregnant woman. Appropriate wording with regard to the absence of animal reproduction data and warning statement for use during pregnancy and lactation is included the SmPC section 4.6.

5. Potential safety concern not verified in humans

Increased bleeding time

There has been a concern that prolonged exposure to inhaled NO may impair platelet adhesion and have adverse effects on haemostasis and increase bleeding time[29]. Cumulative data suggest that this effect is a result of the transfer of NO to vascular beds by S-nitroso proteins such as S-nitroso albumin and S-nitroso haemoglobin[30].

In addition, rabbits have shown an increase in bleeding time after iNO when compared to pre-dose values while no effects were noted on coagulation parameters, including in vitro coagulation time[31]. However, no control group was included in this study and the blood sampling volume was large (25-30 mL). In contrast to the rabbit study, no increase in bleeding time was noted in pigs and

mice after iNO administration[32,33.] Also, no signal for effects on this system has been observed in the Sponsor-conducted GLP toxicology studies with iNO. The findings do not support the hypothesis that iNO increases the risk of bleeding in humans.

Data in adult humans are conflicting, and there has been no increase in bleeding complications in randomized controlled trials in term and near-term neonates with hypoxic respiratory failure. Albert et al.[34] studied also the effects of 30 ppm iNO in healthy volunteers. They found that nitric oxide inhalation causes only mild, if any, attenuation of platelet function in healthy subjects. In another study Albert et al.[35] found no significant effects from iNO in a prospective randomised trial in healthy volunteers (n=15) inhaled NO (30 ppm, 30 min) or control gas. There is also a study by de Mol AC[35] that found no difference in bleeding complication associated to ECMO in patients treated with prior iNO or not. At present there is no data to suggest that these systemic effects are seen at therapeutic concentrations of NO (20 ppm and below).

Therefore, the impact of iNO on platelet function and subsequently on haemostasis cannot be excluded based on the mode of action, the increase in cGMP, and thus potential effects on the IIb/IIIa platelet receptor complex. On the other hand, no impact of iNO on haemostasis has been clinically demonstrated or verified: the clinical data in adult humans is conflicting, and there has been no increase in bleeding complications in randomised controlled trials in term and near-term neonates with hypoxic respiratory failure.

As preventive measure this effect is a warning in the current SmPC (see Part V for further details).

Goldstein and colleagues evaluated the co-administration of iNO and heparin in healthy volunteers[36]. Twelve healthy adult males were enrolled in a single-centre, randomized, single-blind, four-way crossover trial. Subjects received 80 ppm NO or medical air (placebo) inhalation for 30 min with simultaneous injection of placebo or heparin**.** Aspirin capsules were used as a positive control. Parameters of haemostasis were measured before treatment and at post-treatment intervals. Activated clotting time (ACT), prothrombin time (PT) and activated partial thromboplastin time (aPTT) increased only in groups that received heparin. Changes in bleeding time and platelet aggregation were observed only in aspirin groups. No clinically significant changes in haemoglobin, red blood cell counts or haematocrit were observed in any group. It was concluded that inhaled NO (80 ppm), when administered with heparin, exhibited no significant interaction/additive effects on; ACT, PT, aPTT, bleeding time or platelet aggregation[37]. In addition, Tanriverdi S et al.[38] evaluated the effects of iNO on the coagulation by so called Thromboelastogram (TEG). TEG shows the combined effects of coagulation factors and platelet functions. It shows that neonates with PPHN have an impaired coagulation and that the cloth formation is further delayed by iNO. The authors summaries their results that clot formation occurs late and is weaker in newborns with PPH. iNO treatment further prolongs clot reaction but increases the strength of clot in these patients.

There is one further study in healthy volunteers by Miller et al.[39]: ten healthy adult volunteers (5 males, 5 females; 20-62 years) were recruited and inhaled 163.3 ppm (standard deviation (SD): 4.0) NO for 30 min, 5 times daily, for 5 consecutive days. Lung function and blood levels of MetHb, nitrites/nitrates, prothrombin, pro-inflammatory cytokines and chemokines were determined before and during treatment. All individuals tolerated the NO treatment courses well. No significant AEs occurred and three minor AEs, not attributable to NO, were reported. Forced expiratory volume in 1 sec % predicted and other lung function parameters, serum nitrites/nitrates, prothrombin, pro-inflammatory cytokine and chemokine levels did not differ between baseline and day 5, while MetHb increased significantly during the study period to a level of 0.9% (SD: 0.08) ($p<0.001$).

Conclusions from non-clinical data

The iNO acute toxicity is primarily related to the formation of MetHb and subsequent decrease in oxygenation and oxygen delivery. The dose-limiting toxicity from iNO in both rats and dogs at higher concentrations of iNO are related to anoxia due to methaemoglobinemia. Long-term studies in clinical doses have not shown any adverse findings. Carcinogenicity studies are negative in doses studied. There is no formal investigational program on reproductive and developmental toxicity done. Nitric oxide reacts with oxygen forming NO_2 and other NO_x reactive spices. The reaction seen in some animal studies may well be related to the formation of NO_2/NO_x. Therefore, it is likely that the formation of NO_2 may have played a role in the literature reported adverse findings e.g. in the respiratory tract and that iNO *per se* does not adversely affect respiratory tissues. iNO may cause an effect on coagulation, primarily by a platelet effect. Still review of available pre-clinical literature indicates that iNO is well-tolerated in various animal disease models using sheep, rabbits, rats, and mice.

Taken together, clinically relevant safety signals from preclinical data have not been identified for iNO in animal studies conducted at clinical doses.

As of today no significant new critical non-clinical impact changing the benefits vs. risk profile for the clinical use of INOmax has emerged.

Based on review of pre-clinical data throughout the life-cycle for INOmax no safety issues that would prevent the use of inhaled NO in accordance to appropriate warning and contraindication statements in the SmPC has emerged.

Table 4 Part SII.2. Key safety findings from non-clinical studies

Key Safety findings from non-clinical studies	**Relevance to human usage**
Single and repeat-dose toxicity	• Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. • No significant treatment-related effects were observed. • Acute toxicity is related to anoxia resulting from elevated MetHb levels.
Genotoxicity	• No new findings. • Nitric oxide is genotoxic in some test systems. • It was suggested that NO-induced DNA repair likely contribute to the accumulation of single base substitutions.
Carcinogenicity	• No evidence of a carcinogenic effect was apparent, at inhalation exposures up to the recommended dose (20 ppm), in rats for 20 h/day for up to two years. Higher exposures have not been investigated.

Table 5 Part SII.3. Key safety findings from mechanisms for drug interactions

Key Safety findings from Mechanisms for drug interactions	**Relevance to human usage**
MetHb formation	• Hypoxia; Reduced blood pressure.
Vasodilators (co)-acting by cGMP or cyclic adenosine 3',5'-monophosphate (cAMP?	• Additive effects on central circulation, PAP and RV performance.
NO_2 formation	• Impact to individual patient: Potential airway inflammation and damage to lung tissues. • Public health impact: Nitrogen dioxide may be released into the ambient room air and thus cause environmental exposure to healthcare professionals (HCP) and others.

Part II: Module SIII - Clinical trial exposure

SIII.1 Brief overview of development

a) **Persistent Pulmonary Hypertension in the Newborn (PPHN)**

The product is indicated for the treatment of newborn infants ≥ 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of PH, in order to improve oxygenation and to reduce the need for ECMO.

b) **PH associated with heart surgery**

The product is indicated as part of the treatment of peri- and post-operative PH 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 RV function and oxygenation.

Nitric oxide received an orphan drug designation by the Food and Drug Administration (US) in June 1993 for PPHN. The MA registration was approved in the US on December 23, 1999. In Europe the MA for PPHN was granted through the centralised procedure on August 1, 2001. An extension of indication to include PH associated with heart surgery was granted approval by EMEA on January 20, 2011. The MA for the new indication was predominantly based on studies from Public Domain.

Linde Healthcare AB is not conducting any non-clinical or clinical trials.

SIII.2 Clinical Trial exposure

The clinical trial exposure data is presented in two separate sections, one section for each approved indication for INOmax – PPHN and PH associated with heart surgery.

The reason for this is that the populations and treatments are different for these two indications. Also, the MA for the PH associated with heart surgery indication was mainly based on studies from the public domain, which make it difficult to combine with the data from the initial MA application for the PPHN indication.

Persistent Pulmonary Hypertension in the Newborn (PPHN)

iNO has been studied in a huge variety of other patient populations including premature neonates, adult respiratory distress syndrome, cardiac surgery, transplant surgery, sickle cell disease crises, pneumonia, bronchiolitis, pulmonary thrombectomy, diagnostic use, high altitude pulmonary oedema, paraquat poisoning, left ventricular assist device replacement, primary PH, chronic obstructive pulmonary disease, congestive heart failure and asthma. Because of the fundamental differences in the pathophysiology in these conditions, the efficacy demonstrated in these studies provides little information on its utility in neonatal respiratory failure.

The initial MA registration for INOmax in Europe was based on two pivotal studies, the Neonatal Inhaled Nitric Oxide Study (NINOS) and the Clinical Inhaled Nitric Oxide Research Group Initiative (CINRGI). General safety data was also included from two additional company sponsored clinical studies; the Davidson trial (also referred to as Ohmeda 01/02 or INO-01/INO-02) and the Inhaled Nitric Oxide Study Group (INOSG). The Davidson trial was halted prematurely making the analysis of efficacy problematic but this did not impact on the analysis of safety data. Presented in Table 6 Part SIII.1 are the titles and the numbers of patients included in these four trials.

In the original submission data from four different studies were not pooled, hence the data is presented by study.

Table 6 Part SIII.1: Clinical trials included in the initial marketing authorisation registration for INOmax

Study	**Title**	**Number of patients**
NINOS	Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure	235
CINRGI	Comparison of conventional therapy and inhaled nitric oxide in the management of PPHN	186
INO-01/INO-02	Inhaled nitric oxide for the early treatment of PPHN. A	155

Study	Title	Number of patients
	randomised, double masked, placebo-controlled, dose-response, multicenter study	
INOSG	Inhaled nitric oxide and PPHN	58

Data regarding the clinical trial exposure has been extracted from the initial MA application for the PPHN indication. The extent of the exposure of inhaled treatment gas and the baseline demographics of the patients receiving nitric oxide in these studies are summarised below.

In the four trials, a total of 272 patients were randomised to receive iNO therapy and 277 patients actually received treatment. In all four studies, the patients received gas therapy until the condition worsened and other aggressive rescue therapy required, the patient died, the patient suffered an AE assessed as related to iNO or until the condition improved. The median durations of treatment in each study for the PPHN indication are given in Table 7 Part SIII.

Table 7 Part SIII.2: Median durations of gas therapy with inhaled nitric oxide in PPHN studies

Study	Number of patients	Duration
NINOS	114	40 hours
CINRGI	97	28 hours
Davidson	114	38 hours
INOSG	30	2 days

Presented in Table 8 Part SIII.3 to Table 10 Part SIII.5 is the extent of exposure in the different studies NINOS, CINRGI and Davidson (INO-1/INO-2)[40]. The data for the INOSG study is displayed in a graph from the study manuscript included in the MA application.

Table 8 Part SIII.3: Study gas administration of nitric oxide in NINOS

Study gas administration	iNO N=114
Received study gas	113 (99.1%)
Mean duration of study gas in hours ± std	71.3 (79.0)
<1 day	48 (42.5%)
1-2 days	11 (9.7%)
2-5 days	25 (22.1%)
5-10 days	24 (21.2%)
10-14 days	5 (4.4%)

In CINRGI, the protocol mandated the maximal duration of therapy at 20 ppm of iNO would be 24 hours and the total time that an infant could receive any dose of iNO (target of 5 ppm after the initial 24 hours) was 96 hours. The actual duration of use of study gas is shown for the primary analysis group in Table 9 Part SIII.4 (information missing for 3 infants).

Table 9 Part SIII.4: Hours on treatment inhaled nitric oxide in the CINRGI study

Study gas administration	**iNO** **N=93**
Mean time on study gas in hours	40.1
SD	31.65
Median time on study gas in hours	27.8

Table 10 Part SIII.5: Duration of treatments for nitric oxide in INO-1/INO-2 (Davidson)

Variable	**5 ppm**	**20 ppm**	**80 ppm**	**Pooled NO**
N	41	36	37	114
Mean	70.1	54.7	49.0	58.4
SD	67.0	49.0	53.2	57.6
Median	50.8	38.7	25.5	37.6
Range	1.6, 253	0.7, 193	2.4, 168	0.7, 253

The extent of exposure in the INOSG study is presented in the Figure , below. Half of the infants were exposed to less than 2 days of nitric oxide therapy, and the longest treatment lasted 8.5 days.

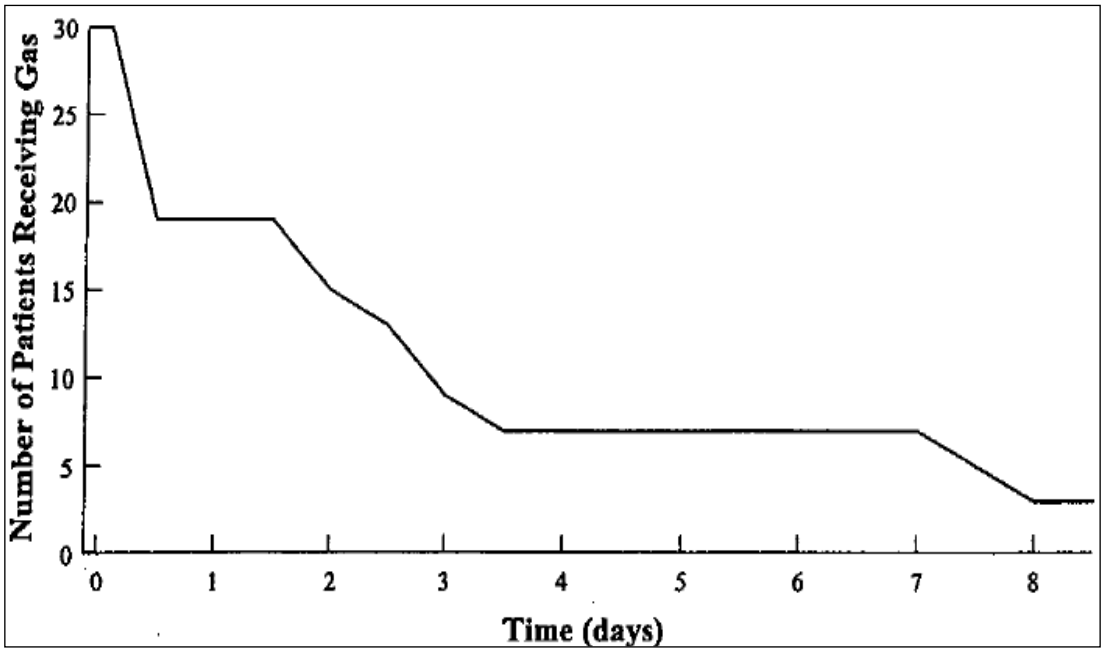

Figure 1: Study gas administration of nitric oxide in INOSG

The baseline demographics of the patients in the four PPHN studies receiving iNO are presented in Table 11 Part SIII.6. In Table 12 Part SIII.7 the patient distribution by racial origin for the different studies are displayed and Table 13 Part SIII.8 provides the totals based on the information in Table 12 Part SIII.7.

Table 11 Part SIII.6: Gender, mean age, estimated gestational age and birth weight of the patients receiving nitric oxide in the four PPHN studies

CINRGI	**Inhaled NO n=97**
Mean age in hours ± std	30.0 ±20.2
Males % of group)	44 (45.5%)
Estimated gestational age, weeks ± std (n)	39.1 ±1.8 (91)
Mean birth weight in kg ± std	3.3 ± 0.6

NINOS	**Inhaled NO n=114**
Mean age in days ± std	1.7 ±1.8
Males (% of group)	63 (55%)
Estimated gestational age, weeks ± std (n)	39.3 ± 1.8 (113)
Mean birth weight in grams ± std	3460 ±578

INO-1/INO-2	**Inhaled NO n=114 (pooled)**
Mean age in hours ± std	24.5 ± 17.1
Males (% of group)	58 (51%)
Estimated gestational age, weeks ± std (n)	39.8 ± 1.6 (114)
Mean birth weight in kg ± std	3.5 ± 0.5

INOSG	**Inhaled NO n=30**
Mean age in hours ± std (n)	38.3 ± 42.6 (29)
Males (% of group)	16 (53%)
Estimated gestational age, weeks ± std (n)	39.8 ± 1.5 (30)
Mean birth weight in kg ± std	3.44 ± 0.58

Table 12 Part SIII.7: Patient distribution in the four PPHN studies by racial origin

CINRGI	**Inhaled NO n=97**
White (% of treatment group)	40 (41.2%)
Black (% of treatment group)	43 (44.3%)
Hispanic (% of treatment group)	8 (8.2%)
Asian (% of treatment group)	1 (1.0%)
Other (% of treatment group)	5 (5.2%)

NINOS (patients with data)	**Inhaled NO n=111**
White (% of patients with data)	70 (63%)
Black (% of patients with data)	19 (17%)
Hispanic (% of patients with data)	13 (12%)
Other (% of patients with data)	9 (8%)

INO-1/INO-2	**Inhaled NO n=114 (pooled)**
Caucasian (%)	59 (52%)

Black (%)	25 (22%)
Hispanic (%)	20 (18%)
Asian (%)	4 (4%)
Other (%)	6 (5%)

INOSG	**Inhaled NO n=30**
Caucasian (% of dose group)	11 (37%)
Black (% of dose group)	8 (27%)
Hispanic (% of dose group)	7 (23%)
Asian (% of dose group)	1 (3%)
Other (% of dose group)	2 (7%)
Missing (% of dose group)	1 (3%)

Table 13 Part SIII.8: PPHN population by racial origin (totals)*

Total	**Inhaled NO n=352**
Caucasian/white (%)	180 (51%)
Black (%)	95 (27%)
Hispanic (%)	48 (14%)
Other (%) ^	29 (8%)

* Based on data provided in Table 12 Part SIII.7

^ Includes the 'Asian', 'Other' and 'Missing' groups from Table 12 Part SIII.7**¡Error! No se encuentra el origen de la referencia.**

PH associated with heart surgery

LHC AB has further granted a MA for the new indication the use of INOmax for the treatment of PH in conjunction with heart surgery. This MA application was predominantly based on studies from the public domain. The studied population is presented in Table 14 Part SIII.9, which were included in the first RMP for this indication. Data provided in this table refers to patients exposed in both the literature studies and the two IKARIA sponsored clinical studies INOT22 and INOT41. Further data has been also collected from two pharmacodynamic studies[41,42].

Though there is no formal development program investigating the effects of iNO for the treatment of PH in conjunction with heart surgery, a number of clinical studies that have been conducted as investigator-initiated studies in clinical and/or academic settings, have been identified as relevant for collecting efficacy and safety data on this indication. Some of these studies are randomised controlled studies; there are also a number of open label studies and cases series delineating the experience with iNO in this indication.

Clinical studies of iNO have been performed in a wide range of patient populations with regard to age distribution and surgical procedures (See Table 14 Part SIII.9).

In patients undergoing heart surgery, an increase in PAP due to pulmonary vaso-constriction is frequently seen. iNO has been shown to selectively reduce PVR and reduce the increased PAP. This may increase the RV ejection fraction. These effects in turn lead to improved blood circulation and oxygenation in the pulmonary circulation. Studies of paediatric populations have focused upon younger children aged from a day or month up to a few years. This, in large part, reflects current trends within medical management – specifically a preference for the early surgical correction of

congenital heart disease before irreversible sequelae have occurred. In the adult cohorts, the most common indications for cardiac surgery are open heart repair of mitral and/or aortic valve stenosis; open heart mitral/aortic valve reconstruction and open-heart valve replacement. Coronary artery bypass graft (CABG) surgery and combined procedures have also been studied. Other sub-categories of cardiac surgery, such as heart transplantation and Left Ventricular Assist Device insertions are, at least within the clinical trial setting, limited to adult patient populations.

Following Table 14 Part SIII.9 resumes the populations studied for the indication pulmonary hypertension associated with heard surgery.

Table 14 Part SIII.9: Study populations in submitted studies for the pulmonary hypertension associated with heart surgery

	Nº patients on iNO	**Patient population**	**NO dose ppm**	**Duration of treatment**	**Type of intervention**
Cardiac surgery, Congenital Heart Disease (CHD), children					
Cai J, 2008[43]	46	Children mean 5.6 years	10	24 hours	CHD correction with PAH
Day RW, 2000[44]	20 out to 40	Children 1 day to 20 years	20	1 hour	CHD correction with PAH
Goldman AP, 1995[45]	13	Children 3 day - 1 years	20	10 minutes (cross over)	CHD correction with PAH
Miller OI, 2000[46]	124	Children median 3 months	10	Up to 7 days	CHD correction with PAH
Morris K, 2000[47]	12	Children 2 m - 18 years	5 and 40	30 minutes	CHD correction with PAH
Russell IA, 1998[48]	40	Children	80	20 minutes	CHD
Stocker C, 2003[49]	15	Children 130 day	20	20 minutes +/- sildenafil	CHD with PAH

	Nº patients on iNO	Patient population	NO dose ppm	Duration of treatment	Type of intervention
Cardiac surgery, including Left Ventricular Assist Device (LVAD) placement and heart transplant, adult patients					
Ardehali, 2001[50]	16 Adults	Mean 47,6 years	20		Heart transplant
Argenziano, 1998[51]	6 out of 11	Mean 55 years	20	Evaluation at 15 minutes	LVAD & PAH
Fattouch, 2005[52]	22 out of 58	Mean 62 years	20	30 minutes	Mitral valve replacement with PAH
Fattouch, 2006[53]	21 out of 58	Mean 63 years	Not stated	Hours	Mitral valve replacement with PAH
Gianetti, 2004[54]	15 out of 29	Mean 69 years	20	8 hours	Cardiac surgery
INOT41	73 out of 150	Adults	40	Up to 48 hours	LVAD placement
Kieler-Jensen, 1994[55]	12	19 - 61 years	20, 40, 80	10 minutes each	Vaso reactivity testing
Radovancevic, 2005[56]	19	Mean 53 years	40, 60 and 80	10 minutes	Pre transplant reactivity testing
Rajek, 2000[57]	35 out of 68	Mean 69 years	4 to 24	6 hours	Heart transplant
Schmid, 1999[58]	14	32-76 years	40	20 minutes	Cardiac surgery
Solina, 2000[59]	30 out of 45	Mean 70 years	20, 40	24 hours	Cardiac surgery
Solina, 2001[60]	62	Mean 70 years	10, 20, 30, 40	hours	Cardiac surgery
Winterhalter, 2008[61]	23 out of 46	Mean 69 years	20	evaluation after 30 min.	Cardiac surgery
Pharmacodynamic studies					
INOT22	124 cross over		Up to 80		Exploratory
Lepore, 2005[41]	9 out of 9	37 – 73 years	Up to 80		Exploratory
Wessel, 1993[42]	9 of 43	1d-11years	20		Exploratory

Additional from Table 15 Part SIII.10, to Table 18 Part SIII.13 the data is presented for the patients in studies published literature and IKARIA sponsored studies segregated by dose and duration.

Table 15 Part SIII.10: Adults and Paediatric iNO Exposure in quoted literature studies segregated by dose and duration

iNO Dose					
Duration	**< 10 ppm**	**10 -20 ppm**	**21-40 ppm**	**41-80 ppm**	**Total any dose**

iNO Dose					
Duration	**< 10 ppm**	**10 -20 ppm**	**21-40 ppm**	**41-80 ppm**	**Total any dose**
0< Dur ≤1 hour	12 (Mellgren, 1998)[62]	22 (Trachsel, 2008)[63] 13 (Breuer, 1998)[64] 15 (INOT41) 12 (de Mol, 2007)[65]	12 (Wessel, 1993)[42]	18 (de Mol, 2007)[65] 9 (Fattouch, 2006)[53] 12 (Wessel, 1993)[42] 9 (Cai, 2008)[43] 124(INOT22)	
in Total	12	62	12	172	**258**
1< Dur ≤2 hour	0	0	0	0	0
2< Dur ≤4 hour	0	0	0	0	0
4< Dur ≤12 hour	0	0	0	0	0
12< Dur ≤ 24 hour	0	14 (Yoshida,1987)[66]	0	0	
in Total		14			**14**
24< Dur ≤ 48 hours	0	15 (Gaston, 2006)[30]	15 (Gaston, 2006)[30] 68 (Muller, 1994 DB)[68]	0	
in Total		15	83		**98**
48 < Dur ≤ 96 hours	0	0	0	0	0
>96 hours	0	0	35 (INOT41)	0	
in Total			35		**35**
Mixed	0	21 (Day 2000)[44] 23 (Albert, 2007)[32] 63 (Albert, 1999)[35] 20 (Miller 1994)[67] 16 (INOT22)	14 (Hoehn, 2001)[29] 24 (Albert, 2007)[32] 23 (Gries 2000)[69] 19 (Day 2000)[44]	19 (Day 2000)[44]	
in Total		143	80	19	**242**
Total Any Duration	**12**	**234**	**210**	**191**	

Table 16 Part SIII.11: Patient iNO Exposure in IKARIA Sponsored Trials (INOT 22 and 41) segregated by dose and duration

iNO Dose **Duration**	**40 ppm**	**80 ppm**	
0< Dur ≤1 hour	3	124 (INOT22)	127
1< Dur ≤2 hour	2	0	2
2< Dur ≤4 hour	2	0	2
4< Dur ≤12 hour	13	0	13
12< Dur ≤ 24 hour	31	0	31
24< Dur ≤ 48 hours	13	0	13

iNO Dose Duration	40 ppm	80 ppm	
48 < Dur ≤ 96 hours	4	0	4
Total Any Duration	**68**	**124**	

Table 17 Part SIII.12: Adults iNO Exposure in both quoted literature studies (see Table SIII.10) and IKARIA Sponsored studies (INOT41 and 22) segregated by dose and duration. Patients from Day RW[44] have been ascribed to the paediatric subgroup

iNO Dose					
Duration	**< 10 ppm**	**10 -20 ppm**	**21-40 ppm**	**41-80 ppm**	**Total any dose**
0< Dur ≤1 hour	0	22 (Trachsel,2008)[63] 12 (Wessel, 1993)[42]	12 (Wessel, 1993)[42]	12 (Wessel, 1993)[42] 9 (Cai, 2008)[43]	
in Total		34	12	21	**67**
1< Dur ≤2 hour	0	0	0	0	0
2< Dur ≤4 hour	0	0	0	0	0
4< Dur ≤12 hour	0	0	0	0	0
12< Dur ≤ 24 hour	0	14 (Yoshida, 1987)[66]	0	0	
in Total		14			**14**
24< Dur ≤ 48 hours	0	15 (Gaston, 2006)[30]	15 (Gaston, 2006)[30] 68 (Muller, 1994 DB)[68]	0	
in Total		15	83		**98**
48 < Dur ≤ 96 hours	0	0	0	0	0
>96 hours	0	0	35(INOT 41)	0	
in Total			35		35
Mixed	0	21 (Yoshida, 1987)[66] 23 (Albert, 2007)[32] 16 (Lepore, 2005)[41]	14 (Hoehn, 2001)[29] 24 (Albert, 2007)[32] 23 (Gries, 2000)[69] 19 (Day, 2000)[44]	19 (Day, 2000)[44]	
in Total		60	80	19	**159**
Total Any Duration		**123**	**210**	**40**	

Table 18 Part SIII.13: Paediatric iNO Exposure in both quoted literature studies (see Table SIII.10) and IKARIA sponsored studies (INOT41 and 22) segregated by dose and duration

iNO Dose					
Duration	**< 10 ppm**	**10 -20 ppm**	**21-40 ppm**	**41-80 ppm**	**Total any dose**
0< Dur ≤1 hour	12 (11)	13 (Breuer, 1997)[64] 15 (INOT41)	0	18 (de Mol, 2007)[65] 9 (Fattouch, 2006)[53] 124 (INOT22)	
in Total	12	28		151	181
1< Dur ≤2 hour	0	0	0	0	0
2< Dur ≤4 hour	0	0	0	0	0
4< Dur ≤12 hour	0	0	0	0	0
12< Dur ≤ 24 hour	0	0	0	0	0
24< Dur ≤ 48 hours	0	0	0	0	0
48 < Dur ≤ 96 hours	0	0	0	0	0
>96 hours	0	0	0	0	0
Mixed	0	63 (Albert, 1999)[35] 20 (Miller, 1994)[67]	0	0	
in Total		83			83
Total Any Duration	**12**	**111**	**0**	**151**	

Demographic and Other Characteristics of Study Population

Table 19 Part SIII.14 gives an overview of numbers of patients in literature and IKARIA Sponsored Clinical Studies in the age 18 and under, and the number of patients over 18 years. Relevant for the proposed indication is the severity of the underlying disease and the type of operative procedure and therefore the data is presented in relation to these parameters. Generally, the broad indication for INO therapy (PH) means that when used the disease is often severe and may even be life threatening. Table 20 Part SIII.15 presents the adult population as divided by operative procedure and where available by estimated severity of disease (defined by NYHA 1/EuroSCORE as calculated by the authors of the different articles). Table 21 Part SIII.16 describes the paediatric patient population by operative procedure.

Data from the literature studies provides a general overview only. Thus, severity of disease is not provided for any of the paediatric studies.

Table 19 Part SIII.14: Demographic Profile of Patients in Controlled Studies [NB Ardehali et al. is not a controlled study]

Studies	**Treatment Group**		
	iNO	**Placebo**	**Active control**
<18 years			

Studies	Treatment Group		
	iNO	Placebo	Active control
Cai, 2008[43]	31		15
Miller, 1994[67]	63	61	
Goldman, 1995[45]	13		13 (crossover)
Morris, 2000[47]	12		12 (crossover)
Russell, 1998[48]	18	18	
Stocker, 2003[49]	15		16 (crossover)
Wessel, 1993[42]	9		22
Day, 2000[44]	20		20
INOT22	124		124
Total < 18 years	**305**	**79**	**222**
≥18 years			
Fattouch, 2005[52]	22		36
Fattouch, 2006[53]	21		37
Gianetti, 2004[54]	14	15	
Schmid, 1999[58]	14		14 (crossover)
Solina, 2000[59]	30		15
Solina, 2001[60]	47	15	
Winterhalter, 2008[61]	23		23
Rajek, 2000[57]			36
Kieler-Jensen, 1994[55]	12		12 (crossover)
Lepore, 2005[41]	9		9 (crossover)
Radovancevic, 2005[56]	19		19 (crossover)
INOT41	73	77	
Argenziano, 1998[51]	6	5	
Total≥18 years	**324**	**112**	**192**
Ardehali, 2001[50]	16		
Total Male			
Male<18y	61	28	18 (10 crossover)
Male ≥18y	159	73	76 (21 crossover)
Total Female			
Female <18y	63	33	27 (20 crossover)
Female ≥18y	63	19	54 (14 crossover)
Day (2000), Russell (1998), Solina (2000 and 2001), Radovancevic (2005) and Argenziano (1998) did not define male and female subpopulations. The aggregate figures do not include uncontrolled studies (Ardehali A, 2001)			

Table 20 Part SIII.15: Demographic Data: Adult Cardiac Surgery by Operative Procedure/Disease Severity

Cardiac Surgery	Treatment Group

(Adults)	iNO	Placebo	Active control
Procedure			
Mitral valve repair*	51		73
Aortic valve repair*	20	15	9
Tricuspid valve repair*	2		4
Pulmonary valve repair*			
Multiple valve repair	13		21
Atrial septal defect (ASD) repair	1		1
Ventricular septal defect (VSD) repair	0	0	0
CABG	4		3
CABG + valve repair	12		13
Pulmonary thrombo-endarterectomy	2		2
Solina et al. (2000 and 2001) did not specify the procedures undertaken			
Severity of Disease			
Mild [NYHA 1/EuroSCORE 0-2]	0	0	0
Moderate [NYHA 2/EuroSCORE 3-5]	0	0	0
Severe [NYHA3+4/EuroSCORE 6+]	96	0	111
Fattouch (2005 and 2006) the NYHA scores for iNO and group C have been erroneously transposed Gianetti (2004), Schmid (1999) and Solina (2000 and 2001) did not provide disease severity scores Fattouch, Solina and Winterhalter (2008) provided aggregate disease severity data for their patients (range analysis confirmed that all patients were appropriately allocated) *includes commissurotomy, annuloplasty or replacement			

Table 21 Part SIII.16: Demographic Data: Paediatric Cardiac Surgery by Operative Procedure

Cardiac Surgery (Children)	Treatment Group		
	iNO	Placebo	Active control
Procedure			
Mitral valve repair*	2/3	0	2
Aortic valve repair*	0	0	0
Tricuspid valve repair*	5	0	3
Pulmonary valve repair*	0	0	0
Multiple valve repair	0	0	0

ASD repair	18/4	18	4
VSD repair	29/2/1/11	18	2/1/11
Atrioventricular septal defect (AVSD) repair	6/3/4	0	6/3/14
Ventricular outflow tract correction (inc Tetralogy of Fallot repair)	/8/	0	3/3
Great vessel surgery*	8/4/3/1	13	4/3/4
Total anomalous pulmonary venous connection (TAPVD) correction	6/4/3/1	11	4/3/4/1
*Includes surgery for pulmonary atresia, transposition of arteries and truncus abnormalities Russell (1998) did not indicate which patients were allocated to which group (6 ASD/6VSD/18 AVSD repair/ 1 Mitral valve repair/3 great vessel repairs and 1 ventricular outflow tract correction) Wessel (1993) did not discriminate between patients with ASD and AVSD (patients were allocated to AVSD repair group).			

Linde Healthcare AB has not done any further clinical trials with iNO and there are no on-going study activities.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Linde Healthcare AB is not conducting any trial activities, pre-clinical or clinical. Apart from the clinical studies mentioned in previous sections and clinical data derived from literature, no additional formal clinical development program investigating potentially untypical effects of iNO have been set-up.

Use in pre-term neonates with severe respiratory insufficiency and PH

Reason for exclusion: iNO has been studied in neonates term and near-term with severe respiratory insufficiency and PH. Despite it has been also studied in pre-term neonates with severe respiratory insufficiency and PH, there is still insufficient data to support its use in pre-term neonates.

Is it considered to be included as missing information?: NO.

Rationale: considered off-label (out of indication); indication as included in SmPC Section 4.1 includes the treatment of newborn infants ≥ 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of PH, in order to improve oxygenation and to reduce the need for ECMO.

Use in patients with congenital diaphragmatic hernia (CDH)

Reason for exclusion: No efficacy has been demonstrated with the use of iNO in patients (infants) with CDH.

Is it considered to be included as missing information?: NO.

Rationale: despite no efficacy has been demonstrated in this population group (as stated in SmPC section 4.4), there are no safety concerns related to the use in this population. Its use could be considered off label, and patient characteristics would justify therapy with nitric oxide.

Use in children 12-17 years of age with PH associated with heart surgery

Reason for exclusion: There is sparse information around the use of iNO in children 12 – 17 years of age. This is a result of the increasing trend to perform corrective surgery for CHD early in life in order to avoid negative health effects caused by the heart vitium. It is unethical to even consider changing the well-established practice, performing corrective surgery as early in life as possible.

Is it considered to be included as missing information?: YES.

Use in patients with severely compromised left ventricular function (patients at risk of ventricular overload caused by the decrease in pulmonary pressure and subsequent increase pulmonary blood flow)

Reason for exclusion: use in this population poses patient at risk of ventricular overload. Nitric oxide should be used with caution in these patients as per SmPC section 4.4, as they may be at an increased risk of developing cardiac failure (e.g. pulmonary oedema).

Is it considered to be included as missing information?: NO.

Rationale: no gap in knowledge about the safety for use in this patient population; covered in Important Identified risk of pulmonary oedema in patients with pre-existing left ventricular dysfunction.

Use in patients with hypersensitivity to the active substance or to the excipient N_2

Reason for exclusion: safety and ethical considerations, as exposure could result in serious adverse drug reactions (ADRs) (product is explicitly contraindicated in this patient population).

Is it considered to be included as missing information?: NO.

Rationale: use is contraindicated in this population (as per SmPC section 4.3).

Use in neonates known to be dependent on right-to-left or significant left-to-right shunting of blood

Reason for exclusion: safety and ethical considerations, as exposure could result in serious ADRs (product is explicitly contraindicated in this patient population).

Is it considered to be included as missing information?: NO.

Rationale: contraindicated in this population (as per SmPC section 4.3).

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Clinical studies of iNO have been performed in a wide range of patient populations with regard to age distribution, surgical procedures and/or severity of the disease.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 22 Part SIV.3: Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**
Pregnant women	Not included in the clinical development program. It is not known if nitric oxide for inhalation can cause foetal harm when administered to pregnant women or can affect reproductive capacity. It is not known whether nitric oxide is excreted in human milk. However, this group of patients is not part of the target population for the proposed indication.
Breastfeeding women	Not included in the clinical development program.
Patients with relevant comorbidities: - Patients receiving other vasodilators	Not included in the clinical development program. The combined used with other vasodilators (e.g. sildenafil) is not extensively studied. Available data (as stated in SmPC section 4.5) suggest additive effects on central circulation, PAP and RV performance. iNO combination with other vasodilators acting by the cGMP or cAMP systems should be done with caution.
Patients with relevant comorbidities: - Patients with CDH	Not included in the clinical development program.
Patients with relevant comorbidities: - Patients with hepatic impairment - Patients with renal impairment	There are no studies addressing the use explicitly in patients with hepatic nor renal impairment. Inhaled NO exerts its activity mainly by vasodilatation in ventilated lung regions,

	relaxing the pulmonary vascular smooth muscle. Having in mind the selective effects on the pulmonary vasculature and rapid binding to the haemoglobin hepatic effects are not expected, there is no hepatic metabolism. Inhaled NO is a selective pulmonary vasodilator that can acutely lower PAP and PVR without altering systemic arterial pressure and no systemic effects are expected.
Neonates known to be dependent on right-to-left or significant left-to-right shunting of blood	Not included in the clinical development program.
Premature infants less than 34 weeks of gestation	Not included in the clinical development program. The safety and efficacy of INOmax in premature infants less than 34 weeks of gestation has not yet been established. Currently available data are described in section 5.1 of current SmPC. No recommendation or posology can be made.
Children 12-17 years of age with PH associated with heart surgery*	Clinical data is limited. Heart surgery is not frequently performed in this age group.

*Dated 13.11.2009, the European Medicines Agency (EMA) waived the obligation to submit the results of studies with INOmax in all subsets of the paediatric population in PPHN and other pulmonary heart disease (EMEA/PDCO/696166/2001, EMEA-000612-IP01-09). See section 4.2 of the SmPC for information on paediatric use.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 *Method used to calculate exposure*

Linde Healthcare AB had, since the initial approval of INO for PPHN until 01-August 2014, a collaboration agreement with INO Therapeutics LLC, a member of the pharmaceutical company IKARIA, (US-MAH in those days and later acquired by Mallinckrodt) around the global safety database and the collection and handling of AEs. This collaboration included the data management, compilation and tabulation of safety data as well as the preparation of Periodic Safety Update Reports (PSURs). LHC AB has thus submitted PSURs including safety data covering both the MAH granted by Linde covering the EU/EEA and certain countries in South America as well as safety data collected from the US and Canada and certain countries of Asia. The PSURs has also covered the study activities performed by and/or sponsored by US-MAH.

INOmax was launched in the US in Jan 2000 and in the European Union (EU) in Dec 2001 following corresponding MA on 23 Dec 1999 and on 01 Aug 2001, respectively. INOmax is approved in all EU/EEA member states in addition to other national approvals, as in Switzerland and South

America. The extended indication of peri- and post-operative PH in adults and children (ages 0-17 years) in conjunction to heart surgery is approved in the EU/EEA (with Norway and Iceland), and in South America.

Despite that the only applicable route of administration of INOmax is inhalation and that the treatment and its duration depend on the state of the patient and on the decision of the physician in charge it is not possible to determine the exact usage on the market because the product is delivered directly to the hospitals and used in different units. Thus, estimates for patient exposure are made using an algorithm that considers cylinder consumption (assumed to correlate to returned cylinders), actual total treatment times (INOmeter readings), and an estimate of individual patients treated by analysing the treatment time data. The estimate of the number of patients treated has been made by comparing start and stop times of the individual treatments. Treatments that were sequential within a narrow time period (30 minutes or less) were assumed to be continuations of the same patient. Treatments that started outside of this programmed time frame were assumed to be new patient starts.

Recognized limitations in this algorithm exist. In some cases, patients are removed from nitric oxide therapy for several hours or days, and then placed back on treatment, resulting in the same patient counted as two patients. Use of iNO for indications other than the initially approved P pulmonary hypertension (PPHN in neonates ≥ 34 weeks gestation or for the treatment of peri- and post-operative PH) will also change the treatment durations, which may potentially skew the reliability of estimated exposure. Nonetheless, there has been strong consistency in the calculation made that links logically to sales recorded. The MAH considers this supportive for continuing to use the algorithmic approach. The use of this algorithm was accepted by PRAC already in the approved PSUR 10 covering the period from 24 Dec 2011 to 23 Dec 2012. Thus, it has been used in following PSURs and in this RMP.

To account for the cylinder size and concentration difference the algorithm applied is 0.47 patients per cylinder of 10 L and 400 ppm, 0.94 per cylinder of 10 L and 800 ppm, and 1.1 patients per cylinder with the size D (US) and 800 ppm. As the 2 L cylinders are used during the transport of a patient in treatment, these 2 L cylinders will be not more considered in the patient exposure calculation for avoiding double entry of the same patient.

SV.1.2 Exposure

The estimated cumulative patient exposure from International Birth Date (IBD) or from obtaining MA to 23 December 2024 (Data Lock Point (DLP) of the recent PSUR prepared for nitric oxide, PSUR#20) is provided in Table 23 Part SV.1: Exposure table per region from IBD or from obtaining MA until 23 December 2024. In total, it is estimated that 244,081 patients world-wide have been exposed to iNO within the post-marketing setting since INOmax was put on the market.

Table 23 Part SV.1: Exposure table per region from IBD or from obtaining MA until 23 December 2024

Time interval	**No. of circulated cylinders**		**Estimated patient exposure**	
	RoW	**EU**	**RoW**	**EU**
IBD or MA to 23 Dec 2006 *	35,529	(8,596) ¤	41,569	(4,040) ¤
IBD or MA to 23 Dec 2013 PSUR#12	3,104	102,011	3,632	47,945
24 Dec 2013 to 23 Jun 2014 PSUR# 13	-	8,135	-	3,823
24 Jun 2013 to 23 Dec 2014 PSUR#14	-	7,682	-	3,611

24 Dec 2013 to 23 Dec2014 **	1,433	-	1,677	-
24 Dec 2014 to 23 Jun 2015 PSUR#15	623	8,197	729	3,853
24 Jun 2015 TO 23 Jun2016 PSUR#16	2,495	13,461	2,744	9,330
24 Jun 2016 TO 23 Jun2017 PSUR#17	1,969	10,471	2,137	8,335
24 Jun 2017 to 23 Dec 2018 PSUR#18	3,142[#]	21,501	2,938	16,790
24 Dec 2018 to 23 Dec 2021 PSUR#19	15,217	45,351	13,172	35,982
24 Dec 2021 to 23 Dec 2024 PSUR#20	14,117	35,846	12,385	29,389
Sub Total	**77,629**	**261,251**	**80,983**	**163,098**
Grand Total	**338,880**		**244,081**	

Sources: *Annual Safety Report from INO Therapeutics for FDA; ** Data requested from Ikaria.
¤ Data included in the cumulative number presented in PSUR#12. # All RoW are 800PPM cylinders, 16 pcs in 2l, the rest 3126 are in 10L.

The calculation of exposed patients is an approximation. The data is calculated from circulated cylinder data, and as cylinders may be in circulation for more than 1-year period therefore the calculation is fragile. Due to differences in concentration (400 ppm and 800 ppm), the number of cylinders cannot be compared with the number of treated patients between the years. There has been a transition from using 400 ppm cylinders to 800 ppm cylinders, and now the most frequent used cylinders are the 800 ppm cylinders.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

INOmax is used in intensive care units under well controlled conditions. The risk for misuse for illegal purposes is negligible.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Medicinal NO is a well-established medicinal product that has been used for decades and its safety has been well characterised. The following risks have been considered important for inclusion in the list of safety concerns in the RMP of the product due to the frequency and/or the potential severity of these adverse effects based on clinical available data and published literature.

Important Identified Risk: Methaemoglobinemia

Risk-benefit impact: High MetHb levels will compromise oxygen delivery and thus cause serious risk compromising organ oxygenation potentially causing critical ischemia especially in fragile patients. Nevertheless, the risk when the product is used in accordance to instruction is low. The

impact of this risk on the individual patient is considered acceptable considering the anticipated benefits of therapy.

Important Identified Risk: Risk of acute cardiac failure with circulatory collapse in certain patient populations

Risk-benefit impact: Potentially severe, life-threatening cardiovascular collapse. Nevertheless, the risk when the product is used in accordance to instruction is low. The impact of this risk on the individual patient is considered acceptable considering the anticipated benefits of therapy.

Important Identified Risk: Risk of pulmonary oedema in patients with pre-existing left ventricular dysfunction

Risk-benefit impact: Potentially severe, life-threatening pulmonary oedema and/or circulatory collapse; thus, cause severe cardiorespiratory distress. Nevertheless, the risk when the product is used in accordance to instruction is low. The impact of this risk on the individual patient is considered acceptable considering the anticipated benefits of therapy.

Important Identified Risk: Risk of rebound reaction; PH and/or oxygen saturation decrease/desaturation associated to abrupt withdrawal

Risk-benefit impact: The patient may potentially experience rebound pulmonary arterial hypertension with subsequent circulatory instability and risk of hypoxemia. Signs and symptoms of rebound PH syndrome include hypoxemia, systemic hypotension, bradycardia, and decreased cardiac output. This is a potentially severe - life threatening risk. Nevertheless, the risk when the product is used in accordance to instruction is low. The impact of this risk on the individual patient is considered acceptable considering the anticipated benefits of therapy

Important Identified Risk: Critical failure of the Nitric Oxide Delivery System (NODS)

Risk-benefit impact: From minor increase in PAP to severe Pulmonary Hypertensive Crisis. The patient may potentially experience rebound PAH with subsequent circulatory instability and risk of hypoxemia. Signs and symptoms of rebound PH syndrome include hypoxemia, systemic hypotension, bradycardia, and decreased cardiac output. This is a serious risk. Nevertheless, the risk when the product is used in accordance to instruction is low. The impact of this risk on the individual patient is considered acceptable considering the anticipated benefits of therapy.

Important Identified Risk: Risk of NO_2 formation

Risk-benefit impact: Potential airway inflammation and damage to lung tissues. This is a serious risk. Nevertheless, the risk when the product is used in accordance to instruction is low. The impact of this risk on the individual patient is considered acceptable considering the anticipated benefits of therapy

Important Potential Risk: Increased bleeding time

Risk-benefit impact: Potential hemorrhagic events. This is a serious risk. Nevertheless, the risk when the product is used in accordance to instruction is low. The impact of this risk on the individual patient is considered acceptable considering the anticipated benefits of therapy.

Missing information: Combined use with other vasodilators

Risk-benefit impact: The combined used with other vasodilators (e.g. sildenafil) is not extensively studied. Available data suggest additive effects on central circulation, PAP and RV performance. iNO combination with other vasodilators acting by the cGMP or cAMP systems should be done with caution.

Missing information: Use during pregnancy and lactation

Risk-benefit impact: Animal reproduction studies have not been conducted with nitric oxide for inhalation. It is not known if nitric oxide for inhalation can cause foetal harm when administered to pregnant women or can affect reproductive capacity. It is not known whether nitric oxide is excreted in human milk. The potential risk for humans is unknown.

Missing information: Paediatric use (patients 12-17 years treated for PH in conjunction with heart surgery)

Risk-benefit impact: There are limited clinical data supporting a nitric oxide dose for patients in the age range of 12-17 years being treated for PH in conjunction with heart surgery.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Risk of pulmonary oedema in patients with PVOD is a new important identified risk. Reason for the addition is the PRAC recommendation on signals (EMA/PRAC/537837/2024); see Section SVII.3 for further details.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk: Methaemoglobinemia

Potential mechanisms: Nitric oxide is absorbed systemically after inhalation. Most of it traverses the pulmonary capillary bed where it combines with haemoglobin that is 60 % to 100 % oxygen-saturated. At this level of oxygen saturation, nitric oxide combines predominantly with oxyhaemoglobin to produce MetHb and nitrate. At low oxygen saturation, nitric oxide can combine with deoxyhaemoglobin to transiently form nitrosylhaemoglobin, which is converted to nitrogen oxides and MetHb upon exposure to oxygen. Within the pulmonary system, nitric oxide can combine with oxygen and water to produce nitrogen dioxide and nitrite, respectively, which interact with oxyhaemoglobin to produce MetHb and nitrate. Thus, the end products of nitric oxide that enter the systemic circulation are predominantly MetHb and nitrate.

Evidence source(s) and strength of evidence: This risk is based on the known safety profile of nitric oxide as reflected in the current product information and the publicly available scientific literature[66,70-72].

Characterisation of the risk: MetHb concentrations increase during the first 8 hours of nitric oxide exposure. Acute toxicity is related to anoxia resulting from elevated MetHb levels. Hypoxia and Pressure reduction have been reported. MetHb may have an impact on the oxygen saturation of the haemoglobin and thus oxygen delivery, which might lead to organ ischemia.

Clinical trial exposure: Not applicable.

Post-marketing experience: A cumulative safety database output search for the relevant events received with PT "Methemoglobinemia" was conducted and retrieved twenty-nine (29) case reports, 22 assessed as serious and 7 as non-serious, encompassing 29 events, 21 of which were serious and 8 non-serious. All patients were recovered or were recovering at the time of the report, except for 5 for which the outcome of the event was unknown.

Risk factors and risk groups: There may be an additive effect with INOmax on the risk of developing methahemoglobinemia with nitric oxide donor substances, including sodium nitroprusside and nitroglycerin. There is an increased risk of MetHb formation if substances with a

known tendency to increase MetHb concentrations are administered concomitantly with nitric oxide (e.g. alkyl nitrates and sulphonamides). Substances known to cause increased MetHb levels should thus be used with caution during therapy with iNO. Prilocaine, whether administered as oral, parenteral, or topical formulations may cause methahemoglobinemia. Care must be taken when INOmax is given at the same time as medicinal products containing prilocaine. In addition, neonates and infants are known to have diminished MetHb reductase activity compared to adults. MetHb level should be measured within one hour after initiation of INOmax therapy. Finally, Overdose with INOmax will be manifest by elevations in MetHb.

Preventability: Measures to prevent this risk are included in SmPC Sections 4.2, 4.4, 4.5, 4.8, 4.9, 5.1, 5.2 and 5.3. Also, additional risk minimisation measures are in place, please see Part V.

Impact on the risk-benefit balance of the product: High MetHb levels will compromise oxygen delivery and thus cause serious risk compromising organ oxygenation potentially causing critical ischemia especially in fragile patients. Nevertheless, the risk when the product is used in accordance to instruction is low. The impact of this risk on the individual patient is considered acceptable considering the anticipated benefits of therapy.

Public health impact: None.

Important Identified Risk: Risk of acute cardiac failure with circulatory collapse in certain patient populations

Potential mechanisms: Treatment with iNO might aggravate cardiac insufficiency in a situation with left-to-right shunting. This is due to unwanted pulmonary vasodilation caused by iNO, resulting in a further increase of already existing pulmonary hyperperfusion thus potentially giving raise to forward or backward failure.

Evidence source(s) and strength of evidence: This risk is based on the known safety profile of nitric oxide as reflected in the current product information and the publicly available scientific literature[73,74].

Characterisation of the risk: About 60% of patients undergoing heart surgery have chronic heart failure. Abrupt increase in left ventricular filling pressure secondary to sudden reduction in PVR may cause acute left ventricular failure and subsequent backward or forward cardiac failure, pulmonary oedema or cardiogenic collapse.

Clinical trial exposure: Not applicable.

Post-marketing experience: A cumulative safety database output search for the relevant events received associated to the SMQ Shock-associated circulatory or cardiac conditions (excl. torsade de pointes) retrieved one hundred and eighty-five (185) case reports, all of them serious, encompassing one hundred and ninety-eight (198) events: cardio-respiratory arrest (n=58), cardiac arrest (n=82), cardiac arrest neonatal (n=28), circulatory collapse (n=9), shock (n=5), ventricular tachycardia (n=4),ventricular fibrillation (n=3), cardiogenic shock (n=4), cardiac death (n=2), cardio-respiratory arrest neonatal (n=1), pulseless electrical activity (n=1) and pulse absent (n=1).

Out of the 198 events, 159 events were fatal, for 37 events the outcome was recovered or recovering at the time of the report, and for the remaining 2 events the outcome was unknown at the time of the report.

Analyzing the 158 fatal cases reporting the 159 fatal events, in 143 cases the death was assessed as not related to iNO, and in another 10 cases ([redacted] the death was most probably related to the concurrent conditions of the patient. The remaining 5 cases are described below:

- [redacted] case identified from literature, concerned a 32-year-old pregnant woman (32 weeks of gestation) referred for semi-emergency cesarean section, with heart failure (NYHA Class III), dyspnea and tachypnoea on mild exertion. She was diagnosed with Eisenmenger syndrome, and 5 hours after section, she developed uterine atony leading to a massive hemorrhage. She was treated in view of disseminated intravascular coagulation (DIC), and given the worsening PAP, iNO was commenced at 8 hours after the resuscitation up to 40 ppm. She had a cardiopulmonary arrest 24 hours after surgery and resuscitation was futile. In this case, the massive hemorrhage started before iNO therapy, and it is not known if iNO was applied in the final stage. In addition, DIC has been recognized as a rare complication in obstetrics. Of note, platelet dysfunction is a known potential risk for iNO therapy, as reflected in the CCDS.

- [redacted] case concerning an adult male patient with pneumonia and acute respiratory distress syndrome (ARDS) who was on a ventilator and started treatment with INOMAX. It was noted that the INOMAX cylinder was less than 300 pounds per square inch (PSI) and required changing. Post switching of the cylinder, the monitored NO levels decreased and patient went into cardiac arrest. The INOvent was switched to a back-up unit but patient subsequently died. No further information on the investigation is available.

- [redacted] case concerning a newborn delivered via cesarean section due to fetal distress who was placed on INOmax for PH. A device issue occurred: the gas outlet line from the jet ventilator became disconnected, and the staff found the tubing leading to the injector module saturated with water. The staff did a low range purge of the line and a calibration. However, the infant developed bradycardia and hypotension resulting in cardiopulmonary arrest.

- [redacted] case concerning a 28-year-old female hospitalized for a lung transplantation surgery who was placed on INOmax for PH. A device failure with INOvent occurred and the nurse hand bagged the patient due to a significant decrease in oxygen saturation, however patient experienced cardiopulmonary arrest and expired. No further information is available.

- [redacted] case concerning a 75-year-old female with an underlying unspecified critical condition who was in treatment with iNO when supply failed due to a technical defect, and therapy was discontinued without weaning. Patient showed symptoms of rebound effect with hypotension and cardiac arrest. HCPs were not able to use the backup supply.

Overall, most of the fatal cases were considered not related to the treatment with INOmax, and/or related to concurrent conditions of the patients, and the remaining cases were mostly related to device failures/issues. Abrupt discontinuation of iNO therapy is known for the risk of rebound, which is why weaning of iNO is mandatory. See Important Identified Risk of Critical failure of the NODS for further information on device failures.

Risk factors and risk groups: iNO should be used with caution in patients with complex heart defect, where high pressure in the pulmonary artery is of importance for maintaining circulation. iNO should also be used with caution in patients with compromised left ventricular function and elevated baseline PCWP as they may be at an increased risk of developing cardiac failure (e.g. pulmonary oedema).

Preventability: Measures to prevent this risk are described in SmPC Sections 4.3 and 4.4. Also, additional risk minimisation measures are in place, please see Part V.

Impact on the risk-benefit balance of the product: May cause severe cardiovascular collapse. Thus, this is a potentially life-threatening risk. Nevertheless, the risk when the product is used in

accordance to instruction is low. The impact of this risk on the individual patient is considered acceptable considering the anticipated benefits of therapy.

Public health impact: None.

Important Identified Risk: Risk of pulmonary oedema in patients with pre-existing left ventricular dysfunction

Potential mechanisms: Reduction in PAP/PVR may cause left ventricular overload and subsequent cardiovascular collapse.

Evidence source(s) and strength of evidence: This risk is based on the known safety profile of nitric oxide as reflected in the current product information and the publicly available scientific literature[46,75,76].

Characterisation of the risk: A low proportion of patients with congenital heart disease are dependent on high PAP to maintain central haemodynamics. Reduction in PAP/PVR may cause left ventricular overload and subsequent cardiovascular collapse. Pulmonary oedema is associated with impaired oxygenation and may cause circulatory collapse and may thus cause severe cardiorespiratory distress. Thus life-threatening.

Clinical trial exposure: Not applicable.

Post-marketing experience: A cumulative safety database output search for events under the PTs Pulmonary oedema, Acute pulmonary oedema, Pulmonary oedema neonatal and Non-cardiogenic pulmonary oedema retrieved seventeen (17) case reports, all of them serious, encompassing 20 events of pulmonary oedema and 1 event of non-cardiogenic pulmonary oedema. Among the 21 reported events, for 18 the outcome was recovered/recovering at the time of the report, for 1 event it was not recovered and for the remaining 2 events the outcome was unknown at the time of the report.

Risk factors and risk groups: Patients with congenital heart disease that are dependent (absolute contraindication) on high PVR or where high PAP support adequate circulation (relative contra indication).

Preventability: Measures to prevent this risk are described in SmPC Section 4.4. Also, additional risk minimisation measures are in place, please see Part V.

Impact on the risk-benefit balance of the product: Pulmonary oedema is associated with impaired oxygenation and may cause circulatory collapse and severe cardiorespiratory distress. Thus life-threatening. Nevertheless, the risk when the product is used in accordance to instruction is low. The impact of this risk on the individual patient is considered acceptable considering the anticipated benefits of therapy.

Public health impact: None.

Important Identified Risk: Risk of pulmonary oedema in patients with PVOD

Potential mechanism: Elevation of pulmonary capillary pressure.

Occurrence of pulmonary oedema in PVOD, which may be precipitated by the administration of pulmonary vasodilators resulting in preferential dilatation of pulmonary arterioles and flooding of pulmonary capillaries.

Evidence source(s) and strength of evidence: This risk is based on the known safety profile of nitric oxide as reflected in the current product information. This risk arised from the evaluation of a signal of pulmonary edema in patients with PH related to PVOD, which was initially received by Health Canada and informed to the EMA. As outcomes of the procedure, a PRAC recommendation

was adopted in PRAC meeting 25-27 Nov 2024 (EMA/PRAC/537837/2024), with the need to amend the SmPC and Package Information Leaflet (PIL). Product information was amended as requested.

Characterisation of the risk: PH is a haemodynamic state of the pulmonary circulation defined by a mean pulmonary artery pressure (mPAP) ⩾25 mmHg. PVOD represents a rare form of PH characterised by preferential involvement of the pulmonary venous system. The pathological hallmark is obliteration of small pulmonary veins by fibrous intimal thickening and patchy capillary proliferation. PVOD results in a progressive increase in pulmonary vascular resistance, culminating in right heart failure. Nitric Oxide and other inhalative vasodilataors relaxe the vascular smooth muscles and produce pulmonary vasodilatation. For an unknown short period after initiating therapy with vasodilatators, the perfusion – ventilation mismatch seams to improve. However, due to the high resistance in the pulmonary venouse capillars and micro-vessels, this increased blood flow causes flooding of the pulmonary capillars, which again leads to serum exacervation presenting as pulmonary oedema. This again worsen the perfusion – ventilation mismatch and can result in death.

Overall, in the total patient group with PH the use of vasodilators is considered acceptable anticipating benefits of therapy. Incidence rate for idiopathic PVOD is estimated with 0.5 per million persons per year. Referring to a register trial from France Cancer register[77], PVOD is seen in 3.9 patients post anal cancer therapy. Specific chemotherapeutics are suspected to contribute to the development of PVOD.

Clinical trial exposure: Not applicable.

Post-marketing experience: A cumulative safety database output search for events under the PTs Pulmonary oedema, Acute pulmonary oedema, Pulmonary oedema neonatal and Non-cardiogenic pulmonary oedema retrieved seventeen (17) case reports, all of them serious, encompassing 20 events of pulmonary oedema and 1 event of non-cardiogenic pulmonary oedema. Among the 21 reported events, for 18 the outcome was recovered/recovering at the time of the report, for 1 event it was not recovered and for the remaining 2 events the outcome was unknown at the time of the report.

Risk factors and risk groups: patients with PVOD.

It should be considered that patients with a history of cancer and chemotherapy could have a higher risk for PVOD than the overall patient population. PVOD and PAH share a common clinical presentation and are characterised by fatigue and breathlessness, in the end stage with right heart failure. In those patients a PVOD should be considered when shortly after starting therapy with a pulmonary vasodilatator develop pulmonary oedema.

Preventability: Measures to prevent this risk are described in SmPC Section 4.4. Also, additional risk minimisation measures are in place, please see Part V.

Impact on the risk-benefit balance of the product: Pulmonary oedema is associated with impaired oxygenation and may cause circulatory collapse and severe cardiorespiratory distress. Thus life-threatening. Nevertheless, the risk when the product is used in accordance to instruction is low. The impact of this risk on the individual patient is considered acceptable considering the anticipated benefits of therapy.

Public health impact: None.

Important Identified Risk: Risk of rebound reaction; PH and/or oxygen saturation decrease/desaturation associated to abrupt withdrawal

Potential mechanisms: Abrupt discontinuation of iNO therapy may cause rebound reactions increased PAP, pulmonary vasoconstriction and hypoxemia, i.e. decrease in oxygen saturation/arterial oxygen tension, with a subsequent risk for cardiopulmonary collapse.

Evidence source(s) and strength of evidence: This risk is based on the known safety profile of nitric oxide as reflected in the current product information and the publicly available scientific literature[40,78].

Characterisation of the risk: Abrupt discontinuation of the administration of iNO may cause rebound reaction; decrease in oxygenation and increase in central pressure and subsequent decrease in systemic blood pressure. Rapid rebound reactions such as intensified pulmonary vasoconstriction and hypoxia after sudden withdrawal of iNO therapy has been described, precipitating cardiovascular collapse. Rebound reaction is the most commonly ADR in association with the clinical use of INOmax. The rebound may be seen early as well as late during therapy.

Clinical trial exposure: Not applicable.

Post-marketing experience: A cumulative safety database output search for the relevant events received under the SMQ Drug withdrawal did not retrieve any case. In addition, the cumulative search performed for the SMQ Pulmonary hypertension retrieved a total of one hundred and eighty-five (185) case reports, 179 of which were serious and 6 non-serious, encompassing the following two hundred and five (205) events: PH (n=144), RV failure (n=17), pulmonary arterial pressure increased (n=13), pulmonary arterial wedge pressure increased (n=10), pulmonary arterial hypertension (n=10), tricuspid valve incompetence (n=6), pulmonary arterial wedge pressure increased (n=2), central venous pressure increased (n=1), pulmonary vein stenosis (n=1) and RV hypertrophy (n=1).

Analyzing the 205 events, for 28 of them the outcome was recovered/recovering, 21 events were fatal, in another 3 the patient had not recovered at the time of the report and in 2 the outcome was unknown at the time of the report. For the remaining 135 events, the outcome was not reported but considering that the related events were reported in patients who expired, these are evaluated below as fatal.

From the 156 events considered fatal, 138 were assessed as not related to the INOmax therapy but generally related to concurrent conditions of the patients, another 15 events were reported in cases poorly described ([redacted]: it was only reported that patient expired while receiving INOmax but no further information could be obtained), and thus causality between therapy and the patient's death could not be properly assessed, and the remaining 3 cases are described below:

- [redacted] case concerning a female infant born at 26 weeks gestation, admitted with respiratory distress and who was enrolled in a blinded placebo-controlled trial of nitric oxide for inhalation for the prevention of chronic lung disease. Her condition had deteriorated and a heart ultrasound showed PH. The neonate was treated with INOmax and her condition improved a little bit. She had metabolic acidosis and developed bradycardia and hypotension, requiring cardiac resuscitation. Resuscitative efforts were unsuccessful and in agreement with her parents, intensive care was discontinued and the neonate expired. The cause of death was attributed to PH, refractory metabolic acidosis and hypotension. Despite a causal relationship between INOmax and the events cannot be excluded, the events and resulting death could be explained by the concurrent conditions of the newborn.

- [redacted] case concerning a four-year-old male with a history of congenital heart disease with increased RV pressure who underwent a cardiac catheterization for pulmonary artery stenosis. During the last part of the procedure the patient experienced severe hypotension with hypoxemia and bradycardia. The protocol was discontinued and the patient was treated with dobutamine and 100% oxygen. There was an initial improvement in oxygen saturation, arterial tension and sinus rhythm recovery were obtained. The patient was transferred to the intensive care unit and in the following hours he suffered a severe deterioration with PH and RV failure. Despite administration of 100% oxygen, nitric oxide at 20 ppm, dobutamine, milrinone, adrenalin, sildenafil and hyperventilation the patient expired after ventricular fibrillation.

- [redacted] case concerning a female infant born at 25 weeks gestation who was intubated at the time of delivery and treated with high frequency oscillation ventilation (HFOV). The infant was enrolled in a blinded placebo-controlled trial of INOmax for the prevention of chronic lung disease and received nitric oxide. She developed bilateral interstitial emphysema and PH. The infant had progressive respiratory failure on HFOV. Also, a drop in hematocrit was observed during the day and a new cranial ultrasound revealed a bilateral grade III IVH. She had massive bilateral interstitial emphysema which made her impossible to ventilate on HFOV. She had increasing respiratory acidosis which led to metabolic acidosis. The combination of severe respiratory failure and IVH resulted in a decision to discontinue treatment. The investigator defined the cause of death as a severe IVH with the pulmonary interstitial emphysema and PH resolved at the time of death.

Other PTs related to this risk were also analyzed cumulatively: Oxygen saturation decreased and hypoxia, and the cumulative search retrieved three hundred and seven (307) case reports, of which 238 were serious and 69 non-serious. These cases encompassed 254 events of oxygen saturation decreased (175 serious and 79 non-serious) and 79 events of hypoxia (77 serious and 2 non-serious).

Among the total of 307 cases, twenty-five (25) cases were fatal; however, 15 of these cases were assessed as not related to INOmax. Out of the remaining 10 cases, 6 cases ([redacted] were related to device issues/failures and are evaluated in the Important Identified Risk of Critical failure of the NODS, one case ([redacted]) was related to drug withdrawal and is described above in this Section, another case ([redacted]) is related to the Important Identified Risk of acute cardiac failure with circulatory collapse in certain patient populations and evaluated also above in this Section, and case [redacted] was poorly described (it was only reported that a 18-year-old patient died while on INOmax) and thus a proper assessment cannot be performed. The last case is described below:

- [redacted] this case was reported by an attorney, who alleged that an adult male with a history of pulmonary fibrosis was hospitalized awaiting a lung transplant and received INOmax. Therapy was discontinued as he was transferred from the ICU to the operating room, and at the time of arrival in the operating room, the patient's oxygen saturation had deteriorated and the lung transplant surgery was cancelled. The patient died. No further information is available.

Overall, in most of the cases reporting death of the patient the events and related outcome were considered not related to the administration of nitric oxide, and among other cases most of them were either poorly described or there were other contributing factors for the death, such as the severe concurrent conditions of the patients.

The outcomes of the non-fatal events were the following: recovered (n=228), recovered with sequelae (n=3), recovering (n=3), not recovered (n=11) and unknown (n=23). In addition, there were 39 events for which the outcome was not provided as these occurred in cases resulting in death but events were not related to INOmax.

Risk factors and risk groups: All patients.

Preventability: Measures to prevent this risk are described in SmPC Section 4.2, 4.4 and 4.8. Also, additional risk minimisation measures are in place, please see Part V.

Impact on the risk-benefit balance of the product: The patient may potentially experience rebound pulmonary arterial hypertension with subsequent circulatory instability and risk of hypoxemia. Signs and symptoms of rebound PH syndrome include hypoxemia, systemic hypotension, bradycardia, and decreased cardiac output. This is a potentially severe - life threatening risk. Nevertheless, the risk when the product is used in accordance to instruction is low. The impact of this risk on the individual patient is considered acceptable considering the anticipated benefits of therapy.

Public health impact: None.

Important Identified Risk: Critical failure of the Nitric Oxide Delivery System (NODS)

Potential mechanisms: Accidental discontinuation of delivery with subsequent sudden/abrupt cessation of administration may cause rebound increase in PAP and decrease in oxygen saturation/arterial oxygen tension.

Evidence source(s) and strength of evidence: This risk is based on the known safety profile of nitric oxide as reflected in the current product information and the publicly available scientific literature[79,80].

Characterisation of the risk: Failure of the delivery system.

Clinical trial exposure: Not applicable.

Post-marketing experience: A cumulative safety database output search for the relevant events received under the PTs Device failure, Device issue, and Device delivery system issue retrieved one hundred and eighty-six (186) case reports, 118 of which were assessed as serious and 68 as non-serious.

Among the total of 186 cases, 12 were fatal: six (6) ([redacted] fatal cases were considered not related to INOmax nor related device issues, one case [redacted]) is related to Risk of acute cardiac failure with circulatory collapse in certain patient populations and is described above in this section, and the remaining 5 cases are described below:

- [redacted] case concerning a 2-month-old infant with respiratory failure who was ventilated with INOmax for seven days. INOvent alarmed and showed there was a failure, for which it was restarted but failed again. Attempts to hand ventilate failed as there was reportedly no flow into the bag. Of note, the infant had been hand ventilated earlier in the day during routine nursing care procedures. The infant became bradycardic, the blood pressure and oxygen saturation levels decreased and intravenous adrenaline was administered. A replacement INOvent was quickly obtained and ventilation was reinstated. It was estimated about seven minutes had elapsed. Following the restart of therapy the ventilator settings were restored to maximum pressure levels, but the infant's condition returned to her previous poor state and she expired four hours later.

- [redacted] case concerning a full-term infant born with respiratory failure who was intubated at 18 minutes of age and was placed on INOmax, but INOvent had an electrical failure possibly due to a malfunctioning injector module cable. The staff contacted INO therapeutics' technical support and they were advised to use the manual back-up system to administer INOmax, however the infant had failure to oxygenate. The infant had a CDH, was removed from support and expired.

- [redacted]case concerning a 74-year-old male patient with concurrent conditions of severe respiratory failure with multiple organ failure and extremely hypoxic who was being treated with INOmax when a device issue occurred. A second cylinder was opened and still appeared that no nitric was being delivered. The patient was then bagged whilst the backup machine was made ready. It was reported that this machine was not delivering either but it transpired that the sample line had not been connected. It was concluded that the incident was due to human error and further training was conducted. In addition, the severe patient's underlying condition should be acknowledged.

- [redacted] case concerning a 2-day old neonate with a most complicated post-delivery course, repeated cardiac arrest and PH. The newborn was put on iNO from other manufacturer but was subsequently switched to INOmax delivered via a INOvent because the first delivery device failed. The neonate had further cardiac arrest in conjunction to INOvent issue. The resuscitation was unsuccessfully and neonate died. The relation to the INOvent issue cannot be assessed, but the complex and complicated course with repeated cardiac arrests and parents wish to stop resuscitation efforts must be acknowledged. Relation to iNO was considered unlikely.

- [redacted]case concerning a 25-week-old patient who suffered a severe neonatal PH, for which it was suspected he received NOXIVENT nitric oxide. After this (temporal relationship was not specified), serious fluctuations occurred (device delivery system inaccurate flow rate) and patient died. It was reported that it was not certain whether a deficit device could have contributed to death and the case is confounded by the patient's condition previous to treatment. Further details should be provided for a proper assessment, e.g. if the instructions in product information were followed, or MetHb levels were measured, if the dose was adequate, when the fluctuations started, and if a corrective action was taken.

Furthermore, there were 3 additional cases also related to the risk of Rebound reactions associated to abrupt withdrawal (see Important Identified Risk of rebound reaction; PH and/or oxygen saturation decrease/desaturation associated to abrupt withdrawal for further details), which described device issues/failures and that were fatal:

- [redacted]case concerning a newborn female with a medical history of overwhelming sepsis, pulmonary hemorrhage, and a chemical code order who was treated with INOmax to keep her oxygen saturation up. The patient was being transported out of the hospital via ambulance for ECMO at another hospital, and while INOvent was being loaded into the ambulance, the device was damaged due to a hit, the INOvent screen went black and no alarms activated. A subsequent attempt to provide nitric oxide with the manual backup system integral to the INOvent device was unsuccessful. The patient's heart rate decreased and her oxygen saturation was 0-10%. The patient transport was cancelled and she was treated with dopamine, dobutamine, antibiotics, and maintenance fluids but finally expired. The cause of death was overwhelming sepsis and abrupt discontinuation of INOmax.

- [redacted] case concerning a 61-years-old male who was being treated with iNO for PH when a device failure occurred. Following drop of patient's heart rate and

oxygen saturation, resuscitation was initiated, but it was stated that the manual resuscitator was not connected to either the device's INOblender or any oxygen supply. However, it was thereafter observed that the patient had a Do Not Resuscitate/Do No Intubate order and all ventilation efforts were stopped. Of note, the customer stated that due to the patient's already compromised condition and the fact that no respiratory therapist witnessed the device issue, they could not state that the INOmax device was or was not responsible for the patient's worsening condition.

- [redacted] case concerning a 5-week neonate who was receiving INOmax when there was an issue with the inovent screen, for which it was uncertain initally if nitric oxide was being administered. It was reported that, although the issue was intermittent, there was never a 'delivery stopped' alarm: the cylinder just kept disappearing off the screen for 5-30 seconds and this resulted in the 'cylinder valve closed'. Of note, it was reported that patient experienced oxygen saturation decreased, for which he required manual breaths, but the patient had experienced this situation previously due to his instability. The patient subsequently died; however, it was reported that this was down to the patient's diagnosis and not because of the product issue. In addition, investigation showed that there was no sign of damage or anything visual to the INOmeter that would cause any problem.

Overall, in the 8 cases described above the failure in the delivery of INOmax was accompanied by underlying conditions/status of the patients, which most likely had a significant contribution to patient's outcome.

In addition, from the non-fatal events, the outcomes were: recovered (n=96), recovering (n=1), not recovered (n=1) and unknown (n=38). In addition, there were 22 events for which the outcome was not provided as these were not related to INOmax.

Risk factors and risk groups: All patients.

Preventability: Measures to prevent this risk are described in SmPC Sections 4.2, 4.8, 6.4 and 6.6. Also, additional risk minimisation measures are in place, please see Part V.

Impact on the risk-benefit balance of the product: The patient may potentially experience rebound pulmonary arterial hypertension with subsequent circulatory instability and risk of hypoxemia. Signs and symptoms of rebound PH syndrome include hypoxemia, systemic hypotension, bradycardia, and decreased cardiac output. This is a serious risk. Nevertheless, the risk when the product is used in accordance to instruction is low. The impact of this risk on the individual patient is considered acceptable considering the anticipated benefits of therapy.

Public health impact: None.

Important Identified Risk: Risk of NO_2 formation

Potential mechanisms: In the presence of oxygen, nitric oxide is rapidly oxidized to derivatives which are toxic to the bronchial epithelium and alveolo-capillary membrane (the time to reach a concentration of 5 ppm NO_2 from 20 ppm nitric oxide in 100% oxygen is about 12 minutes, while in air (21% oxygen) it is more than one hour). NO_2 is the main substance formed, and it may cause airway inflammation and damage. There are also animal data suggesting an increased susceptibility to airway infections upon exposure to low levels of NO_2.

Evidence source(s) and strength of evidence: This risk is based on the known safety profile of nitric oxide as reflected in the current product information and the publicly available scientific literature[68,81-84].

Characterisation of the risk: NO_2 is a known pollutant in ambient air. Exposure to NO_2 is known to be directly toxic to the respiratory tract and there are explicit recommended exposure limits to NO_2 to secure health. Increased airway reactivity has been reported following exposure to

concentrations in the magnitude of 2 ppm. When using a dedicated dosing device to provide a constant NO concentration independent of the ventilatory pattern, the NO_2 formation is minimal and the risk for adverse effect is low.

Clinical trial exposure: Not applicable.

Post-marketing experience: A cumulative safety database search for events related to NO_2 formation was performed and did not retrieve any case.

Risk factors and risk groups: Patients requiring high oxygen fraction risk factors; incorrectly calibrated device non-trained personnel.

Preventability: Measures to prevent this risk are described in the SmPC Section 4.2, 4.4, 4.5, 4.9, 5.2, 6.2 and 6.6. Also, additional risk minimisation measures are in place, please see Part V.

Impact on the risk-benefit balance of the product: Potential airway inflammation and damage to lung tissues. This is a serious risk. Nevertheless, the risk when the product is used in accordance to instruction is low. The impact of this risk on the individual patient is considered acceptable considering the anticipated benefits of therapy.

Public health impact: Nitrogen dioxide may be released into the ambient room air and thus cause environmental exposure to HCPs and others. Nevertheless, the risk when product is used in accordance to instruction is low.

Important Potential Risk: Increased bleeding time

Potential mechanisms: Nitric oxide may have an effect on the platelet and subsequently cause a reduced clot formation. The effect on coagulation is also addressed in Toxicology; Potential effect on platelet function and subsequently on haemostasis.

Evidence source(s) and strength of evidence: This risk is based on the known safety profile of nitric oxide as reflected in the current product information.

Characterisation of the risk: Animal models have shown that nitric oxide may interact with homeostasis, resulting in an increased bleeding time. Data in adult humans are conflicting, and there has been no increase in bleeding complications in randomized controlled trials in term and near-term neonates with hypoxic respiratory failure. Regular monitoring of haemostasis and measurement of bleeding time is recommended during the administration of INOmax for more than 24 hours to patients with functional or quantitative platelet anomalies, a low coagulation factor or receiving anticoagulation treatment.

Clinical trial exposure: Not applicable.

Post-marketing experience: A cumulative safety database output search for events under the PT bleeding time prolonged did not retrieve any case.

Risk factors and risk groups: All patients.

Preventability: Measures to prevent this risk are described in the SmPC Section 4.4. Also, additional risk minimisation measures are in place, please see Part V.

Impact on the risk-benefit balance of the product: Potential hemorrhagic events (e.g. pulmonary or cerebral bleed), which could lead to circulatory instability. This is a serious risk. Nevertheless, the risk when the product is used in accordance to instruction is low. The impact of this risk on the individual patient is considered acceptable considering the anticipated benefits of therapy.

Public health impact: None.

Missing information: Combined use with other vasodilators

Evidence source: Nitric oxide is a compound produced by many cells of the body. It relaxes vascular smooth muscle by binding to the haemopoietic of sGC, activating guanylate cyclase and increasing intracellular levels of cGMP, which then leads to vasodilation. When inhaled, nitric oxide produces selective pulmonary vasodilation. No formal drug-interaction studies have been performed.

Anticipated risk/consequence of the missing information: The combined used with other vasodilators (e.g. sildenafil) is not extensively studied. Available data suggest additive effects on central circulation, PAP and RV performance. iNO combination with other vasodilators acting by the cGMP or cAMP systems should be done with caution.

Missing information: Use during pregnancy and lactation

Evidence source: Animal reproduction studies have not been conducted with nitric oxide for inhalation.

Population in need of further characterisation: It is not known if nitric oxide for inhalation can cause foetal harm when administered to pregnant women or can affect reproductive capacity. It is not known whether nitric oxide is excreted in human milk. The potential risk for humans is unknown.

Missing information: Paediatric use (patients 12-17 years treated for pulmonary hypertension in conjunction with heart surgery)

Evidence source: dose adjustments in the age range of 12-17 years being treated for pulmonary hypertension in conjunction with heart surgery are not supported by available clinical data.

Population in need of further characterisation: There are limited clinical data supporting a nitric oxide dose for patients 12-17 years treated for PH in conjunction with heart surgery.

Part II: Module SVIII - Summary of the safety concerns

Table 24 Part SVIII.1: Summary of safety concerns

	Summary of safety concerns
Important Identified Risks	1. Methaemoglobinemia
	2. Risk of acute cardiac failure with circulatory collapse in certain patient populations
	3. Risk of pulmonary oedema in patients with pre-existing left ventricular dysfunction
	4. Risk of pulmonary oedema in patients with PVOD
	5. Risk of rebound reaction; pulmonary hypertension and/or oxygen saturation decrease/desaturation associated to abrupt withdrawal
	6. Critical failure of the Nitric Oxide delivery system (NODS)
	7. Risk of NO_2 formation

Important Potential Risks	8. Increased bleeding time
Missing Information	9. Combined use with other vasodilators
	10. Use during pregnancy and lactation
	11. Paediatric use (patients 12-17 years treated for pulmonary hypertension in conjunction with heart surgery)

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

A Pharmacovigilance Plan was developed to fulfil the legal requirements for pharmacovigilance contained within Directive 2001/83/EC and Regulation (EC) No 726/2004 when the new indication "Pulmonary hypertension associated with heart surgery" was submitted and approved in March 2011. This Pharmacovigilance Plan is applicable for the product discussed in this RMP. A Pharmacovigilance system master file (PSMF) is in place since June 2015 according to the new governing pharmacovigilance legislation (Regulation (EU) No 1235/2010 and Directive 2010/84/EU).

Nonetheless, the benefit-risk balance of INOmax is since 23 June 2016 (DLP of PSUR) evaluated by means of single assessment (EU Periodic Safety Update Single Assessment). PSURs are prepared for the European Union (with Norway and Iceland) in PBRER-format (Periodic Benefit Risk Evaluation Report); aligning the Dir. 2010/84/EC and in accordance with the EURD (European Union reference date) List.

III.1 Routine pharmacivigilance activities

Routine pharmacovigilance activities are considered adequate and sufficient to monitor and analyse relevant safety data from post-marketing experience to fully assess the safety of the product. Routine pharmacovigilance activities will allow the monitoring and follow-up of any concern which may arise and facilitate the modification and/or planning of further actions than those detailed below. In any case, any eventual future recommendations from the PRAC, CHMP or Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) as well as national competent authorities on specific activities will be considered and applied. Consequently, the Pharmacovigilance Plan of the aforementioned product will be updated accordingly.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for the safety concerns:

- None proposed.

Other forms of routine pharmacovigilance activities for the safety concerns:

- None proposed.

III.2 Additional pharmacovigilance activities

In conjunction with the approval of the "Pulmonary hypertension associated with heart surgery" indication the EMA requested a RMP which was implemented in all EU/EAA countries providing INOmax.

Routine pharmacovigilance activities are considered sufficient for Medicinal NO, INOmax. There are no company sponsored study activities around Medicinal NO, INOmax.

III.3 Summary Table of additional Pharmacovigilance activities.

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

Based on the current knowledge, the MA applicant considers that there are no gaps in knowledge about efficacy of Medicinal NO, INOmax; thus, there is no need for post-authorisation efficacy studies.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation measures)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table 25 Part Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	**Routine risk minimisation activities**
Methaemoglobinemia	Routine risk communication and risk minimisation activities recommending specific clinical measures to address the risk: - **Posology and method of administration in SmPC section 4.2**. There is a specific subsection (Monitoring formation of methaemoglobin (MetHb)) stating the following: Neonates and infants are known to have diminished MetHb reductase activity compared to adults. Methaemoglobin level should be measured within one hour after initiation of INOmax therapy, using an analyser which can reliably distinguish between foetal haemoglobin and methaemoglobin. If it is > 2.5 %, the INOmax dose should be decreased and the administration of reducing medicinal products such as methylene blue may be considered. Althoug h it is unusual for the methaemoglobin level to increase significantly i f the first level is low, it is prudent to repeat methaemoglobin measurements every one to two days. In adults undergoing heart surgery, methaemoglobin level should be measured within one hour of the initiation of INOmax therapy. If the fraction of methaemoglobin rises to a level that potentially compromises adequate oxygen delivery, the INOmax dose should be

	decreased and the administration of reducing medicinal products such as methylene blue may be considered. - **Special warnings and precautions for use in SmPC section 4.4.** There is a specific subsection (Formation of methaemoglobin) stating the following: A large portion of nitric oxide for inhalation is absorbed systemically. The end medicinal products of nitric oxide that enter the systemic circulation are predominantly methaemoglobin and nitrate. The concentrations of methaemoglobin in the blood should be monitored, see section 4.2. - **Interactions with other medicinal products and other forms of interactions are included in SmPC section 4.5**: No interaction studies have been performed. A clinically significant interaction with other medicinal products used in the treatment of hypoxic respiratory failure cannot be excluded based on the available data. There may be an additive effect with INOmax on the risk of developing methaemoglobinemia with nitric oxide donor substances, including sodium nitroprusside and nitroglycerin. INOmax has been safely administered with tolazoline, dopamine, dobutamine, steroids, surfactant, and high-frequency ventilai on. There is an increased risk of methaemoglobin formation if substances with a known tendency to increase methaemoglobin concentrations are administered concomitantly with nitric oxide (e.g. alkyl nitrates and sulphonamides). Substances known to cause increased methaemoglobin levels should thus be used with caution during therapy with inhaled nitric oxide. Prilocaine, whether administered as oral, parenteral, or topical formulations may cause methaemoglobinemia. Care must be taken when INOmax is given at the same time as medicinal products containing prilocaine. - **Methaemoglobinemia is listed in SmPC Section 4.8.** - **Risk addressed in SmPC Section 4.9 Overdose:** it is stated that: Overdose with INOmax will be manifest by elevations in methaemoglobin and NO_2. Elevated NO_2 may cause acute lung injury. Elevations in methaemoglobinemia reduce the oxygen delivery capacity of the circulation. In clinical studies, NO_2 levels > 3 ppm or methaemoglobin levels > 7 % were treated by reducing the dose of, or discontinuing, INOmax. Methaemoglobinemia that does not resolve after reduction or discontinuation of therapy can be treated with intravenous vitamin C, intravenous methylene blue, or blood transfusion, based upon the clinical situation. - **Pharmacodynamic properties in SmPC Section 5.1:** it is stated that in the CINRGI trial, […] of the 97 patients treated with INOmax, 2 (2%) were withdrawn from study drug due to methaemoglobin levels >4 %. The frequency and number of adverse events were similar in the two study groups.

	- **<u>Pharmacokinetic properties in SmPC Section 5.2:</u>** The pharmacokinetics of nitric oxide has been studied in adults. Nitric oxide is absorbed systemically after inhalation. Most of it traverses the pulmonary capillary bed where it combines with haemoglobin that is 60 % to 100 % oxygen-saturated. At this level of oxygen saturation, nitric oxide combines predominantly with oxyhaemoglobin to produce methaemoglobin and nitrate. At low oxygen saturation, nitric oxide can combine with deoxyhaemoglobin to transiently form nitrosylhaemoglobin, which is converted to nir ogen oxides and methaemoglobin upon exposure to oxygen. Within the pulmonary system, nitric oxide can combine with oxygen and water to produce nitrogen dioxide and nitrite, respectively, which interact with oxyhaemoglobin to produce methaemoglobin and nitrate. Thus, the end products of nitric oxide that enter the systemic circulation are predominantly methaemoglobin and nitrate. Methaemoglobin disposition has been investigated as a function of time and nitric oxide exposure concentration in neonates with respiratory failure. Methaemoglobin concentrations increase during the first 8 hours of nitric oxide exposure. The mean methaemoglobin levels remained below 1 % in the placebo group and in the 5 ppm and 20 ppm INOmax groups, but reached approximately 5 % in the 80 ppm INOmax group. Methaemoglobin levels > 7 % were attained only in patients receiving 80 ppm, where they comprised 35 % of the group. The average time to reach peak methaemoglobin was 10 ± 9 (SD) hours (median, 8 hours) in these 13 patients; but o ne patient did not exceed 7 % until 40 hours. - **<u>Preclinical safety data in SmPC Section 5.3:</u>** it includes that acute toxicity is related to anoxia resulting from elevated methaemoglobin levels. - **<u>Risk addressed in PIL Section 2:</u>** it is included in warnings and precautions that inhaled nitric oxide may influence the oxygen carrying capacity of the blood. This will be monitored by blood samples and if required the dose of inhaled nitric oxide must be reduced. Also, the following is included in other medicines and INOmax: some medicines can affect the ability of blood to carry oxygen. These include prilocaine (a local anaesthetic used for pain relief in association to minor painful procedures e.g. suturing, and minor surgical or diagnostic procedures) or glyceryl trinitrate (used to treat chest pain). Your doctor will take care to check that the blood can carry enough oxygen when you are taking these medicines. It is also stated in subsection "If you or your child receive more INOmax than you should" that too much of inhaled nitric oxide

	may influence the oxygen carrying capacity of the blood. This will be monitored by blood samples and if required the INOmax dose will be decreased and the administration of medicines such as vitamin C, methylene blue, or eventually blood transfusion, in order to improve the oxygen carrying capacity, may be considered. - **Possible side effects in PIL Section 4:** included in uncommonly seen side effects: increase in methaemoglobin, thus reduced oxygen carrying capacity. Other routine risk minimisation measures beyond the Product Information: Legal status: subject to medical prescription.
Risk of acute cardiac failure with circulatory collapse in certain patient populations	Routine risk communication and risk minimisation activities recommending specific clinical measures to address the risk: - **Contraindication in SmPC Section 4.3:** Neonates known to be dependent on right-to-left, or significant left-to-right, shunting of blood. - **Special warnings and precautions for use in SmPC section 4.4.** The following is included in subsection for Special patient populations: Treatment with inhaled nitric oxide might aggravate cardiac insufficiency in a situation with left-to-right shunting. This is due to unwanted pulmonary vasodilation caused by inhaled nitric oxide, resulting in a further increase of already existing pulmonary hyperperfusion thus potentially giving raise to forward or backward failure. It, therefore, is recommended that prior to the administration of nitric oxide, pulmonary artery catheterisation or echocardiographic examination of central haemodynamics be performed. Inhaled nitric oxide should be used with caution in patients with complex heart defect, where high pressure in the pulmonary artery is of importance for maintaining circulation. Inhaled nitric oxide should also be used with caution in patients with compromised left ventricular function and elevated baseline pulmonary capillary pressure (PCWP) as they may be at an increased risk of developing cardiac failure (e.g. pulmonary oedema). - **PIL Section 2 What you need to know before you begin a treatment with INOmax:** do not use INOmax if you have been told that you (as the patient) or your child (as the patient) have an abnormal circulation within the heart. Also, it is included in warnings and precautions that in newborn babies with special malformations of the heart, 'what doctors calls congenital heart defects' inhaled nitric oxide may cause a worsening of the circulation. Other routine risk minimisation measures beyond the Product Information:

	Legal status: subject to medical prescription.
Risk of pulmonary oedema in patients with pre-existing left ventricular dysfunction	Routine risk communication and risk minimisation activities recommending specific clinical measures to address the risk: - **Special warnings and precautions for use in SmPC section 4.4.** The following is included in subsection for Special patient populations: Inhaled nitric oxide should also be used with caution in patients with compromised left ventricular function and elevated baseline pulmonary capillary pressure (PCWP) as they may be at an increased risk of developing cardiac failure (e.g. pulmonary oedema). - **PIL Section 2 What you need to know before you begin a treatment with INOmax:** do not use INOmax if you have been told that you (as the patient) or your child (as the patient) have an abnormal circulation within the heart. Other routine risk minimisation measures beyond the Product Information: Legal status: subject to medical prescription.
Risk of pulmonary oedema in patients with PVOD	Routine risk communication and risk minimisation activities recommending specific clinical measures to address the risk: - **Special warnings and precautions for use in SmPC section 4.4.** There is a specific subsection for PVOD stating the following: cases of life-threatening pulmonary oedema have been reported with nitric oxide in patients with pulmonary veno-occlusive disease. Therefore, the possibility of a veno-occlusive disease should be carefully evaluated if signs of pulmonary oedema occur following the administration of nitric oxide to patients with pulmonary hypertension. If confirmed, the treatment is to be discontinued. - **PIL Section 2 What you need to know before you begin a treatment with INOmax:** in subsection warnings and precautions it is included that cases of fluid retention in the lungs have been reported with nitric oxide in patients with disease due to a blocked or narrow vein in the lungs, and patients are instructed to contact doctor immediately if they develop shortness of breath or difficulty breathing. Other routine risk minimisation measures beyond the Product Information: Legal status: subject to medical prescription.
Risk of rebound reaction; pulmonary hypertension and/or oxygen saturation decrease/desaturation associated to abrupt	Routine risk communication and risk minimisation activities recommending specific clinical measures to address the risk: - **Posology and method of administration in SmPC section 4.2**. There are specific subsections for Weaning for the two different indications: Persistent Pulmonary Hypertension in the Newborn (PPHN):

withdrawal	Attempts to wean INOmax should be made after the ventilator support is substantially decreased or after 96 hours of therapy. When the decision is made to discontinue inhaled nitric oxide therapy, the dose should be reduced to 1 ppm for 30 minutes to one hour. If there is no change in oxygenation during administration of INOmax at 1 ppm, the FiO2 should be increased by 10 %, the INOmax is discontinued, and the neonates monitored closely for signs of hypoxaemia. If oxygenation falls >20 %, INOmax therapy should be resumed at 5 ppm and discontinuation of INOmax therapy should be reconsidered after 12 to 24 hours. Infants who cannot be weaned off INOmax by 4 days should undergo careful diagnostic work-up for other diseases. Pulmonary hypertension associated with heart surgery: Attempts to wean INOmax should be commenced as soon as the haemodynamics have stabilised in conjunction to weaning from ventilator and inotropic support. The withdrawal of inhaled nitric oxide therapy should be performed in a stepwise manner. The dose should be incrementally reduced to 1 ppm for 30 minutes with close observation of systemic and central pressure, and then turned off. Weaning should be attempted at least every 12 hours when the patient is stable on a low dose of INOmax. Too rapid weaning from inhaled nitric oxide therapy carries the risk of a re-bound increase in PAP with subsequent circulatory instability. - **Special warnings and precautions for use in SmPC section 4.4.** There is a specific subsection for Discontinuation of therapy stating the following: the INOmax dose should not be discontinued abruptly as it may result in an increase in PAP and/or worsening of blood oxygenation (PaO2). Deterioration in oxygenation and elevation in PAP may also occur in neonates with no apparent response to INOmax. Weaning from inhaled nitric oxide should be performed with caution. For patients transported to other facilities for additional treatment, who need to continue with inhaled nitric oxide, arrangements should be made to ensure the continuous supply of inhaled nitric oxide during transportation. The physician should have access at the bedside to a reserve nitric oxide delivery system. - **Risk is addressed in SmPC Section 4.8.** It includes that: Abrupt discontinuation of the administration of inhaled nitric oxide may cause rebound reaction; decrease in oxygenation and increase in central pressure and subsequent decrease in systemic blood pressure. Rebound reaction is the most commonly adverse reaction in association with the clinical use of INOmax. The rebound may be seen early as well as late during therapy. It is also mentioned that rapid rebound reactions such as intensified pulmonary vasoconstriction and hypoxia after sudden withdrawal of inhaled nitric oxide therapy has been described, precipitating cardiovascular collapse. - **Risk addressed in PIL Section 3 how to use INOmax.** There is a specific subsection "if you stop using INOmax" stating the

	following: treatment with INOmax should not be stopped suddenly. Low blood pressure or a rebound increase in pressure in the lungs has been known to occur if treatment with INOmax is stopped suddenly without first lowering the dose. At the end of treatment, the doctor will slowly lower the amount of INOmax being given to you or your child, so that the circulation in the lungs is able to adjust to oxygen/air without INOmax. Thus, it may take a day or two before you or your child is off INOmax therapy. - **Possible side effects in PIL Section 4:** included in side effects with an unknown frequency that bradycardia (low cardiac frequency) or too low amount of oxygen in the blood (oxygen desaturation/hypoxemia) may be seen due to sudden withdrawal of the treatment. Other routine risk minimisation measures beyond the Product Information: Legal status: subject to medical prescription.
Critical failure of the Nitric Oxide Delivery System (NODS)	Routine risk communication and risk minimisation activities recommending specific clinical measures to address the risk: - **Posology and method of administration in SmPC section 4.2**. The following is included in Method of administration: Nitric oxide is delivered to the patient via mechanical ventilation after dilution with an oxygen/air mixture using an approved (CE-marked) nitric oxide delivery system. Before initiation of therapy, during set-up, secure that the device setting is in agreement with the cylinder gas concentration. The delivery system must provide a constant inhaled INOmax concentration irrespective of the ventilator. With a continuous flow neonatal ventilator, this may be achieved by infusing a low flow of INOmax into the inspiratory limb of the ventilator circuit. Intermittent flow neonatal ventilation may be associated with spikes in nitric oxide concentration. The nitric oxide delivery system for intermittent flow ventilation should be adequate to avoid spikes in nitric oxide concentration. The inspired INOmax concentration must be measured continuously in the inspiratory limb of the circuit near the patient. The nitrogen dioxide (NO_2) concentration and FiO_2 must also be measured at the same site using calibrated and approved (CE-marked) monitoring equipment. For patient safety, appropriate alarms must be set for INOmax ($\pm$ 2 ppm of the prescribed dose), NO_2 (1 ppm), and FiO_2 ($\pm$ 0.05). The INOmax gas cylinder pressure must be displayed to allow timely gas cylinder replacement without inadvertent loss of therapy and backup gas cylinders must be available to provide timely replacement. INOmax therapy must be available for manual ventilation such as suctioning, patient transport, and resuscitation. In the event of a system failure or a wall-outlet power failure, a backup battery power supply and reserve nitric oxide delivery system should be available. The power supply for the monitoring equipment should be independent of the delivery device function.

	The upper limit of exposure (mean exposure) to nitric oxide for personnel defined by worker's legislation is 25 ppm for 8 hours (30 mg/m3) in most countries and the corresponding limit for NO_2 is 2-3 ppm (4-6 mg/m3). In addition, there is a specific subsection for Training in administration, including the key elements that need to be covered in training hospital personnel: Correct set-up and connections: Connections to the gas cylinder and to the ventilator patient breathing circuit Operation: - Pre-use check list procedure (a series of steps required immediately prior to each patient initiation to ensure that the system is working properly and that the system is purged of NO_2); - Setting the device for the correct concentration of nitric oxide to be administered; - Setting the NO, NO_2 and O_2 monitors for high and low alarm limits; - Using the manual backup delivery system; - Procedures for correctly switching gas cylinders and purging system; - Troubleshooting alarms; - NO, NO_2 and O_2 monitor calibration; - Monthly system performance check-up procedures. - **SmPC Section 4.8:** it includes effects associated with acute withdrawal of the medicinal product, and/or delivery system failures. - **Special precautions for storage in SmPC Section 6.4.** The following is included: All regulations concerning handling of pressure vessels must be followed. Store gas cylinders indoors in well-ventilated rooms or outdoors in ventilated sheds where they are protected from rain and direct sunlight. Protect the gas cylinders from shocks, falls, oxidising and flammable materials, moisture and sources of heat or ignition. Storage in the pharmacy department: The gas cylinders should be stored in an airy, clean and locked place, for storage of medicinal gas only. Inside this place, a separate premise should be dedicated to the storage of nitric oxide gas cylinders. Storage in the medical department: The gas cylinder should be put in an equipped site with appropriate material in order to hold the gas cylinder vertically. Transport of gas cylinders: The gas cylinders should be transported with appropriate material in order to protect them from risks of shocks and falls. During inter- or within-hospital transfers of patients treated with INOmax, the gas cylinders should be fixedly stowed away in order to hold the gas cylinders vertically and to avoid the risk of fall or untimely modifying output. A particular attention should be also turned to the fastening of the pressure regulator so as to avoid the risks of accidental failures. - **Preclinical safety data in SmPC Section 6.6:** it includes the following Instructions for use/handling INOmax:

	When connecting an INOmax cylinder to the delivery system, always secure that the cylinder concentration is of the same concentration for which the system is configured. In order to avoid all incidents, the following instructions should be absolutely respected: - the good condition of the material should be checked before use - the gas cylinders should be fixedly stowed away in order to avoid untimely fall - the valve should be fully open when used but not be opened - a defective valve should neither be used nor be repaired. Return to distributor / manufacturer - a gas cylinder whose valve is not protected by a cap or a shell should not be used - a specific connection, with a 30 mm thread which is designated for medical use, complying with ISO 5145 and a pressure regulator which admits a pressure at least equal to 1.5 the maximum operating pressure (155 bar) of the gas cylinder should be used - the pressure regulator should be purged by the nitrogen-nitric oxide mixture before each new use in order to preclude nitrogen dioxide inhalation - a defective valve should not be repaired - the pressure regulator should not be tightened with pliers, at the risk of crushing the gasket All equipment, including connectors, tubing, and circuits, used in the delivery of nitric oxide must be made of materials compatible with the gas. From a corrosion point of view the supply system can be divided into two zones: 1) From the gas cylinder valve to the humidifier (dry gas) and 2) From the humidifier to outlet (moist gas which may contain NO_2). Tests show that dry nitric oxide mixtures can be used with most materials. However, the presence of nitrogen dioxide and moisture creates an aggressive atmosphere. Among metallic construction materials, only stainless steel can be recommended. Tested polymers which can be used in nitric oxide administration systems include polyethylene and polypropylene. Butyl rubber, polyamide, and polyurethane should not be used. Polytrifluorochloroethylene, hexafluoropropene-vinyliden copolymer and polytetr a flourethylene have been used extensively with pure nitric oxide and other corrosive gases. They were considered so inert that testing was not required. The installation of a nitric oxide pipeline system with supply station of gas cylinders, fixed network and terminal units is forbidden. There is in general no need for scavenging of excess gas, the work place ambient air quality should however be considered and trace concentrations of NO or NO_2/NOx must not exceed set national occupational exposure limits. Accidental exposure to INOmax in hospital staff has been associated with adverse events (see section 4.8). Instruction for disposal of gas cylinder: When the gas cylinder is

	empty, it should not be discarded. Empty gas cylinders will be collected by the supplier. - **PIL Section 5 How to store INOmax** states the following: Keep this medicine out of the sight and reach of children. Do not use this medicine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month. INOmax therapy should only be used and handled by hospital personnel. INOmax cylinders should be stored secured in order to avoid falling and thus potentially causing harm. INOmax should be used and administered only by personnel specially trained in the use and handling of INOmax. All re - gulations concerning ha - ndling of pressurised gas cylinders must be followed. Storage is supervised by the specialists at the hospital. Gas cylinders are to be stored in well-ventilated rooms or in ventilated sheds where they are protected from rain and direct sunlight. Protect the gas cylinders from shocks, falls, oxidising and flammable materials, moisture, sources of heat or ignition. Storage in the pharmacy department: the gas cylinders should be stored in an airy, clean and locked place, for storage of medicinal gas only. I nside this place, a separate premise should be dedicated to the storage of nitric oxide gas cylinders. Storage in the medical department: the gas cylinder should be put in an equipped site with appropriate material in order to hold the cylinder vertically. When the gas cylinder is empty, do not discard. Empty gas cylinders will be collected by the supplier. Other routine risk minimisation measures beyond the Product Information: Legal status: subject to medical prescription.
Risk of NO_2 formation	Routine risk communication and risk minimisation activities recommending specific clinical measures to address the risk: - **Posology and method of administration in SmPC section 4.2**. In Method of administration the following is included: The inspired INOmax concentration must be measured continuously in the inspiratory limb of the circuit near the patient. The nitrogen dioxide (NO_2) concentration and FiO2 must also be measured at the same site using calibrated and approved (CE-marked) monitoring equipment. For patient safety, appropriate alarms must be set for INOmax (±2 ppm of the prescribed dose), NO_2 (1 ppm), and FiO2 (± 0.05). The upper limit of exposure (mean exposure) to nitric oxide for personnel defined by worker's legislation is 25 ppm for 8 hours (30 mg/m^3) in most countries and the corresponding limit for NO_2 is 2-3 ppm (4-6 mg/m^3). Also, in Training in administration the key elements that need to be covered in training hospital personnel include the following:

	Operation: - Pre-use check list procedure (a series of steps required immediately prior to each patient initiation to ensure that the system is working properly and that the system is purged of NO_2) - Setting the NO, NO_2 and O_2 monitors for high and low alarm limits - NO, NO_2 and O_2 monitor calibration Monitoring formation of nitrogen dioxide (NO_2): immediately prior to each patient initiation, proper procedure must be applied to purge the system of NO_2. The NO_2 concentration should be maintained as low as possible and always < 0.5 ppm. If the NO_2 is > 0.5 ppm, the delivery system should be assessed for malfunction, the NO_2 analyser should be recalibrated, and the INOmax and/or FiO_2 should be reduced if possible. If there is an unexpected change in INOmax concentration, the delivery system should be assessed for malfunction and the analyser should be recalibrated. - **Special warnings and precautions for use in SmPC section 4.4.** There is a specific subsection for Formation of NO_2 which includes that NO_2 rapidly forms in gas mixtures containing nitric oxide and O_2, and nitric oxide may in this way cause airway inflammation and damage. The dose of nitric oxide should be reduced if the concentration of nitrogen dioxide exceeds 0.5 ppm. - **Interactions with other medicinal products and other forms of interactions are included in SmPC section 4.5**: it includes that in the presence of oxygen, nitric oxide is rapidly oxidised to derivatives which are toxic to the bronchial epithelium and alveolo-capillary membrane. Nitrogen dioxide (NO_2) is the main substance formed, and may cause airway inflammation and damage. There are also animal data suggesting an increased susceptibility to airway infections upon exposure to low levels of NO_2. During treatment with nitric oxide, the NO_2 concentration should be < 0.5 ppm in the nitric oxide dose range < 20 ppm. If at any time the NO_2 concentration exceeds 1 ppm, the nitric oxide dose should immediately be reduced. See section 4.2 for information on monitoring for NO_2. - **Risk addressed in SmPC Section 4.9 Overdose:** it is stated that overdose with INOmax will be manifest by elevations in methaemoglobin and NO_2 may cause acute lung injury. Elevations in methaemoglobinemia reduce the oxygen delivery capacity of the circulation. In clinical studies, NO_2 levels > 3 ppm or methaemoglobin levels > 7 % were treated by reducing the dose of, or discontinuing, INOmax. - **Pharmacokinetic properties in SmPC Section 5.2.** The following is included: within the pulmonary system, nitric oxide can combine with oxygen and water to produce nitrogen dioxide and nitrite, respectively, which interact with oxyhaemoglobin to produce methaemoglobin and nitrate. Thus, the end products of nitric oxide that enter the systemic circulation are predominantly

	methaemoglobin and nitrate. Also, it is mentioned that nitrate has been identified as the predominant nitric oxide metabolite excreted in the urine, accounting for > 70 % of the nitric oxide dose inhaled. Nitrate is cleared from the plasma by the kidney at rates approaching the rate of glomerular filtration. - **Incompatibilities in SmPC Section 6.2:** it is mentioned that in the presence of oxygen, NO rapidly forms NO_2, see section 4.5. - **Special precautions for disposal and other handling in SmPC Section 6.6:** Instructions for use/handling INOmax includes the following: When connecting an INOmax cylinder to the delivery system, always secure that the cylinder concentration is of the same concentration for which the system is configured. All equipment, including connectors, tubing, and circuits, used in the delivery of nitric oxide must be made of materials compatible with the gas. From a corrosion point of view the supply system can be divided into two zones: 1) From the gas cylinder valve to the humidifier (dry gas) and 2) From the humidifier to outlet (moist gas which may contain NO_2). Tests show that dry nitric oxide mixtures can be used with most materials. However, the presence of nitrogen dioxide and moisture creates an aggressive atmosphere. There is in general no need for scavenging of excess gas, the work place ambient air quality should however be considered and trace concentrations of NO or NO_2/NOx must not exceed set national occupational exposure limits. Accidental exposure to INOmax in hospital staff has been associated with adverse events (see section 4.8). - **Risk addressed in PIL Section 2 What you need to know before you begin a treatment with INOmax:** it is included in warnings and precautions that: Nitric oxide may react with oxygen forming nitrogen dioxide that may cause airway irritation. Your or your child's doctor will undertake monitoring of nitrogen dioxide and in case of elevated values the INOmax therapy will be adjusted, decreased accordingly. - **How to use INOmax in PIL Section 3. It states the following:** For you or your child's safety, the delivery systems intended for administration of INOmax are fitted with devices that constantly measure the amount of nitric oxide, oxygen, and nitrogen dioxide (a chemical formed when nitric oxide and oxygen are mixed) being delivered to the lungs. Other routine risk minimisation measures beyond the Product Information: Legal status: subject to medical prescription.
Increased bleeding time	Routine risk communication and risk minimisation activities recommending specific clinical measures to address the risk: - **Special warnings and precautions for use in SmPC section 4.4.** There is a specific subsection for effects on platelets

	including the following: Animal models have shown that nitric oxide may interact with haemostasis, resulting in an increased bleeding time. Data in adult humans are conflicting, and there has been no increase in bleeding complications in randomised controlled trials in term and near-term neonates with hypoxic respiratory failure. Regular monitoring of hemostasis and measurement of bleeding time is recommended during the administration of INOmax for more than 24 hours to patients with functional or quantitative platelet anomalies, a low coagulation factor or receiving anticoagulation treatment. - **Risk addressed in PIL Section 2 What you need to know before you begin a treatment with INOmax:** it is included in warnings and precautions that inhaled nitric oxide may have a mild but influence on the platelets (components that help the blood to clot) of you or your child and any signs of bleeding and or haematoma should be observed. If you see any signs or symptoms that may be associated to bleeding, you should directly inform the doctor. Other routine risk minimisation measures beyond the Product Information: Legal status: subject to medical prescription.
Combined use with other vasodilators	Routine risk communication and risk minimisation activities recommending specific clinical measures to address the risk: - **Interactions with other medicinal products and other forms of interactions are included in SmPC section 4.5**: The combined used with other vasodilators (e.g. sildenafil) is not extensively studied. Available data suggest additive effects on central circulation, PAP and right ventricular performance. Inhaled nitric oxide combination with other vasodilators acting by the cGMP or cAMP systems should be done with caution. - **Risk addressed in PIL Section 2 What you need to know before you begin a treatment with INOmax.** The following is included included in Other medicines and INOmax: please tell your doctor if you (as the patient) or your child (as the patient) are taking or have recently taken or used any other medicines, including medicines obtained without a prescription. Other routine risk minimisation measures beyond the Product Information: Legal status: subject to medical prescription.
Use during pregnancy and lactation	Routine risk communication and risk minimisation activities recommending specific clinical measures to address the risk: - **Fertility, pregnancy and lactation in SmPC Section 4.6:** it states that there are no adequate data from the use of nitric oxide in pregnant women. The potential risk for humans is unknown. It is unknown whether nitric oxide is excreted in human milk. INOmax should not be used during pregnancy or breastfeeding. No fertility studies have been performed.

	- **<u>Risk addressed in PIL Section 2 What you need to know before you begin a treatment with INOmax.</u>** The following is stated in Pregnancy and breastfeeding: INOmax is not recommended for use during pregnancy and breastfeeding. Tell your doctor before treatment with INOmax if you are pregnant, think you could be pregnant or are breastfeeding Ask your doctor or pharmacist for advice before taking any medicine. Other routine risk minimisation measures beyond the Product Information: Legal status: subject to medical prescription.
Paediatric use (patients 12-17 years treated for pulmonary hypertension in conjunction with heart surgery)	Routine risk communication and risk minimisation activities recommending specific clinical measures to address the risk: - **<u>SmPC Section 4.2 Posology and method of administration.</u>** It is included in the indication for Pulmonary hypertension associated with heart surgery that clinical data supporting the suggested dose in the age range 12-17 years is limited Other routine risk minimisation measures beyond the Product Information: Legal status: subject to medical prescription.

V.2. Additional Risk Minimisation Measures

Healthcare Professional training program

<u>Objectives:</u> To minimise the drug and device-related risk, including the following safety concerns:

1. Methaemoglobinemia
2. Risk of acute cardiac failure with circulatory collapse in certain patient populations
3. Risk of pulmonary oedema in patients with pre-existing left ventricular dysfunction
4. Risk of pulmonary oedema in patients with PVOD
5. Risk of rebound reaction; pulmonary hypertension and/or oxygen saturation decrease/desaturation associated to abrupt withdrawal
6. Critical failure of the Nitric Oxide delivery system (NODS)
7. Risk of NO_2 formation
8. Increased bleeding time
9. Combined use with other vasodilators
10. Use during pregnancy and lactation
11. Paediatric use (patients 12-17 years treated for pulmonary hypertension in conjunction with heart surgery)

Rationale for the additional risk minimisation activity: INOmax is supplied as an integrated therapy, consisting of NO and the device. Nitric oxide is administered to patients with a specialized delivery system in conjunction with ventilatory support. The delivery of iNO is complex, and the safe and effective administration of nitric oxide involves a multi-faceted interaction among the drug, a NODS, and a ventilation system (e.g., ventilator, anaesthesia, or respiratory care device (e.g., continuous PAP). The drug is delivered through a NOD into the breathing circuit of the ventilation system. The combination and interaction of the three modalities (drug, NODS, and ventilation system) is critical to the safety of iNO.

Therefore, a continuous and documented training program for both INOmax and devices based on currently approved product information (i.e., SmPC for INOmax, Instruction For Use (IFU) and operations manual for the device) is considered needed for all relevant healthcare staff in countries for which LHC AB is the MAH of INOmax. Sections 4.2 and 6.6 of the current SmPC include details on the key training elements required in the administration of iNO for hospital personnel, including the correct connection and operation in order to prevent accidental discontinuation of delivery which can result in rebound PH. The MAH also provides a technical operations manual which includes customer-specific detailed medical device training with all necessary technical background information for the safe administration of iNO. This all together is the base for the training for the iNO-therapy.

Target audience and planned distribution path: Prior to launch of the new indication of the product in each Member State, the MAH agrees the content and format of the educational material with the NCA. The MAH ensures that, at launch of the new indication, all HCPs who are expected to use and/or prescribe INOmax as part of the treatment of peri- or post- operative PH in adults and children in conjunction to heart surgery are provided with an Educational pack. This involves staff working in neonatal units (indication for PPHN) and in cardiothoracic anaesthesia and intensive care (indication for PH associated with heart surgery).

Initiating an INOmax account includes a dedicated training, theoretic as well as practical around the use of INOmax and the set-up of the delivery system placed at that account. The account managers and product specialists are also available for follow-up and any field request for trouble shooting around any issue related to INOmax and/or alternative CE-marked delivery. The training program for the delivery system is based on the IFU manual and the SmPC. The product specialists and account managers are trained in the device use in a special train-the-trainer program.

Plans to evaluate the effectiveness of the interventions and criteria for success: The effects of the minimisation measure are assessed by routine pharmacovigilance activities such as routine review of cases related to device malfunctions/failures, or other device-related issues including user error, to identify any trends in reporting that may be suggestive of potential safety signals. Periodic signal detection process includes the analysis of the frequency and severity of AEs reported. In the evaluation of the effectiveness of the interventions described in this section, the criteria for judging the success of the proposed risk minimisation measures involves that there is no increase in frequency and/or severity of AE reporting.

Of note, the MAH monitors potential signals detected during the signal detection and also outcomes of signal validation, signal analysis and prioritization, signal assessment and related recommendations for action and helds monthly safety monitoring meetings where the mentioned steps and outcomes are discussed. Also, whenever a validated signal or a safety issue from any source meets the definition of an Emergin Safety Issue, this is escalated to the safety team as applicable and managed as per regulatory requirements.

In addition, reports and evaluation of AEs associated with failure of a delivery device or user errors, as well as those related to other safety concerns, are gathered and presented in periodic reports such as PSURs.

Regarding milestones for reporting, planned dates for assessment include the routine signal detection process (continuous evaluation), the monthly safety monitoring meetings and also the inclusion in planned PSURs and related PSUSAs.

V.3 Summary of risk minimisation measures

Table 26 Part Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Methaemoglobinemia	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.5, 4.8, 4.9, 5.1, 5.2 and 5.3. PL sections 2 and 4. Legal status: subject to medical prescription. Additional risk minimisation measures: • HCP training program.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Additional pharmacovigilance activities: None
Risk of acute cardiac failure with circulatory collapse in certain patient populations	Routine risk minimisation measures: SmPC sections 4.3 and 4.4. PL section 2. Legal status: subject to medical prescription. Additional risk minimisation measures: • HCP training program.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Additional pharmacovigilance activities: None
Risk of pulmonary oedema in patients with pre-existing left ventricular dysfunction	Routine risk minimisation measures: SmPC section 4.4. PL section 2. Legal status: subject to medical prescription. Additional risk minimisation measures: • HCP training program.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Additional pharmacovigilance activities: None
Risk of pulmonary oedema in patients with PVOD	Routine risk minimisation measures: SmPC section 4.4.	Routine pharmacovigilance activities beyond

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	PL section 2. Legal status: subject to medical prescription. Additional risk minimisation measures: HCP training program.	adverse reactions reporting and signal detection Additional pharmacovigilance activities: None
Risk of rebound reaction; pulmonary hypertension and/or oxygen saturation decrease/desaturation associated to abrupt withdrawal	Routine risk minimisation measures: SmPC sections 4.2, 4.4 and 4.8. PL sections 3 and 4. Legal status: subject to medical prescription. Additional risk minimisation measures: • HCP training program.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Additional pharmacovigilance activities: None
Critical failure of the Nitric Oxide delivery system (NODS)	Routine risk minimisation measures: SmPC sections 4.2, 4.8, 6.4 and 6.6. PL section 5. Legal status: subject to medical prescription. Additional risk minimisation measures: • HCP training program.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Additional pharmacovigilance activities: None
Risk of NO_2 formation	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.5, 4.9, 5.2, 6.2 and 6.6. PL sections 2 and 3. Legal status: subject to medical prescription. Additional risk minimisation measures: • HCP training program.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Additional pharmacovigilance activities: None
Increased bleeding time	Routine risk minimisation measures: SmPC section 4.4. PL section 2. Legal status: subject to medical prescription.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: • HCP training program.	Additional pharmacovigilance activities: None
Combined use with other vasodilators	Routine risk minimisation measures: SmPC section 4.5. PL section 2. Legal status: subject to medical prescription. Additional risk minimisation measures: • HCP training program.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Additional pharmacovigilance activities: None
Use during pregnancy and lactation	Routine risk minimisation measures: SmPC section 4.6. PL section 2. Legal status: subject to medical prescription. Additional risk minimisation measures: • HCP training program.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Additional pharmacovigilance activities: None
Paediatric use (patients 12-17 years treated for pulmonary hypertension in conjunction with heart surgery)	Routine risk minimisation measures: SmPC section 4.2. Legal status: subject to medical prescription. Additional risk minimisation measures: • HCP training program.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Additional pharmacovigilance activities: None

Part VI: Summary of the risk management plan

Summary of risk management plan for INOmax

This is a summary of the risk management plan (RMP) for Medicinal NO, INOmax. The RMP details important risks of Medicinal NO, INOmax, how these risks can be minimised, and how more information will be obtained about Medicinal NO, INOmax's risks and uncertainties (missing information).

Medicinal NO, INOmax's summary of product characteristics (SmPC) and its package leaflet give essential information to HCPs and patients on how Medicinal NO, INOmax should be used.

This summary of the RMP for Medicinal NO, INOmax should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Medicinal NO, INOmax's RMP.

I. The medicine and what it is used for

Medicinal NO, INOmax is authorised for the following indications:

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

It contains nitric oxide as the active substance and it is given via inhalation.

Further information about the evaluation of Medicinal NO, INOmax's benefits can be found in Medicinal NO, INOmax's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage INOmax | European Medicines Agency (EMA).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Medicinal NO, INOmax, together with measures to minimise such risks and the proposed studies for learning more about Medicinal NO, INOmax' risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Medicinal NO, INOmax, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Medicinal NO, INOmax is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Medicinal NO, INOmax are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Medicinal NO, INOmax. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important Identified Risks	1. Methaemoglobinemia
	2. Risk of acute cardiac failure with circulatory collapse in certain patient populations
	3. Risk of pulmonary oedema in patients with pre-existing left ventricular dysfunction
	4. Risk of pulmonary oedema in patients with PVOD
	5. Risk of rebound reaction; pulmonary hypertension and/or oxygen saturation decrease/desaturation associated to abrupt withdrawal
	6. Critical failure of the Nitric Oxide delivery system (NODS)
	7. Risk of NO_2 formation
Important Potential Risks	8. Increased bleeding time
Missing Information	9. Combined use with other vasodilators
	10. Use during pregnancy and lactation
	11. Paediatric use (patients 12-17 years treated for pulmonary

	hypertension in conjunction with heart surgery)

II.B Summary of important risks

Important Identified Risk: Methaemoglobinemia	
Evidence for linking the risk to the medicine	This risk is based on the known safety profile of nitric oxide as reflected in the current product information and the publicly available scientific literature[66,70-72].
Risk factors and risk groups	There may be an additive effect with INOmax on the risk of developing methahemoglobinemia with nitric oxide donor substances, including sodium nitroprusside and nitroglycerin. There is an increased risk of MetHb formation if substances with a known tendency to increase MetHb concentrations are administered concomitantly with nitric oxide (e.g. alkyl nitrates and sulphonamides). Substances known to cause increased MetHb levels should thus be used with caution during therapy with iNO. Prilocaine, whether administered as oral, parenteral, or topical formulations may cause methahemoglobinemia. Care must be taken when INOmax is given at the same time as medicinal products containing prilocaine. In addition, neonates and infants are known to have diminished MetHb reductase activity compared to adults. MetHb level should be measured within one hour after initiation of INOmax therapy. Finally, Overdose with INOmax will be manifest by elevations in MetHb.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.5, 4.8, 4.9, 5.1, 5.2 and 5.3. PL sections 2 and 4. Legal status: subject to medical prescription. Additional risk minimisation measures: • HCP training program.

Important Identified Risk: Risk of acute cardiac failure with circulatory collapse in certain patient populations	
Evidence for linking the risk to the medicine	This risk is based on the known safety profile of nitric oxide as reflected in the current product information and the publicly available scientific literature[73,74].
Risk factors and risk groups	iNO should be used with caution in patients with complex heart defect, where high pressure in the pulmonary artery is of importance for maintaining circulation. iNO should also be used with caution in patients with compromised left ventricular function and elevated baseline PCWP as they may be at an increased risk of developing cardiac failure (e.g. pulmonary oedema).

Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3 and 4.4. PL section 2. Legal status: subject to medical prescription. Additional risk minimisation measures: • HCP training program.

Important Identified Risk: Risk of pulmonary oedema in patients with pre-existing left ventricular dysfunction	
Evidence for linking the risk to the medicine	This risk is based on the known safety profile of nitric oxide as reflected in the current product information and the publicly available scientific literature[46,75,76].
Risk factors and risk groups	Patients with congenital heart disease that are dependent (absolute contraindication) on high PVR or where high PAP support adequate circulation (relative contra indication).
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4. PL section 2. Legal status: subject to medical prescription. Additional risk minimisation measures: • HCP training program.

Important Identified Risk: Risk of pulmonary oedema in patients with PVOD	
Evidence for linking the risk to the medicine	This risk is based on the known safety profile of nitric oxide as reflected in the current product information. This risk arised from the evaluation of a signal of pulmonary edema in patients with PH related to PVOD, which was initially received by Health Canada and informed to the EMA. As outcomes of the procedure, a PRAC recommendation was adopted in PRAC meeting 25-27 Nov 2024, with the need to amend the SmPC and PIL. Product information was amended as requested.
Risk factors and risk groups	Patients with PVOD. It should be considered that patients with a history of cancer and chemotherapy could have a higher risk for PVOD than the overall patient population. PVOD and PAH share a common clinical presentation and are characterised by fatigue and breathlessness, in the end stage with right heart failure. In those patients a PVOD should be considered when shortly after starting therapy with a pulmonary vasodilatator develop pulmonary oedema.

Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4. PL section 2. Legal status: subject to medical prescription. Additional risk minimisation measures: • HCP training program.

Important Identified Risk: Risk of rebound reaction; pulmonary hypertension and/or oxygen saturation decrease/desaturation associated to abrupt withdrawal	
Evidence for linking the risk to the medicine	This risk is based on the known safety profile of nitric oxide as reflected in the current product information and the publicly available scienti*fic* literature[40,78].
Risk factors and risk groups	All patients.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4 and 4.8. PL sections 3 and 4. Legal status: subject to medical prescription. Additional risk minimisation measures: • HCP training program.

Important Identified Risk: Critical failure of the Nitric Oxide delivery system (NODS)	
Evidence for linking the risk to the medicine	This risk is based on the known safety profile of nitric oxide as reflected in the current product information and the publicly available scientific literature[79,80].
Risk factors and risk groups	All patients.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.8, 6.4 and 6.6. PL section 5. Legal status: subject to medical prescription. Additional risk minimisation measures: • HCP training program.

Important Identified Risk: Risk of NO_2 formation	
Evidence for linking the risk to the medicine	This risk is based on the known safety profile of nitric oxide as reflected in the current product information and the publicly available scientific literature[68,81-84].

Risk factors and risk groups	Patients requiring high oxygen fraction risk factors; incorrectly calibrated device non-trained personnel.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.5, 4.9, 5.2, 6.2 and 6.6. PL sections 2 and 3. Legal status: subject to medical prescription. Additional risk minimisation measures: • HCP training program.
Important Potential Risk: Increased bleeding time	
Evidence for linking the risk to the medicine	This risk is based on the known safety profile of nitric oxide as reflected in the current product information.
Risk factors and risk groups	All patients.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4. PL section 2. Legal status: subject to medical prescription. Additional risk minimisation measures: • HCP training program.

Missing information: Combined use with other vasodilators	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.5. PL section 2. Legal status: subject to medical prescription. Additional risk minimisation measures: • HCP training program.

Missing information: Use during pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6. PL section 2. Legal status: subject to medical prescription.

	Additional risk minimisation measures: • HCP training program.

Missing information: Paediatric use (patients 12-17 years treated for pulmonary hypertension in conjunction with heart surgery)	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2. Legal status: subject to medical prescription. Additional risk minimisation measures: • HCP training program.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the MA or specific obligation of Medicinal NO, INOmax.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Medicinal NO, INOmax.

Part VII: Annexes

Table of contents

Annex 1 – EudraVigilance Interface

Not applicable.

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not applicable.

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Not applicable.

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Additional risk minimisation activities for Medicinal NO, INOmax consist on a HCP continuous and documented training program for INOmax and devices based on currently approved product information, i.e. SmPC for INOmax, IFU and OMS.

Key elements for the training are included in Annex II of the MA for Medicinal NO, INOmax. Sections 4.2 and 6.6 of the current SmPC include details on the key training elements required in the administration of iNO for hospital personnel, including the correct connection and operation in order to prevent accidental discontinuation of delivery which can result in rebound PH. The OMS includes customer-specific detailed medical device training with all necessary technical background information for the safe administration of iNO. This all together is the base for the training for the iNO-therapy.

Annex 7 - Other supporting data (including referenced material)

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