20 January 2011
EMA/231748/2011
Human Medicines Development and Evaluation

Assessment report
for
INOmax

International non-proprietary name:

nitric oxide

Procedure no: EMEA/H/C/000337/II/0019

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.
1. Steps taken for the assessment

<table>
<thead>
<tr>
<th>Step</th>
<th>Step date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submission date:</td>
<td>18 March 2010</td>
</tr>
<tr>
<td>Start of procedure:</td>
<td>28 March 2010</td>
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<tr>
<td>Rapporteur’s assessment report circulated on:</td>
<td>21 May 2010</td>
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<tr>
<td>Co-Rapporteur’s assessment report circulated on:</td>
<td>25 May 2010</td>
</tr>
<tr>
<td>Rapporteurs’ updated joint assessment report circulated on:</td>
<td>18 June 2010</td>
</tr>
<tr>
<td>Request for supplementary information and extension of timetable adopted by the CHMP on:</td>
<td>24 June 2010</td>
</tr>
<tr>
<td>MAH’s responses submitted to the CHMP on:</td>
<td>7 July 2010</td>
</tr>
<tr>
<td>Rapporteur’s and Co-Rapporteur’s joint preliminary assessment report on the MAH’s responses circulated on:</td>
<td>6 September 2010</td>
</tr>
<tr>
<td>Rapporteur’s and Co-Rapporteur’s joint updated assessment report on the MAH’s responses circulated on:</td>
<td>23 September 2010</td>
</tr>
<tr>
<td>Second request for supplementary information and extension of timetable adopted by the CHMP on:</td>
<td>23 September 2010</td>
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<tr>
<td>MAH’s responses submitted to the CHMP on:</td>
<td>18 October 2010</td>
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<tr>
<td>Rapporteur’s and Co-Rapporteur’s joint preliminary assessment report on the MAH’s responses circulated on:</td>
<td>9 November 2010</td>
</tr>
<tr>
<td>Third request for supplementary information and extension of timetable adopted by the CHMP on:</td>
<td>18 November 2010</td>
</tr>
<tr>
<td>MAH’s responses submitted to the CHMP on:</td>
<td>17 December 2010</td>
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<tr>
<td>Rapporteur’s and Co-Rapporteur’s joint preliminary assessment report on the MAH’s responses circulated on:</td>
<td>12 January 2011</td>
</tr>
<tr>
<td>CHMP opinion:</td>
<td>20 January 2011</td>
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2. Scientific discussion

2.1. Introduction

INOmax (nitric oxide, iNO) was firstly authorised in the European Union (EU) on 1 August 2001. INOmax, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of newborns ≥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. There are two authorised presentations of
INOmax approved within the EU, both intended for endotracheopulmonary use and with strength of 400 ppm.

This Type II application is being submitted to seek an extension of the current indication to include the use of inhaled nitric oxide (iNO) in adults and in children with pulmonary hypertension in conjunction with cardiac surgery. The initially applied for indication was:

“INOmax, in conjunction with ventilatory support and other appropriate agents, is indicated for: 
- the treatment of pulmonary hypertension peri and post heart surgery in children and adults in order to improve right ventricular performance and oxygenation, and to facilitate weaning from bypass, ventilatory and inotropic support.”

Posology instructions for this new indication including attempts for weaning/to wean from INOmax have been proposed in section 4.2. Furthermore, consequential changes have been proposed for section 4.4, 4.8 and 5.1 of the SmPC. The PIL would be modified accordingly. Moreover, Annex II was to be updated and an Annex 127a has been introduced. In addition, the MAH took the opportunity to include minor clarifications changes in IIIA (Labelling).

To support the application for this indication, the Marketing Authorisation Holder (MAH) submitted literature references available in the public domain as well as results from two company-sponsored clinical trials (INOT22 and INOT44). In addition, the MAH submitted a non-clinical overview based on literature data, a detailed description of the pharmacovigilance system, a risk management plan and the results of a patient consultation on the package leaflet (PL).

Severe pulmonary hypertension adversely affects the clinical course and management and is a significant cause of morbidity and mortality in children and adults after cardiac surgical procedures. Increased pulmonary vascular resistance has a significant effect on post-operative recovery. Rapid and effective control of pulmonary artery pressure, reducing the workload on the right ventricle, is an important clinical objective. The overall objective is to reduce pulmonary hypertension and restore right ventricular function, thereby improving and restoring oxygenation/oxygen delivery.

### Variation requested

<table>
<thead>
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<th>Variation requested</th>
<th>Type</th>
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<tr>
<td>C.I.6.a</td>
<td>II</td>
</tr>
<tr>
<td>Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</td>
<td></td>
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</tbody>
</table>

Extension of the therapeutic indication to include the treatment of pulmonary hypertension peri- and post heart surgery in children and adults in 4.1 of the SmPC. Posology instructions for this new indication including attempts for weaning/to wean from INOmax have been proposed in section 4.2. Furthermore, changes to the SmPC have been proposed for section 4.4, 4.8 and 5.1. The PIL has been modified accordingly. Finally, Annex II was updated and an Annex 127a is introduced.

**Information on Paediatric requirements**

Pursuant to Article 8 of Regulation (EC) N° 1901/2006 as amended, the application included an EMA decision (P/256/09) on the granting of a product specific waiver for inhaled nitric oxide (INOmax).

**2.2. Toxico-pharmacological aspects**

The MAH submitted a non-clinical overview based on a literature search performed to identify articles which further support the current non-clinical documentation for iNO and also information supporting
this new indication. Eighteen literature references were considered of relevance by the MAH: 15 papers are discussed within the Pharmacology section and three papers are discussed within the Toxicology section.

2.2.1. Pharmacology

2.2.1.1. Primary pharmacodynamics

Mechanism of action

The primary mechanism by which inhaled NO relaxes constricted pulmonary vasculature is by stimulating soluble guanylate cyclase (sGC) to synthesize cGMP that subsequently activates cGMP-dependent protein kinase.

Effects in therapeutic models (non-comparative and comparative studies)

When subjected to cardiopulmonary bypass (CPB), a systemic inflammatory response is induced that is characterized clinically by alterations in cardiovascular and pulmonary function (reviewed in Kozik & Tweddell, 2006). In a study examining the cardiopulmonary effects of iNO (20 ppm) given perioperative for a duration of 24 hours to an anaesthetized and mechanically ventilated pig model of extracorporeal circulation, improvements were observed in lung haemodynamics, inflammation and oxygenation (Troncy et al, 2006). There were, however, no long-term beneficial effects on lung mechanics and surfactant homeostasis.

Although PDE-5 inhibitors have been shown to worsen arterial oxygenation at dose levels that decrease pulmonary artery pressure (PAP), there could potentially be a role for a combination treatment with iNO if the dose of the PDE-5 inhibitor is held at a level that would not worsen arterial oxygenation. This was investigated in a rat model of acute lung injury, induced by E-coli endotoxin, and where the lungs were isolated, perfused and ventilated 16-18 hours post induction of lung injury (Klein et al, 2007).

The combined treatment of sub-threshold doses of zaprinast or sildenafil with inhaled NO (10 ppm) was more effective than inhaled NO alone in reducing the pulmonary hypertension induced by the thromboxane mimetic U46619.

Effects in therapeutic models (combination studies)

Another study examined the effectiveness of the combination of 10 ppm iNO with either aerosolized prostacyclin or adrenomedullin versus iNO alone (10 ppm) in a pig model of pulmonary hypertension (Dani et al, 2007). The combination treatments were more effective than iNO alone in lowering PAP and improving oxygenation. All treatment arms increased lung compliance and tidal volume and decreased airway resistance. There were no effects on surfactant surface activity and lung tissue oxidation measured as total hydroperoxide and oxidation protein adducts in bronchial aspirate samples.

The impact of iNO on hypoxia-induced pulmonary hypertension in rabbits was compared to that of iv infused iloprost, a stable prostacyclin analogue and oral sildenafil, a PDE-5 inhibitor (Weissmann et al, 2007). The study demonstrated that the vasoconstrictor response to acute hypoxia (HPV) was prevented by 15 ppm NO but not by the other treatments. Iloprost was particularly effective in inhibiting vascular remodeling whereas sildenafil was effective in preventing right ventricular hypertrophy (RVH). In this model, inhaled NO had no effect on the vascular remodeling and only a minor effect on RVH.
2.2.1.2. Secondary pharmacodynamics

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 (Hoehn & Krause 2001). A placebo-controlled study in healthy volunteers that received 30 ppm NO for 30 min did not show, however, any effect on bleeding time, platelet activity or skin perfusion (Albert et al, 1999). In a recent study in pigs subjected to long term (30 hours) exposure to 40 ppm NO, no effects on bleeding time or platelet function were observed (Albert et al, 2007).

2.2.1.3. Safety pharmacology programme

There have been no investigations published since the renewal of the marketing authorisation that can be classified as PK-related.

2.2.2. Toxicology

There have been no investigations conducted by the MAH or relevant published literature on NO that can be classified as single or repeat dose toxicity studies.

2.2.2.1. Genotoxicity

There have been no studies identified in the recent literature that contribute to the assessment of genotoxic risk beyond that already performed.

2.2.2.2. Carcinogenicity

The carcinogenic potential of inhaled NO has been investigated in a two years study in rats (N005243). The results of this have been previously assessed and relevant information has been included in section 5.3 of the SPC.

2.2.2.3. Reproduction Toxicity

There have been no investigations conducted by the MAH or relevant published literature on NO 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 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.

2.2.3. Ecotoxicity/environmental risk assessment

The MAH provided a justification for the absence of an ERA report based on the fact that NO is a natural, endogenously formed signalling substance in humans. Moreover, the increase in NO release linked to this extension of indication is considered negligible as compared to the huge amount of NO release from industrial and commercial sources.

The justification for ERA absence is considered to be appropriate to meet the requirements of the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00).
2.2.4. Conclusion on the non-clinical section

The MAH provided an up to date overview based on published data on iNO (NO). No new nonclinical data has been generated by the MAH for this particular application, which is considered acceptable.

NO is a vasodilating compound able to inhibit platelet aggregation. Its use in the context of cardiac surgery might be a source of concern. It has indeed been shown in animal models that NO inhalation prolongs bleeding time and/or affects platelet aggregation. This is only very briefly discussed by the MAH. The MAH reports a recent study in pigs subjected to 30 hours exposure to 40 ppm NO, and in which no effects on bleeding time or platelet function were observed (Albert et al, 2007). The SmPC indicates a common treatment duration of 24 to 48 hours. The MAH also reports a study in healthy volunteers that received 30 ppm NO for 30 min and did not show any effect on bleeding time, platelet activity or skin perfusion (Albert et al, 1999). However, in other studies, for example in neonates (George et al, 1998) or in patients with acute respiratory distress syndrome (Samama et al, 1995), a doubling of bleeding time and inhibition of platelet aggregation were observed, respectively. Moreover, it is also unknown what would be the effect of inhaled NO in patients with coagulation anomalies. And again the treatment duration is very limited and haemorrhage risks remain a concern. This risk is included in the in the Risk management plan (see also discussion of clinical aspects). Moreover, since the risk of haemorrhage cannot be excluded, haemostasis should be monitored (4.2 of the SPC) in treated patients and a warning is included in the section 4.4 of the SPC.

2.3. Clinical aspects

This application is based on clinical data from randomised controlled trials (RCT) from published literature, as well as two company-sponsored clinical trials which are considered supportive: INOT41 in adult patients undergoing Left Ventricular Assists Device (LVAD) placement, and INOT22, a pharmacodynamic study investigating vasoreactivity in children with pulmonary artery hypertension. It is recognized that due to the nature of the condition being studied RCTs are difficult to conduct.

The two company-sponsored studies were performed in accordance with GCP as claimed by the applicant.

The literature search aimed to identify publications presenting relevant RCTs that evaluate the efficacy of iNO in the treatment of pulmonary hypertension in conjunction with heart surgery. Thirteen RCTs in adult patients undergoing heart surgery (including heart transplant and insertion of LVAD) have been identified and evaluated (Table 1 and 2). In the paediatric population, seven RCTs in children undergoing surgery (mostly for congenital heart disease) have been included (Table 3). The list of all the references submitted by the MAH is included in attachment 1.

Table 1  Studies in adult patients undergoing cardiac surgery (excluding heart transplant and LVAD insertion).

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Design</th>
<th>No. Pts</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fattouch 2005</td>
<td>R, C, DB</td>
<td>58</td>
<td>iNO was as effective in treating PAH as inhaled prostacycline. Both inhaled treatments superior to nitroprusside.</td>
</tr>
<tr>
<td>Fattouch 2006</td>
<td>R, C, DB</td>
<td>58</td>
<td>iNO was as effective in treating PAH as inhaled prostacycline. Both inhaled treatments superior to nitroprusside. Inhaled treatments superior w regards to time to weaning, intubation time and ICU stay (p&lt;0.05)</td>
</tr>
<tr>
<td>Gianetti 2004</td>
<td>R, C</td>
<td>29</td>
<td>Low concentration iNO can blunt release of markers of myocardial injury and antagonise LV dysfunction after CPB.</td>
</tr>
<tr>
<td>Schmid 1999</td>
<td>R, XO</td>
<td>14</td>
<td>iNO and prostacycline iv decreased PVR and increased cardiac index.</td>
</tr>
</tbody>
</table>
Solina 2000  R, C  45  iNO lead to lower HR, higher RV ejection fraction and lower vasopressor requirement compared to milrinone.

Solina 2001  R, C  62  Doses of iNO >10p pm showed no difference in PVR response.

Winterhalter 2008  R, C  46  iNO and iloprost both reduced PAP and PVR immediately after weaning from CPB. Iloprost gave larger reductions in PVR and mPAP and greater increase in CO.

Table 2. Studies in adult patients undergoing heart transplant or Left Ventricular Assist Device (LVAD) insertion

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Design</th>
<th>No. Pts</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ardehali 2001</td>
<td>Pr, Ch</td>
<td>16</td>
<td>Post transplant iNO significantly reduced RV stroke work and PVR.</td>
</tr>
<tr>
<td>Argenziano 1998</td>
<td>R,C</td>
<td>11</td>
<td>LVAD. iNO at 20 ppm induced significant reductions in mPAP and increases in LVAD.</td>
</tr>
<tr>
<td>INOT41 2009</td>
<td>R,C</td>
<td>150</td>
<td>LVAD. iNO reduced the incidence of right ventricular dysfunction, but not significantly. Time on mechanical ventilation reduced for iNO (p=0.0077)</td>
</tr>
<tr>
<td>Kieler-Jensen 1994</td>
<td>Pr, C</td>
<td>12</td>
<td>iNO significantly reduced PCWP and PVR at a dose of 20ppm.</td>
</tr>
<tr>
<td>Radovancevic 2005</td>
<td>R, XO</td>
<td>19 i</td>
<td>NO and PGE1 have comparable dilatory effects in PAH.</td>
</tr>
<tr>
<td>Rajek 2000</td>
<td>R, C</td>
<td>68</td>
<td>iNO 4 ppm cause selective reduction in PAP iNO aided weaning from CPB more successfully than PGE$_1$.</td>
</tr>
</tbody>
</table>

Table 3  Studies in children undergoing cardiac surgery for congenital heart disease

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Design</th>
<th>No. Pts</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cai 2008</td>
<td>R, C</td>
<td>46</td>
<td>Combined iNO and milrinone were more effective in lowering PVR, PAH compared to either drug alone. The combined group had significant shorter time on mechanical ventilation (p&lt;0.043)</td>
</tr>
<tr>
<td>Day 2000</td>
<td>R, C</td>
<td>40</td>
<td>No significant reduction in PHTC for iNO compared to conventional therapy.</td>
</tr>
<tr>
<td>Goldman 1995</td>
<td>R,C, XO</td>
<td>13</td>
<td>mPAP lower during iNO compared to prostacyclin.</td>
</tr>
<tr>
<td>Miller 2000</td>
<td>R, C, DB</td>
<td>124</td>
<td>Routine iNO post cardiac surgery can reduce the risk of Pulmonary hypertensive crises with no adverse effects.</td>
</tr>
<tr>
<td>Morris 2000</td>
<td>R, C, XO</td>
<td>12</td>
<td>iNO vs. hyperventilation. NO selective for pulmonary circulation and did not increase SVR.</td>
</tr>
<tr>
<td>Russell 1998</td>
<td>R, C, DB</td>
<td>40</td>
<td>iNO selectively reduced mPAP in those who had evidence of postoperative PAH.</td>
</tr>
<tr>
<td>Stocker 2003</td>
<td>R, XO, C</td>
<td>15</td>
<td>Both drugs, iNO20 ppm and intravenous sildenafil lowered pulmonary vascular resistance index. Sildenafil also lowered systemic blood pressure.</td>
</tr>
</tbody>
</table>

R= randomized; C=controlled; XO=cross-over; DB=double-blind

2.3.1. Pharmacokinetics

Inhaled nitric oxide, INOmax, is administered in ppm doses by inhalation. It may be administered either during controlled mechanical ventilation or during spontaneous respiration. The uptake of nitric oxide takes place in the aerated alveoli. Nitric oxide diffuses across the alveolar capillary membrane...
and acts upon the smooth muscle layers of the vessel wall. Absorbed nitric oxide reaching the pulmonary capillary bed combines rapidly with haemoglobin that is 60-100% oxygen-saturated. At this level of oxygen saturation, iNO combines predominantly with oxyhaemoglobin to produce methaemoglobin and nitrate. At lower oxygen saturation levels, iNO can combine with deoxyhaemoglobin to transiently form nitrosylhaemoglobin which converts to nitrogen dioxide and methaemoglobin on exposure to oxygen. The half-life of NO in humans is approximately 3-6 seconds and it is this short duration of action that explains the selective pulmonary vascular dilatation that occurs following inhalation.

Nitrate is cleared from plasma by the kidney; the predominant NO metabolite is nitrate which is excreted in the urine and accounts for >70% of the iNO dose received.

The uptake and metabolism of iNO is not affected by gender or genetics, however, there is some indication that diffusion of iNO decreases with age. When a specific concentration (e.g. 10 ppm) iNO is administered, the concentration of NO that reaches the lungs is the same irrespective of the size of the patient. However, while the concentration is the same in neonates and adults, the minute ventilation is much higher in neonates, resulting in a relatively higher dose administered. Dosing is therefore adjusted on the physiological effects seen so that the dose is reduced gradually if an improvement is seen in PAP or oxygenation, whichever parameter is being monitored.

The current application concerns administration of iNO to children and adults in conjunction with heart surgery. The previously approved indication concerned newborns of gestation age >34 weeks. The uptake, metabolism and elimination of iNO is similar in newborns, children and adults. There have been no investigations conducted by the MAH or relevant published literature on the pharmacokinetics of NO.

### 2.3.2. Pharmacodynamics

#### 2.3.2.1. Mechanism of action

Nitric oxide is a continually produced endogenous vascular dilator. Nitric oxide is the signalling substance previously referred to as endothelial-derived relaxing factor EDRF. Changing the natural regulation of nitric oxide production causes profound vascular effects.

Administration of NO/NO donor compounds is known to cause vasodilatation. Sublingual nitroglycerin has an established therapeutic role and is regarded as the gold-standard treatment for reversing coronary arterial vasospasm induced acute angina. Intravenous administration of NO donor compounds such as nitro-glycerine and nitroprusside effects peripheral vasodilatation in arterioles and venules and are often administered to patients who are experiencing a hypertensive emergency. Shortly after the pioneer studies showing that administration of low dose NO gas by inhalation reversed hypoxia induced pulmonary hypertension, a paper from Girard and al. suggested that 40 ppm inhaled NO caused a rapid decrease in pulmonary artery pressure in patients exhibiting pulmonary hypertension post mitral valve surgery.

Since then, further publications suggested that NO in doses between 2 and 40 ppm has a rapid and selective vasodilatory effect in adult and paediatric patients with increased pulmonary artery pressure in conjunction to cardiac surgery. Further publications suggested that iNO could rapidly lower the pulmonary artery pressure, reduce pulmonary vascular resistance and improve oxygenation in children having undergone corrective surgery for congenital heart disease, in adults having had open heart surgery or heart transplantation.
The effects of iNO are selective for the pulmonary circulation and restricted to patients with elevated pulmonary pressure; iNO has no effect on the pulmonary vascular pressures in patients with a normal pulmonary artery pressure.

No formal dose response studies have been conducted.

2.3.3. Clinical efficacy

The MAH evaluated publications available in the public domain involving the use of NO in adults and children who have undergone cardiac surgery. Thirteen, mostly investigator-initiated randomised controlled trials (RCT) involving a total of 588 adult patients undergoing heart surgery, including heart transplant and insertion of LVAD have been identified through the literature search procedure. In addition, two company sponsored clinical studies performed by the MAH have been provided (INOT22 (children) and INOT41 (adults)) which were considered supportive.

2.3.4. Main studies

2.3.4.1. Adult population

High pulmonary pressure interferes with clinical management of the patient and is a recognised marker for poor prognosis and increases morbidity and mortality. Therefore, most studies focus on haemodynamic endpoints such as the rapid and selective effects on pulmonary vascular resistance (PVR) and pulmonary arterial hypertension (PAH) and oxygenation saturation. A few studies evaluated clinical endpoints such as pulmonary hypertensive crises and time to extubation. The results of these key RCT are further supported by additional RCT with haemodynamic endpoints and open studies/case series supporting safety and efficacy in the proposed indication. The majority of the studies in adult populations have compared iNO with other therapies for the same purpose, i.e. inhaled prostacyclin (Fattouch, Winterhalter), intravenous prostacyclin (Rajek), and intravenous milrinone (Solina).

Fattouch et al. (J Cardiovasc Med, 2006)

The aim of this study, conducted in 58 patients, was to compare the haemodynamic effects of inhaled prostacyclin and NO and the administration of i.v. nitroprusside during cardiac surgery with a clinical, pharmacodynamic dose-response, prospective, randomized, and double-blind study (Group A: inhaled prostacyclin (PGI2); Group B: iNO; Group C: nitroprusside).

Methods

Fifty-eight patients with mitral valve stenosis and elevated PVR (>200 dynes sec/cm⁵) after mitral valve surgery were studied. Inhaled prostacyclin and NO were administered at concentrations of 10 g/min and 20 ppm, respectively. Nitroprusside i.v. was administered at the dose of 5–15 g/min.

Results

Prostacyclin and NO produced a significant dose-related decrease of mean pulmonary arterial pressure, pulmonary vascular resistance, and transpulmonary gradient. A significant increase in cardiac output was observed in both groups. In Group C, nitroprusside administration was interrupted in 62% patients due to occurrence of systemic hypotension.

Cardiopulmonary bypass produced in each group an increase in PVR, mean pulmonary arterial pressure (MPAP) and Pulmonary Capillary Wedge Pressure (PCWP).
Inhalation of PGI2 reduced significantly PVR (−50%), Transpulmonary Pressure Gradient (TPG) (−64%), and MPAP (−20%), while PCWP did not change significantly; after inhalation of PGI2 the Cardiac Output (CO) and Stroke Volume (SV) were increased.

Inhalation of NO reduced significantly PVR (−45%), TPG (−62%), and MPAP (−19%), the CO and SV were not significantly modified.

In Group C, the effects of administration of sodium nitroprusside were calculated in 11/18 patients because in other patients treatment was interrupted. The sodium nitroprusside reduced significantly PVR (−45%), SVR (−51%), TPG (−44%), and MPAP (−21%).

Inhaled prostacyclin and NO are effective in the treatment of postoperative pulmonary hypertension in patients with mitral valve stenosis undergoing mitral valve surgery. Both drugs improve cardiac output and reduce mean pulmonary arterial pressure, pulmonary vascular resistance, and transpulmonary gradient. They may be useful in patients with acute right ventricular failure following cardiac surgery. In comparison to NO, inhaled prostacyclin is free from toxic side effects and is easier to administer.

The inhaled NO level was continuously monitorized and maintained at 20 ppm. The administration started immediately after patient admission in intensive care unit.

This publication concludes that the inhalation of 20 ppm NO in adult patients who have undergone cardiac surgery will obtain similar benefits to inhaled prostacyclin.

**Solina et al. (J Cardiothorac Vasc Anesth, 2000)**

**Objective**

To investigate the relative effects of milrinone and NO on pulmonary and systemic hemodynamic responses in cardiac surgery patients with a history of pulmonary hypertension.

**Methods**

Design: Prospective and randomized.

Participants: Forty-five (45) adult cardiac surgery patients.

Interventions: Cardiac surgery patients with pulmonary hypertension were randomly assigned to one of three study groups: Group 1 patients (n = 15) were treated with intravenous milrinone on separation from cardiopulmonary bypass, group 2 patients (n = 15) with 20 ppm of iNO, and group 3 patients (n = 15) with 40 ppm of iNO. Heart rate, right ventricular ejection fraction, and pulmonary vascular resistance were measured throughout the perioperative period at specific data points.

**Results**

Please see Figure 1 for PVR values. There were no significant differences in demographics, anesthesia, surgery, or baseline hemodynamics among the groups. The group receiving 40 ppm NO had a significantly higher (p < 0.05) right ventricular ejection fraction on arrival in the intensive care unit (40% vs 30% for the milrinone group and 33% for the NO 20 ppm group). The milrinone group required significantly more phenylephrine in the intensive care unit (p < 0.05).
This study establishes that the optimal dose of inhaled NO is 40 ppm. In this study, the higher dose of NO appears to be more efficacious to milrinone.

Rajek et al. *(Anesth Analg, 2000)*

**Objective**

To evaluate the ability of prostaglandin E1 (PGE1) and iNO to reduce pulmonary vascular resistance during heart transplantation.

**Design**

Parallel, open two arm randomised study

**Participants**

70 adult patients undergoing orthotopic heart transplantation

**Methods**

70 adult patients (59 men, 11 women) undergoing orthotopic heart transplantation were enrolled in a two arm randomised study. Patients were assigned to a Prostaglandin E1 (PGE1) infusion or iNO. Patients assigned to the prostaglandin group (n= 35) were given an IV infusion starting 10 min before weaning from bypass, at an initial rate of 8 ng/kg /min. The dose was increased, stepwise, to 16 ng/kg/min and then to 24 ng/kg/min, as required, to limit pulmonary hypertension. The study protocol specified that the PGE1 dose would be increased as required to maintain mean pulmonary artery pressure at 25 mm Hg. Patients assigned to the NO group (n= 35) were given NO in nitrogen inhalation at a starting concentration of 4 ppm. The concentration was increased, stepwise, as required, to treat pulmonary hypertension, up to a maximal concentration of 24 ppm. Again, the study protocol specified that the dose would be increased as required to maintain mean pulmonary artery pressure 25 mm Hg. Both treatments were discontinued 6 hours postoperatively.
Hemodynamic values were recorded after the induction of anesthesia, 10 and 30 min after weaning from CPB, and 1 h and 6 h postoperatively. Mean arterial pressure, mean pulmonary arterial pressure, right atrial pressure and heart rate were recorded continuously.

Pulmonary vascular resistance (PVR) and systemic vascular resistance were calculated by using standard formulas. The transpulmonary gradient was considered to be the difference between mean pulmonary artery pressure and pulmonary wedge pressure. The relationship between pulmonary vascular resistance and systemic vascular resistance was calculated for all time points.

Results

Figure 2 describes the results for PVR.

**Figure 2 – PVR (Rajek et al.)**

Immediately after the weaning from CPB, mean pulmonary arterial pressure (PAP) in the NO group decreased approximately 30\% (from 34.2 to 23.1 mm Hg, \( p = 0.0001 \)); pressure then remained essentially unchanged until 6 h after surgery. In contrast, mean pulmonary arterial pressure in the PGE1 group decreased only approximately 16\%, from 32.2 to 26.1 mm Hg and remained near that value for an hour. Six hours after surgery, though, pressures were nearly identical in the two groups. Figure 3 describes the results for PAP.
2.3.4.2. Key Studies in Children

In total there are seven RCT evaluating the effects of iNO in treatment of pulmonary hypertension in conjunction with heart surgery. In three of the studies clinical endpoints were evaluated in addition to haemodynamic endpoints. The remaining four studies were short exposure studies investigating haemodynamic effects.

The key studies to evaluate clinical efficacy in children are the studies by Miller, Day and Cai which focused on clinical endpoints. The primary endpoint in Miller and Day was the frequency of pulmonary hypertensive crises (PHT) and this was noted to be considerably higher in the Miller study than the Day study.

Miller et al. (Lancet, 2000)

This was a randomised double-blind study to investigate the role of routinely administered inhaled NO to prevent pulmonary hypertension in infants aged 1 to 6 months at high risk.

Methods

124 infants were enrolled (64 male, 60 female; median age 3 months [IQR 1–5]), 76% with large ventricular or atrioventricular septal defects, who had high pulmonary flow, pressure, or both, and were undergoing corrective surgery for congenital heart disease. They were randomly assigned continuous low-dose iNO 10 parts per million (n=63) or placebo (n=61) from surgery until just before extubation. Figure 4 schematises the study design.
The measures were Primary Hypertensive Crisis (PHTC) which was defined as episodes in which the pulmonary/systemic artery pressure ratio rose to more than 0.75. Episodes were classified as major if there was a fall in the systemic artery pressure of at least 20%, a fall in the transcutaneous oxygen saturation to <90%, or both, and minor if the systemic artery pressure and transcutaneous oxygen saturation remained stable. Time to wean off study gas and hours spent in intensive care were also recorded. The analysis was done by intention to treat. The maximum duration for administration of study gas was prospectively set at 7 days.

Results

The median number of PHTC (per patient) was 4 and 7 crises respectively in the two groups compared to 7 events in total (4 in placebo group and 3 in NO group) in Day. Compared with placebo, infants receiving iNO had fewer PHTC (median four [IQR 0–12] vs seven [1–19]; relative risk, unadjusted 0·66, p<0·001, adjusted for dispersion 0·65, p=0·045). Figure 5 shows the median pulmonary vascular
For other secondary clinical endpoints, such as shorter time until criteria for extubation, the outcome was favourable for the iNO patients (80 [38-121] vs. 122 h [63-164]). Time taken to wean infants off study gas was 35% longer in the NO group than in the placebo group (p=0·19). The shorter total time on study gas was 30 h shorter for the NO group (87 [43-125] vs. 117 h [67-168], p=0.023). Other secondary endpoints, such as length of stay in Intensive Care Unit (ICU) were in favour of iNO treatment, but not statistically significant.

In conclusion, the dose delivered for a maximum of 7 days in neonates (children average age 3months old) was NO 10 ppm. At this dose NO appears to have a beneficial effect as monotherapy in reducing pulmonary hypertension.


This study was performed to determine whether iNO decreases the incidence of pulmonary hypertensive crises after corrective procedures for congenital heart disease.

**Methods**

Patients with a systolic pulmonary arterial pressure of 50% or more of the systolic systemic arterial pressure during the early postoperative period were randomized to receive 20 parts per million iNO (n= 20) or conventional therapy alone (n= 20). The median age was 6 months (range: 1 day to 3 years) in control patients and 7 months (range: 1 day to 20 years) in patients who received iNO. Acute hemodynamic and blood gas measurements were performed at the onset of therapy. The efficacy of sustained therapy was determined by comparing the number of patients in each group who experienced a pulmonary hypertensive crisis. NO was administered at a concentration of 20 ppm until care providers decided to wean the patient from assisted ventilation. Before extubation, NO was gradually withdrawn by decreasing the dose during a period of 6 to 12 hours.

**Results**

In comparison to controls, there were no significant differences in the baseline and 1-hour measurements of patients who were treated with NO. Please refer to Figure 6.
In the study by Day, patients were randomised to either control (conventional therapy) or to treatment with iNO (20 ppm). Treatment was initiated when patients were stabilised in the ICU i.e. after weaning from bypass and completion of surgery and in contrast to the study by Miller. There were no differences between groups in acute haemodynamic and blood gas measurements at base-line. During sustained therapy, PHT crises occurred in 4 patients receiving conventional therapy (control) and in 3 patients treated with iNO. All 4 patients in the control group that experienced pulmonary hypertensive crisis responded with improvements in haemodynamics or oxygenation following institution of iNO. A life-threatening episode of pulmonary hypertension occurred in 1 control patient; however, after being treated with iNO, a marked improvement in haemodynamic and blood gas measurements occurred. The patients in Day were studied in a later, more haemodynamically stable phase of the post-operative course and the studied patients population in Miller and Day are therefore not directly comparable.

Given that no therapeutic benefit was seen when iNO therapy was delivered in this patient population, it is difficult to establish the usefulness of iNO alone.


Early morbidity and mortality after Fontan operations (heart operation used to treat complex congenital heart defects) are related to the elevation of postoperative pulmonary vascular resistance. iNO and intravenous milrinone are being considered to reduce the pulmonary vascular resistance. In this article, it was hypothesized that their combined use could maximally stabilize the pulmonary circulation after Fontan operation.

**Methods**

Forty-six patients aged 5.5yr on average with high pulmonary vascular resistance (transpulmonary pressure gradient >10 mm Hg or central venous pressure >15 mm Hg) and impaired oxygenation after Fontan operation were prospectively randomized into three groups: group Mil (n= 15, milrinone at 0.5 μg/kg/min), group iNO (n= 15, iNO at <20 ppm), and group iNO + Mil (n= 16, iNO plus Mil). Pulmonary hemodynamic and oxygenation changes were compared among the three groups. Inhalation of NO began from 10 ppm with subsequent adjustment aimed at achieving greater than 20% improvement in TPG or greater than 10% oxygen saturation (Sao2) with the lowest possible dose.
of iNO (1 to 20 ppm) within 2 hours after initiation. Gradual weaning from iNO was attempted 24 hours after its use.

Results

Transpulmonary pressure gradient varied from 11.26 (s.d. 1.40) mm Hg at baseline to 7.93 (s.d. 0.90) mm Hg after 24-hour use in group iNO + Mil versus from 11.10 (s.d. 1.38) to 8.69 (s.d. 0.86) mm Hg; p= 0.048 in group iNO and from 11.17 (s.d. 1.41) mm Hg to 9.72 (s.d. 1.32) mm Hg; p < 0.001 in group Mil. Please see figure 7.

Figure 7 - Transpulmonary pressure gradient (Cai et al.)

The ratio of arterial oxygen partial pressure to inspired fraction of oxygen from 68.88 (s.d. 14.09) to 131.25 (s.d. 15.92) in group iNO + Mil versus from 70.07 (s.d. 14.24) to 120.20 (s.d. 5.92); p= 0.047 in group iNO and from 72.60 (s.d. 12.92) to 95.20 (s.d. 13.49); p < 0.001 in group Mil.

The time on mechanical ventilation was shorter in the group iNO + Mil (p= 0.043).

The results of the study by Cai support the assertion that iNO is at least equally effective as milrinone in selectively lowering pulmonary vascular resistance. The most favourable results were seen with combination milrinone and iNO therapy; this group of patients (n=16) had the shortest time on mechanical ventilation (p=0.043) and the largest falls in transpulmonary pressure gradient (p=0.048). The effectiveness of iNO compared to standard therapy (i.e. no pharmacological intervention) is not possible to evaluate because all patients in the study received active therapy for pulmonary hypertension.

In conclusion, this study establishes the usefulness of treating children in the 2 to 6 yr age group with doses up to 20 ppm of NO in association with milrenone. The maximal dosing period appears to be 24 hr with optimal effect at 4hr.

2.3.4.3. Supportive studies

Other studies reviewed in this application (Solina, Schmid, Winterhalter, Rajek) have used other off-label treatments as controls, such as inhaled prostacyclines, intravenous prostacyclin and milrinone. In these studies iNO has proven to be as or more effective than the comparative treatments. In the study by Rajek in heart transplant patients, weaning from CPB was successful in all patients assigned to iNO but failed in 6 patients assigned to intravenous prostacyclin (p= 0.03).
None of these studies mentioned above have a placebo control arm, such as non-pharmacological treatments or nitroprusside. The absolute effect of iNO in these patients groups is therefore difficult to ascertain. However, in all these studies iNO and the other investigated treatments lowered PVR and pulmonary arterial pressure. The effects of iNO were more selective for the pulmonary circulation compared to, e.g. milrinone or intravenous prostacyclin.

**INOT41 (adults)**

This company-sponsored trial studied the Effects of iNO during Left Ventricular Assist Device (LVAD) implantation. The primary objective was to assess the utility of iNO for the management of acute right ventricular failure (RVF) during LVAD placement with cardiopulmonary bypass (CPB).

This was a prospective, multicenter, double-blind, placebo-controlled study. Subjects were randomly assigned to receive either iNO at 40 ppm or placebo (nitrogen). After a maximum period of 48 hours of double-blind treatment, subjects could be crossed over to commercially available, open-label iNO (INOmax) if necessary.

Subjects were ≥18 years and scheduled to undergo their first LVAD implantation (or at least 6 months after explantation of a previous LVAD) with CPB were eligible. Subjects had to have a pulmonary vascular resistance (PVR) of ≥ 2.5 Wood units (200 dynes/sec) in the 30-day period prior to LVAD placement. The primary endpoint was the number of subjects who met failure criteria within 48 hours during treatment with study drug. Meeting failure criteria consisted of having two or more of the following, sustained for 15 minutes after complete removal from CPB support: Left ventricular flow rate index (LVFRI) ≤ 2.0 L/min/m²; Administration of ≥ 20 inotropic equivalents (IE); Mean arterial pressure (MAP) ≤ 55 mm Hg; Central venous pressure (CVP) ≥ 16 mm Hg; Percentage of mixed venous oxygen saturation (SvO2) of ≤ 55% OR failure to wean from CPB at least once due to hemodynamic failure (not including re-initiation of CPB to correct bleeding or other technical issues) or death.

150 subjects were enrolled (iNO n = 73, PBO n = 77) and 137 received study drug (iNO n = 69; PBO n = 68). All 150 were analyzed for efficacy outcomes. 137 were evaluable for safety. The total number of subjects who met failure criteria in this study (n = 19/150, 12.7%) was lower than had been predicted at the time of study initiation. Although fewer subjects in the iNO group met failure criteria within 48 hours (iNO n = 7/73 [9.6%]; PBO 12/77 [15.6%]), the intergroup difference was not statistically significant (p = 0.3301).

In conclusion, in study INOT41 iNO decreased the incidence of failures in the arm receiving iNO. However, the overall occurrence of failures was much lower than expected and the difference did not reach statistical significance. One of the secondary endpoints - time on mechanical ventilation – showed a clear trend in favour of shorter time on mechanical ventilation (median time 2.0 days vs. 3.0 days). Furthermore no difference was seen in incidence or severity of adverse events.

Study INOT41 shows that iNO used on its own at a concentration of 40 ppm has some effect but that it is not strong enough to be considered beneficial. This would support the use of iNO in addition to milrinone and prostacyclin/PGE₁.

**INOT22 (children)**

This trial compared the supplemental oxygen and iNO plus oxygen in the evaluation of the reactivity of the pulmonary vasculature during acute pulmonary vasodilator testing. This trial followed an open, prospective, multicentre, randomized controlled design and compared the utility and side effects of O₂,
NO, and the combination of NO and O₂ in determining pulmonary reactivity. Patients were male or female from 4 weeks to 18 years of age (inclusive); Idiopathic Pulmonary Arterial Hypertension (PAP) PAPm >25 mm Hg at rest, PCWP ≤15 mm Hg, and Pulmonary Vascular Resistance Index (PVRI) >3 u.m², or diagnosed clinically with no previous catheterization), or Cardiomyopathy with PAPm >25 mmHg at rest, and PVRI >3 u.m², or diagnosed clinically with no previous catheterization; Congenital heart disease with PH repaired and unrepaired with PAPm >25 mm Hg at rest, PVRI >3Wu m², or diagnosed clinically with no previous catheterization, or Scheduled to undergo right heart catheterization to assess pulmonary vasoreactivity by acute pulmonary vasodilation testing.

The primary efficacy variable was the number of patients receiving a combination of NO and O₂ versus the number of patients receiving O₂ alone that met response criteria for a pulmonary vasoreactivity response. The response criteria were as follows: Patients with IPAH or patients with CHD who did not have an unrestricted shunt at the level of the ventricle or ductus arteriosus: a decrease in PAPm ≥20% and no decrease in CI (within 5%); Patients with cardiomyopathy or CHD who had an unrestricted shunt at the level of the ventricle or ductus arteriosus: a decrease in PAPm ≥20% and no decrease in CI (within 5%) or a decrease in PVRI ≥25% and no decrease in CI (within 5%).

One hundred thirty six patients were enrolled, and 124 received study drug. One hundred nine were evaluable for the primary efficacy outcome. Mean age was 7.5yrs.

The primary objective was to compare the number of patients with reversible pulmonary hypertension (vasoreactivity) demonstrated by NO for inhalation 80 ppm plus O₂ 90% as compared to 100% O₂ alone. Study results for the intent-to-treat population indicated a significantly higher response rate (25.7%) for NO plus O₂ versus O₂ alone (14.7%) (p = 0.019). Similar trends were noted for response in the per-protocol population as in the ITT population. There was a higher response rate (22.2%) for NO plus O₂ versus O₂ alone (11.5%). The magnitude of this effect appears to be greater than that seen in the ITT population, but this difference did not achieve statistical significance (p = 0.071) due to the smaller sample size.

2.3.4.4. Discussion of clinical efficacy

CHMP acknowledged that there are a substantial number of publications in the public domain regarding the use of NO in the applied for indication (treatment of pulmonary hypertension)/condition which establish that off-label use in this condition occurs.

Efficacy in adults

In adults, the MAH has highlighted key articles that establish that there may be some place for the use of NO at doses of 20 to 40 ppm in the treatment adult post cardiac surgery in the treatment of pulmonary hypertension. The benefits noted are associated with 20 to 40 ppm iNO. iNO at these doses, in particular 40 ppm, offer comparable reduction to post cardiac operative pulmonary hypertension to milrinone or prostaglandins. While these publications establish the potential benefits of these doses of iNO in this patient population, more detail was considered necessary to support the use of the product in the applied for indication. Hence, the MAH was asked to discuss the relevance of the haemodynamic and clinical benefits targeted in the adult population.

In its response, the MAH has argued that in some of the key studies the effects of iNO on pulmonary hypertension have been clearly linked to benefits in the clinical outcome for patients. Since mortality is not a valid outcome in these studies, the most common clinical outcomes studied are pulmonary hypertensive crises (PHTC), time on mechanical ventilation and rate of successful weaning.

As PAH has been shown to predict mortality in adult patients undergoing CABG (coronary artery bypass grafting), whilst the pre-operative ratio of mean arterial pressure:mean pulmonary arterial pressure
has been shown to be an independent predictor of haemodynamic complications in adult cardiac surgery patients, CHMP concurred that the value of haemodynamic improvements noted in published adult studies may be inferred.

In addition, no data regarding the potential benefits associated with the use in association with other agents used to control post cardiac operation pulmonary hypertension had been provided. The applicant was asked to clarify this point either with additional publications or better utilisation of the publications initially submitted. In response, the MAH has reviewed the key studies in more detail with a focus on concomitant medications to evaluate the safety and efficacy of iNO administration combined with other pharmacological interventions traditionally used in conjunction with heart surgery (e.g. milrinone, nitrate containing treatment regimes, dobutamine, dopamine, epinephrine). As iNO was co-administered with inotropic and vasoactive drugs in the majority of clinical studies submitted to document efficacy and safety, the MAH argued that the safety and efficacy considerations previously discussed for iNO are therefore valid when iNO is given as add-on therapy in addition to other standard treatment regimes used in the perioperative setting. The proposed indication has been reworded to better reflect that iNO is one part of treatment given to handle pulmonary hypertension in conjunction to heart surgery.

While the MAH’s response did not differentiate trials in which concomitant administration with other drugs appears potentially beneficial versus those where it does not (e.g. IV prostacyclin appeared to partially offset the beneficial effects of NO in Goldman’s study), CHMP acknowledged that given the bibliographic nature of most of the company’s dossier, it is likely not feasible to derive definitive recommendations in this regard. NO is accepted as a possible constituent of a physiologically-directed treatment armamentarium and the proposed indication wording was considered acceptable by CHMP.

With regard to dose, 40 ppm of iNO appears to be optimal. However, the doses of NO in the evaluated studies varies between 24 ppm to 40 ppm with what appears to be a dose titration step. Therefore, the MAH was asked to further define the dose titration needed as well as the optimal time for therapy. The MAH clarified that in the clinical studies evaluated, iNO has either been administered as a fixed dose or titrated to achieve a pre-determined response. Some dose-response studies have been performed but dose-finding data are not complete. It was argued that outside the clinical trial setting iNO is always titrated according to the individual’s response and that the effects of inhaled nitric oxide should be evaluated by monitoring of the pulmonary artery pressure, oxygen saturation and cardiac output. When the patient is haemodynamically stable, the dose should be adjusted downwards to the lowest effective dose; therefore, only starting doses are given. The posology section (section 4.2) of the SPC has been amended to better describe how treatment may be titrated and how soon a decrease in pulmonary pressure and oxygenation may be observed after initiation after treatment, which was acceptable to CHMP.

**Efficacy in paediatric population**

In the paediatric population, efficacy had not been established in the initial application dossier. The MAH was asked to further discuss the relevance of the haemodynamic and clinical benefits in this population and the evidence of efficacy derived from favourable effects on these parameters. In addition, the MAH had not established the dose in the key publications submitted of the use of inhaled nitric oxide in patients aged 6 months to 2yrs, 6yrs to 12yrs and 12 to 17yrs, which was of major concern to the CHMP.

In their response, the MAH stated that because high pulmonary pressure has been so clearly linked to increased morbidity and mortality in a range of studies (including a study by Lindberg et al. (2002) in 1,349 children), these endpoints are generally recognized as valid surrogate endpoints. Due to the well-established status of iNO in treatment of pulmonary hypertension, studies with mortality as endpoint are considered unethical. Furthermore, studies by Miller et al. (2000), Cai et al. (2008) and
Day et al. (2000) were cited as key studies evaluating the safety and efficacy of iNO in the paediatric population. In addition, the evidence for clinical efficacy in children is supported by the clinical documentation for adults, showing consistent results across age groups, and use in the approved indication, Persistent Pulmonary Hypertension of the Newborn (PPHN), a condition which shares some of the underlying pathophysiology and provides safety data for a vulnerable patient population, similar in age to neonates undergoing heart surgery. Finally, reference was made to recent expert and European treatment guidelines as proof of the well-established nature of iNO use in the acute handling of perioperative severe pulmonary hypertension in conjunction to heart surgery.

The CHMP recognised perioperative pulmonary hypertensive crisis (PHTC), the primary endpoint in the studies by Miller and Day, as an important clinical endpoint and acknowledged the use of NO-induced selective pulmonary vasodilatation in routine clinical practice. However, concerns were raised with regard to the differences in outcome of the two main studies by Miller et al. and Day et al., with Miller’s trial being supportive and Day’s not showing a therapeutic benefit. However, given the larger number of patients of the Miller study and the fact that the findings regarding selective haemodynamic changes were generally consistent with other studies, the results of Miller et al. were regarded as plausible. In summary, the available body of evidence was considered sufficient to support the efficacy of iNO in PHT in this population.

2.3.5. Clinical safety

INOmax (NO) for inhalation was granted a marketing authorisation in the US on 23 December 1999 and in the EU on 01 August 2001. The safety profile of INOmax inhalation gas is well known and documented in the current SPC.

This submission is primarily supported with key publications. The adverse event reporting in these publications is incomplete, making an evaluation of the risk difficult. The MAH has submitted safety data in two company-sponsored studies which are reviewed in this report. In addition, there are substantial Post Marketing Surveillance data.

2.3.5.1. Patient exposure

Clinical studies of iNO have been performed in a wide range of patient populations with regard to age distribution and surgical procedures. Further data has been also collected from two company sponsored trials (INOT22 and INOT41), and two pharmacodynamic studies (Lepore and Wessel). An overview including a summary of the safety data for each study is given in Table 4.

<table>
<thead>
<tr>
<th>AUTHORS</th>
<th>Age</th>
<th>n</th>
<th>n(NO)</th>
<th>iNO Dose/Time</th>
<th>SAFETY DATA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CARDIAC SURGERY – ADULTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fattouch</td>
<td>63±9y</td>
<td>58</td>
<td>22</td>
<td>20ppm/0.5h</td>
<td>No significant changes in HR, MAP, CVP, PCWP, CO and SVR in NO group One patient died during surgery due to right ventricular failure (randomized to NO group but did not receive gas). One patient needed biventricular assist device because of right ventricular failure (group not stated) Two patients had massive bleeding requiring re-exploration (group not stated) Two patients died due to multi-organ failure</td>
</tr>
</tbody>
</table>
### AUTHORS

<table>
<thead>
<tr>
<th>AUTHORS</th>
<th>Age</th>
<th>n</th>
<th>n_{iNO}</th>
<th>iNO Dose/Time</th>
<th>SAFETY DATA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fattouch</td>
<td>65±9y $iNO$</td>
<td>58</td>
<td>21</td>
<td>20ppm</td>
<td>Two deaths occurred - One in the control group from uncontrolled bleeding and one in the iNO group died from right ventricular failure.</td>
</tr>
<tr>
<td>Gianett</td>
<td>70±13y $iNO$</td>
<td>29</td>
<td>14</td>
<td>20ppm/8h</td>
<td>No adverse events documented in either group.</td>
</tr>
<tr>
<td>Schmid</td>
<td>32-76y</td>
<td>14</td>
<td>14</td>
<td>40ppm</td>
<td>Median methHB levels significantly increased from 0.64% to 1.06% with iNO. Maximal methHB was 1.55%. NO2 levels of 2.4 ppm (95% CI: 1.8, 4.2) were detected. In one patient the peak NO2 was 6.4 ppm. No adverse effects due to iNO were observed.</td>
</tr>
<tr>
<td>Solina (2000)</td>
<td>73±11y $iNO$</td>
<td>45</td>
<td>30</td>
<td>20 and 40ppm/24h</td>
<td>No adverse events, serious adverse events or deaths were noted.</td>
</tr>
<tr>
<td>Solina (2001)</td>
<td>68±6y $iNO$</td>
<td>62</td>
<td>47</td>
<td>10,20,30,40 ppm/</td>
<td>No adverse events were noted.</td>
</tr>
<tr>
<td>Winterhalter</td>
<td>68y±10 $iNO$</td>
<td>23</td>
<td>46</td>
<td>20ppm</td>
<td>No major side effects observed.</td>
</tr>
</tbody>
</table>

### CARDIAC SURGERY – CHILDREN

<table>
<thead>
<tr>
<th>AUTHORS</th>
<th>Age</th>
<th>n</th>
<th>n_{iNO}</th>
<th>iNO Dose/Time</th>
<th>SAFETY DATA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller</td>
<td>3m (1-5m) $iNO$</td>
<td>124</td>
<td>63</td>
<td>10ppm for up to 7 days</td>
<td>The methHB level remained less than 3.4% in all and the NO2 level was below 2.1 ppm for all cases.</td>
</tr>
<tr>
<td>Cai</td>
<td>(8)5.5±2.6y $iNO$</td>
<td>46</td>
<td>31</td>
<td>1-20ppm/24h</td>
<td>Methaemoglobin &lt; 2.5%. Expiratory nitrite concentration (for an iNO dose of 20 ppm in 80% O2) was 0.9 ppm. No patient experienced clinical signs of toxicity.</td>
</tr>
<tr>
<td>Goldman</td>
<td>3d-12m</td>
<td>13</td>
<td>13</td>
<td>20ppm/10min x2 (ongoing treatment for 1-17 days)</td>
<td>Four patients died. One died of acute pulmonary hypertension after iNO discontinuation and before iNO could be restarted. 3 died of underlying lung disease, multi-organ failure and left ventricular failure due to severe left ventricular hypoplasia respectively. No NO related toxicity was noted during iNO therapy except in 1 patient where methHB levels rose transiently to 8%. NO2 concentrations ≤ 1.2 ppm.</td>
</tr>
<tr>
<td>Morris</td>
<td>0.2-17.7y</td>
<td>12</td>
<td>12</td>
<td>5 &amp; 40 ppm/15min each</td>
<td>Methaemoglobin remained below 2 % in all patients. No rebound pulmonary hypertension was seen on discontinuation of iNO. No adverse events related to iNO therapy noted.</td>
</tr>
<tr>
<td>Russell</td>
<td>3m-4y iNO PH</td>
<td>36</td>
<td>18</td>
<td>80ppm/20min</td>
<td>Inhalation of iNO compared with placebo did not significantly alter systemic haodynamics (mSAP, heart rate, atrial pressure). The median methaemoglobin level was 1.6% ± 0.4% in the patient group that received inhaled NO. Adverse events were not noted and there were no deaths.</td>
</tr>
<tr>
<td>Stocker</td>
<td>97-171d</td>
<td>16</td>
<td>15</td>
<td>20ppm/40 min</td>
<td>No adverse events were noted.</td>
</tr>
<tr>
<td>Wessel</td>
<td>1d-11y $iNO$</td>
<td>43</td>
<td>9</td>
<td>80ppm/15min</td>
<td>15 minutes following nitric oxide inhalation, methaemoglobin levels were all within</td>
</tr>
<tr>
<td>AUTHORS</td>
<td>Age</td>
<td>n</td>
<td>n_{iNO}</td>
<td>iNO Dose/Time</td>
<td>SAFETY DATA</td>
</tr>
<tr>
<td>---------</td>
<td>-----</td>
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<td>---------</td>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Day</td>
<td>1d-20y _iNO (7m mean, 1 patient over 18 yrs of age)</td>
<td>40</td>
<td>20</td>
<td>20ppm</td>
<td>Maximum Methaemoglobin values were slightly increased in iNO group (1.4% + 0.1% versus 1.1% + 0.1%, p=0.023). No known complications or adverse events were associated with iNO</td>
</tr>
<tr>
<td>Ardehali</td>
<td>47.6±16.4y</td>
<td>16</td>
<td>16</td>
<td>20ppm/12-76h</td>
<td>No methaemoglobinemia. NO2&lt; 0.5 ppm in all pts. RV dysfunction in iNO vs. 6 controls.</td>
</tr>
<tr>
<td>Rajek</td>
<td>54±11y_iNO</td>
<td>70</td>
<td>34</td>
<td>4-24ppm prn/ 6-48h</td>
<td>Cardiac output, heart rate, mean arterial pressure, right atrial pressure, and pulmonary wedge pressure did not differ between the groups. No side effects/adverse events detailed Methaemoglobin levels were not elevated NO2 concentration never &gt; 0.5 ppm. 7 patients required protracted weaning from iNO over 48h. Two patients from the nitric oxide group (and one patient from the PGE1 group) developed systemic infections and died within the first month.</td>
</tr>
<tr>
<td>Kieler-Jensen</td>
<td>19-61y</td>
<td>12</td>
<td>12</td>
<td>20,40,80 ppm/10min each</td>
<td>Inhalation of nitric oxide did not significantly change systemic or pulmonary arterial pressure, cardiac output, right ventricular function, or systemic vascular resistance. Arterial and pulmonary arterial levels of nitrate increased during inhalation of NO and this increase was paralleled by an increase in methaemoglobin levels corresponding to about 2%.</td>
</tr>
<tr>
<td>Lepore</td>
<td>34-73y</td>
<td>9</td>
<td>9</td>
<td>80ppm/5 min x2</td>
<td>No Adverse events No deaths</td>
</tr>
<tr>
<td>Radovancevic</td>
<td>20-63y (mean of 53 ±12y)</td>
<td>19</td>
<td>19</td>
<td>40, 60 &amp; 80 ppm</td>
<td>No mention of adverse events No significant decrease in cardiac index</td>
</tr>
<tr>
<td>Argenziano</td>
<td>55y±3y</td>
<td>11</td>
<td>6</td>
<td>20-2ppm/12h-6d (med=24h)</td>
<td>No systemic hypotension, hypoxia or other adverse consequences. All patients successfully weaned from iNO within one week. Ventilator failure precipitated abrupt iNO cessation in 1 pt. → reversible hemodynamic collapse and VF.</td>
</tr>
<tr>
<td>INOT22</td>
<td>0.1-18.7 y _Mean 7.4y</td>
<td>124</td>
<td>124</td>
<td>80 ppm/10 min x2</td>
<td>Seven patients experienced AEs of which four were related to the study drug. Three of the AEs were fatal and four nonfatal. The overall numbers of SAEs and fatal SAEs (7/124 or 5.6%) were within the range expected for patients with this degree of cardiopulmonary disease. However the study does seem to support earlier reports of acute left ventricular...</td>
</tr>
</tbody>
</table>
2.3.5.2. Adverse events

It is important to note that the quality (both in terms of detail and robustness) of adverse event reporting differs significantly between the MAH-sponsored studies (INOT22 and 41) and studies published in peer reviewed journals. Although a number of the published studies include adverse event data, this does not constitute full reporting of adverse events in accordance with GCP standards.

The most commonly reported adverse events (AEs) are hypotension, hypoxia, haemorrhage, left ventricular failure and organ failure. The data is based on reported AEs; however the AE reporting was incomplete or absent in many studies. Also for many reports no investigator assessment was provided. However, all reported AEs were in the range of expected events for the target population and no indication for safety concern had emerged.

The known adverse effects and risks that need to be considered and evaluated for iNO are:
- formation of methaemoglobin at high dosage levels,
- possible risk of affecting coagulation,
- formation of oxides of nitrogen.
- risk of rebound effects at withdrawal of iNO
- risk of cardiac failure in patients with complex congenital cardiac defects

Effects on Platelets

NO activates the cyclic GMP and thus iNO may, when reaching the blood, have an effect on the platelets. However, it is rapidly taken up by haemoglobin forming methaemoglobin. The effect of iNO on platelet function has been studied both in animal experiments, *in vitro* and *in vivo* in healthy volunteers and in the clinical setting in patients undergoing heart surgery. Animal models have shown that NO may interact with haemostasis. Recommendations for monitoring of haemostasis are included in 4.2 of the SPC.

**INOT41**

Treatment was divided into randomised double-blind and open-label treatment phases. During the open-label INO treatment, the rates of overall AEs, severe AEs, related AEs, and serious AEs were slightly higher than those observed in the double-blind iNO group.

**Double-blind Phase**

The overall safety profile of the two treatment groups was also comparable, except that a higher percentage of subjects in the iNO group had an AE that was suspected to be drug related compared with the placebo group: 9/69 (13.0%) in the iNO group vs. 5/68 (7.4%) in the placebo group. It
should be noted however that this category included adverse events not only categorized as being probable or highly probable but also those regarded as remote and possible as well. The most frequently reported drug-related AEs, occurring in 2 or more subjects in one of the treatment groups, were; Right Ventricular Failure (RVF) in 5 subjects - 3 (4.3%) with iNO and 2 (2.9%) with placebo, Post-procedural haemorrhage in 4 subjects – 3 (4.3%) with iNO and 1 (1.5%) with Placebo Haemorrhage in 2 subjects both in the placebo group (2.9%); Thrombocytopenia in 1 subject in the placebo group (1.5%).

Open Label Phase

The most frequently reported AEs were RVF and haemorrhage: RVF was seen in 8 subjects (iNO DB n = 2/69 [2.9%], OL 1/34 [2.9%]; PBO n = 5/68 [7.4%]), and led to treatment discontinuation in 6 subjects (iNO DB n = 2/69 [2.9%]; PBO 4/68 [5.9%]). The complication was serious but nonfatal in 5 subjects (iNO DB n = 2/69 [2.9%], OL 1/34 [2.9%]; PBO 2/68 [2.9%]) and fatal for 2 subjects (iNO DB n = 1/69 [1.4%]; PBO 1/68 [1.5%]).

Haemorrhage (all types combined, total n = 9: iNO DB n = 3 [4.3%], OL 3 [8.8%]; PBO 3 [4.4%]) and post-procedural haemorrhage (total n = 10: iNO n = 3 [4.3%], OL 2 [5.9%]; PBO 5 [7.4%]) were not fatal nor led to treatment discontinuation although they led to dose modification in 2/34 subjects (5.9%) during OL iNO treatment.

Post-procedural haemorrhage was rated as severe in 5 subjects (iNO DB n = 2/69 [2.9%], OL 1/34 [2.9%]; PBO 2/68 [2.9%]) and haemorrhage was rated as severe in 3/68 subjects (4.4%), all in the placebo group. Ten subjects had a serious hemorrhagic event (iNO DB n = 3/69 [4.3%], OL 1/34 [2.9%]; PBO 6/68 [8.8%]). One subject in the iNO group had 4 episodes of post-procedural haemorrhage and required 2 thoracotomies for post-surgical haemorrhage.

There were no treatment differences in the mean volume of chest tube drainage (iNO 1678.5 ml; PBO 1802.8 ml) or mean volume of blood products used (iNO 4477 ml; PBO 5531 ml). These results indicate that haemorrhage was most likely a complication of the LVAD surgery and not related to study drug.

Methaemoglobin levels remained low and were similar between the 2 treatment groups at all measured time points.

INOT22

Seven patients experienced AEs during the study of which four were related to the study drug. These events included bradycardia, low output syndrome, ST segment elevation on the ECG, low O₂ saturation, pulmonary hypertension, and hypotension.

Both NO with O₂ and O₂ alone slightly increased systemic arterial pressure SAP in both the intent-to-treat and per-protocol populations. The increase for NO plus O₂ was statistically significant in the per-protocol population (2.9 mm Hg, p=0.028). Treatment with NO slightly increased SAP in the intent-to-treat population and decreased it in the per-protocol population.

2.3.5.3. Serious adverse events and deaths

INOT41

A total of 4 SAEs with lethal outcome occurred during the treatment period (double blind and open label period on iNO), and they were equally distributed (one in each arm) during the double blind period. The causes of death were right ventricular failure and multi-organ failure. Only one of the events of death was remotely assessed as possibly related. Further 12 events with outcome death occurred by Day 28 post treatment; none of them were related or remotely related to study drug.
INOT22

Three AEs led to a fatal outcome (low CO output and hypertension in one subject and bradycardia in another) whilst four were nonfatal; one of these led to study discontinuation. Two of the three fatal SAEs were considered related to therapy, as were all of the four non-fatal SAEs.

The overall numbers of SAEs and fatal SAEs (7/124 and 5.6%) were within the range expected for patients with this degree of cardiopulmonary disease and overall rate of SAEs appears to have been more closely related to the underlying severity of illness rather than to the treatments given during this study. The numbers of patients and events were too small to determine whether risk for death differed by treatment, diagnosis, age, gender, or race.

2.3.5.4. Laboratory findings

Methamoglobin and NO2 levels were commented on in the following literature studies. None had shown individual values which were significantly elevated or would have resulted in patient injury except one patient in Schmid and al who had a maximum NO2 value of 6.44% and a single patient in Goldman and al whose metHB levels rose to 8%. Please refer to table 5.

Table 5  Methaemoglobin and NO2 levels compared with controls across all literature studies

<table>
<thead>
<tr>
<th>Study</th>
<th>MetHB</th>
<th>NO2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INOmax</td>
<td>Control INOmax</td>
</tr>
<tr>
<td>Schmid (4) (Crossover study)</td>
<td>1.06% (1.55% max)</td>
<td>0.64% 2.4ppm (6.44% max)</td>
</tr>
<tr>
<td>Miller (8)</td>
<td>&lt;3.4% in all cases</td>
<td>n/a &lt;2.1ppm in all cases</td>
</tr>
<tr>
<td>Cai (9)</td>
<td>&lt;2.5% in all cases</td>
<td>N/S 0.9ppm</td>
</tr>
<tr>
<td>Goldman (10) (Crossover study)</td>
<td>8% max in one case</td>
<td>N/S &lt;1.2ppm</td>
</tr>
<tr>
<td>Morris (11) (Crossover study)</td>
<td>&lt;2% in all cases</td>
<td>N/S N/S</td>
</tr>
<tr>
<td>Russell (12)</td>
<td>Mean of 1.6%±0.4</td>
<td>Mean of 1.0%±0.3%</td>
</tr>
<tr>
<td>Wessell (14)</td>
<td>Mean of 0.8%±0.3% (within normal range)</td>
<td>N/S N/S</td>
</tr>
<tr>
<td>Day (15)</td>
<td>1.4%±0.1% max</td>
<td>1.1%±0.1% max</td>
</tr>
<tr>
<td>Ardelahli (16)</td>
<td>Within normal limits</td>
<td>N/S &lt;0.5ppm in all patients</td>
</tr>
<tr>
<td>Rajek (17)</td>
<td>Within normal limits</td>
<td>N/S &lt;0.5ppm in all patients</td>
</tr>
</tbody>
</table>
The results for Kieler-Jensen et al presented data visually but did not explicitly state NO₂ and methaemoglobin values.

No clinical laboratory evaluations were carried out as part of the INOT22 study.

In study INOT41, the biochemical markers of kidney (creatinine and BUN) and liver (AST and ALT) function would be expected to improve following LVAD placement, as normal circulation is restored. This, combined with the need to cross over to open-label INO, makes interpretation of the laboratory data very difficult. Mean values for the measured laboratory analyses remained fairly constant throughout double-blind treatment except for ALT and AST, which tended to decrease in the 48-hour treatment period. For both analytes, the placebo group had lower baseline values, and the changes in these two analytes were similar between the two treatment groups. These results indicate that iNO did not appear to have an adverse effect on renal or liver function during open-label INO treatment. Most laboratory values remained fairly constant with the exception of AST and, to a lesser extent, ALT, both of which fluctuated. No analyses were performed by individual subject.

The majority of subjects had AST and ALT values that were within normal limits. However, 14 subjects receiving iNO and 12 subjects receiving placebo had AST or ALT values that were at least 10 times the upper limit of normal at baseline or at sporadic post-baseline time points. These outliers caused the difference in intergroup means to be skewed. One subject, 3P12, who was receiving double-blind placebo, had moderate thrombocytopenia that was deemed to be serious. No action was taken and the event resolved. The investigator considered the event to be not related to study drug. No subjects had an abnormal laboratory value that led to treatment discontinuation.

2.3.5.5. Safety in special populations

There are no studies about the effects of iNO therapy in preterm neonates undergoing heart surgery, thus no firm assessment of the perioperative use of iNO can be done.

2.3.5.6. Post marketing experience

The cumulative number of exposed patients across all PSUR reports dating from December 2001 is estimated from cylinder usage to be 297,682 ± 2977 (this does not include patients in blinded clinical trials).

Based upon the same current best algorithm calculation used to calculate patient exposure in the marketplace, the MAH estimates there were 149,846 ±1498 total patients exposed (via commercialised use) to INO over the period covered by the last PSUR 24/12/05-23/12/08. The estimate of patient exposure in a number of countries/geographic territories during the coverage period is as follows: US – 129,500 patients; Canada – 6923 patients; South America – 188 patients; EU – 13,235 patients.

Due to the highly individualised nature of both therapy and response, it is not possible to estimate aggregate dosage values for the entire treated population. Whilst there is currently one approved indication, it is acknowledged that off-label use of iNO is common. Consequently obtaining reliable estimations of use in different indications is extremely difficult.

A search for serious events, including events from spontaneous reporting, literature and clinical studies was done for the time period 23 December 1999 (the international birth date of the drug) until 31 December 2009. The data base was searched for all serious adverse events in the time period.

A large number of adverse events are reported from studies. These studies were to a large extent done in very unwell premature/near full term newborn infants often suffering from a range of co-morbidities (many of which were enrolment criteria in of themselves). There is thus, an increased incidence of
intraventricular haemorrhage, periventricular leukomalacia, pulmonary haemorrhage and patent ductus arteriosus. This is however to be expected given the demographic profile of the treatment population. All these events are associated with increased morbidity in the mentioned groups, and have been discussed in the previous PSURs.

2.3.5.7. Discussion of clinical safety

The safety summary provided in this application has not highlighted major specific adverse events which could be associated exclusively with the use of iNO in paediatric and adult patients who have undergone post cardiac surgery. Of course, the usual precautions of use of iNO would apply in addition to the issues of weaning which are specified in the SPC. These patients are associated with high risk; hence, the adverse event reporting will be higher with higher co-morbidities and mortalities. While the key publications on investigator-initiated studies provided in the submission do not adequately cover the reporting of adverse events, appropriate information has been derived from the two MAH sponsored studies (INOT22 and 41).

In INOT41, the overall safety profile of the two treatment groups was similar, with the possible exception that a higher percentage of subjects in the iNO group had an AE suspected to be drug related compared with the placebo group (13.0% versus 7.4%).

Given that the proposed indication is in patients undergoing heart surgery, the effect of iNO on the coagulation is of major importance. Hence, the MAH was asked to clarify whether bleeding increased in patients on INO undergoing heart surgery and whether the duration of treatment had any impact on this. During the procedure, the MAH has provided further information on the risk of impaired haemostasis and potential increase in the bleeding in these patients. Based on literature review of experimental ex vivo studies and studies in healthy volunteers as well as on results from the company-sponsored INOT41 trial, the MAH concluded that randomised studies have not shown any difference in perioperative bleeding or bleeding complications. This view was endorsed by CHMP.

In study INOT22, the dose was significantly higher than the doses used in the key published data and covered a patient population not described in those studies. Safety considerations of such high doses in higher risk patients as those described in this study need to be further explained as the usefulness of this study in pulmonary hypertension in post cardiac operation patients is not clear.

The bibliography and two studies submitted do not allow estimation of a maximum tolerated dose. The SPC therefore includes caution statements detailing the risk of NO in patients with complex heart defects where high pulmonary pressures are important for maintaining circulation, as well as the risk of NO in patients with compromised left ventricular function who may be at increased risk of developing cardiac failure further to volume overload. These statements are considered appropriate to address the potential risks of NO.

The potential risk of bleedings and haemostasis disorders are identified as important potential risks in the EU-RMP and covered by additional risk minimizing measures (included in educational material).

The safety of iNO when co-administered with standard critical care inotropes/vasopressors, e.g., dopamine or adrenaline, appears to have been demonstrated, most convincingly in Miller et al’s study. In contrast, the safety of iNO in conjunction with other potential (pulmonary) vasodilators, e.g., (inhaled) prostacyclin, endothelin receptor antagonists and PDE-5 inhibitors (e.g. sildenafil) has not been evaluated. Given the potential safety concern associated with the use of iNO in combination with other medications, particularly the potentially additive or synergistic pharmacodynamic effects with other vasodilators, an appropriate warning regarding the lack of extensive data for these combinations has been added in section 4.4 of the SPC.
As this variation introduces a new indication, CHMP requested an amendment of the PSUR cycle for INOmax; the reporting frequency shall be increased to 6-monthly intervals following the approval of the new indication.

### 2.3.6. Pharmacovigilance aspects

#### 2.3.6.1. Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

#### 2.3.6.2. Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

The following additional risk minimisation activities were required.

### Summary of the EU Risk Management Plan

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Proposed pharmacovigilance activities (routine)</th>
<th>Proposed risk minimisation activities (routine and additional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methaemoglobinemia (identified risk)</td>
<td>Routine pharmacovigilance</td>
<td>Monitoring the levels described in SPC section 4.2:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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 &gt; 2.5%, the INOmax dose should be decreased and the administration of reducing agents such as methylene blue may be considered. Although it is unusual for the methaemoglobin level to increase significantly if the first level is low, it is prudent to repeat methaemoglobin measurements every one to two days.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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 agents such as methylene blue may be considered.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Educational material.</td>
</tr>
<tr>
<td>Formation of nitrogen oxides (identified risk)</td>
<td>Routine pharmacovigilance</td>
<td>Monitoring the levels described in SPC section 4.2:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Immediately prior to each patient initiation, proper procedure must be applied to purge the system of</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Proposed pharmacovigilance activities (routine)</td>
<td>Proposed risk minimisation activities (routine and additional)</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Rebound effect (identified risk)</td>
<td>Routine pharmacovigilance</td>
<td>Weaning described in SPC, section 4.2:. 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 iNO. Too rapid weaning from inhaled nitric oxide therapy carries the risk of a re-bound increase in pulmonary artery pressure with subsequent circulatory instability. And section 4.4: Discontinuation of Therapy: The INOmax dose should not be discontinued abruptly as it may result in an increase in pulmonary artery pressure (PAP) and/or worsening of blood oxygenation (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.</td>
</tr>
<tr>
<td>Risk of acute cardiac failure with different degrees in defined populations (identified risk)</td>
<td>Routine pharmacovigilance</td>
<td>Contraindication in SPC section 4.3: Neonates known to be dependent on right-to-left, or significant left-to-right, shunting of blood. Hypersensitivity to the active substance or any of the excipient. Warning in SPC, section 4.4: Treatment with inhaled nitric oxide might aggravate</td>
</tr>
<tr>
<td>Safety concern</td>
<td>Proposed pharmacovigilance activities (routine)</td>
<td>Proposed risk minimisation activities (routine and additional)</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Risk of abrupt discontinuation of INOmax in the event of critical failure of the delivery system (identified risk)</td>
<td>Routine pharmacovigilance</td>
<td><strong>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).</strong></td>
</tr>
<tr>
<td>Potential risk of bleedings and haemostasis disorders (potential risk)</td>
<td>Routine pharmacovigilance</td>
<td><strong>Described in the SPC sections 4.2.</strong></td>
</tr>
<tr>
<td></td>
<td><strong>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.</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>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.</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Educational material.</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Described in SPC, section 4.4:</strong></td>
<td><strong>Effects on platelets</strong></td>
</tr>
<tr>
<td></td>
<td><strong>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.</strong></td>
<td></td>
</tr>
</tbody>
</table>
### Safety concern

<table>
<thead>
<tr>
<th>Proposed pharmacovigilance activities (routine)</th>
<th>Proposed risk minimisation activities (routine and additional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Educational material</td>
<td>Education material</td>
</tr>
</tbody>
</table>

#### The potential risk of combined use with other vasodilators (e.g. sildenafil) (potential risk)

- **Routine Pharmacovigilance**
- **Warning in section 4.5 of the SPC:**
  > The combined used with other vasodilators (e.g. Sildenafil) is not extensively studied. Available data suggest additive effects on central circulation, pulmonary artery pressure and right ventricular performance. Inhaled nitric oxide combination with other vasodilators acting by the cGMP or cAMP systems should be done with caution.

#### Inconclusive results of studies on the effects of inhaled nitric oxide in hypoxic pre-term neonates and no available information about its effects in conjunction to heart surgery in preterm neonates (missing information)

- **Routine Pharmacovigilance**
- **Warning in section 4.2 of the SPC:**
  > Paediatric population
  > 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, but no recommendation or posology can be made.

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### 2.4. Conclusions and Benefit / Risk Assessment

#### Benefits

- **Beneficial effects**

The MAH has presented a brief summary of the biology of Nitric Oxide (NO) as an endogenous signaling molecule playing essential roles in a variety of biological systems, and particularly in the control of vascular tone. Nitric oxide was identified as the “endothelial derived relaxing factor” in the years 1980. The first therapeutic application of NO, by inhalation, was reported in 1991 to decrease pulmonary vascular resistance (PVR) in patients with primary pulmonary hypertension. Inhaled NO has been used in the intensive care unit (ICU) setting to decrease PVR in patients with severe lung injury. This intervention was accompanied by variable improvements in arterial oxygenation, which was explained by improved ventilation-perfusion relationships due to preferential decrease in PVR in the best aerated lung regions.

Pulmonary hypertensive crisis during or in the postoperative course of cardiac surgery is an interesting indication of inhaled NO. The condition is life-threatening. Extensive off-label experience of inhaled NO in the ICU’s has established its efficacy and its safety in this indication. As such, the treatment is included in the recommendations of European and North American expert consensus documents on the treatment of pulmonary hypertension. The rationale behind these recommendations has been adequately summarised in the application. Thus doses from 10-40 ppm of inhaled NO have been
shown to be safe and effective. The strategy of adjustment to the lowest dose allowing for the desired hemodynamic effects is well established.

There have been a total of 20 randomised controlled trials of inhaled NO in acute pulmonary hypertension on cardiac surgery: 13 in 588 adult patients, 7 in 299 pediatric patients. These publications help to understand the usefulness of nitric oxide gas in controlling a life threatening condition namely pulmonary hypertension adults and children following cardiac surgery. The Applicant has identified key publications which establish dose and efficacy of monotherapy with NO versus standard therapies milrinone and prostacyclin and PGE1 in adults. In children key publications have established usefulness in younger children of inhaled NO as a monotherapy (children aged on average 3months) and in combination with milrenone (children aged on average 5.5yrs).

Data showing haemodynamic efficacy in severe pulmonary hypertension have been presented in detail by the MAH in a fair and balanced manner, with appropriate interpretation.

- Uncertainty in the knowledge about the beneficial effects.

Each of the reported studies is relatively small, and there has been variability in end points. This is understandable as mortality studies are extremely difficult in these patients, placebo controls could be unethical, and there is no consensus on a single endpoint as the most adequate surrogate measure of the disease. Also, in the acute unstable situation of the pulmonary hypertensive crisis, physicians in care have to react quickly with decision making essentially guided by pathophysiological reasoning. Nevertheless, the available controlled and uncontrolled evidence is largely in favour of efficacy with minimal and manageable toxicity of inhaled NO in pulmonary hypertensive crisis on cardiac surgery.

**Risks**

- Unfavourable effects

Approximately 300,000 patients have been exposed until now to various durations of inhaled NO. There has been no signal that the treatment (including its formulation, and administration device) is associated with significant safety problems.

Alternative therapies are much more difficult to handle than inhaled NO because of a variety of side effects, of which the most significant are systemic hypotension and alteration of pulmonary gas exchange. None of these alternative therapies show greater efficacy than inhaled NO in controlling acute severe pulmonary hypertension.

The summary of safety data has not highlighted major specific adverse events which could be associated exclusively with the use of NO in post cardiac surgery patients, be they either children or adults. It is evident that the customary precautions of use of inhaled NO apply with in addition the issues of weaning which have been specified in the SPC. It must be remembered that these patients are associated with high risk so adverse event reporting will be higher with higher co-morbidities and mortalities. While the key publications used in the submission do not adequately cover this, some is covered by the two company sponsored studies. Numbers reported will be small because of the smaller number so of patients who undergo cardiac surgery.

The SPC includes information on the prevention and management of side effects reportedly associated with inhaled NO, that is methaemoglobinemia, generation of nitrogen dioxide, rebound pulmonary hypertension, left heart failure with increased pulmonary capillary pressure, and platelet dysfunction with increased bleeding time. Warnings about pregnancy and lactation (unknown effects of inhaled NO) are also included.
Uncertainty in the knowledge about the unfavourable effects.

A Risk Management Plan has been provided in conjunction with this variation to extend the indication for INOmax. The RMP addresses the following identified risks:

- Methaemoglobinaemia
- Formation of nitrogen oxides
- Rebound effect
- Risk of acute cardiac failure (contraindication or warning in different patient populations)
- Risk of critical failure of the delivery system

In addition, the RMP for INOmax also focuses on the potential risks of NO treatment, about which there is some uncertainty:

- Risk of bleedings and haemostasis disorder
- Risk of additive effects from the combined use with other vasodilators acting on the cGMP or cAMP pathway

NO has been used in approximately 300,000 patients to date, and the identified risks are well characterised. The uncertainty surrounding the risks of bleeding and combination use with other vasodilators, along with the better characterised identified risks are managed via information in the SmPC (warnings and precautions, and recommendations for monitoring); training of healthcare personnel who will administer NO; and information provided in a pocket guideline for all relevant healthcare professionals.

The above described risks and the complete overall safety profile of INOmax will be monitored in Periodic Safety Update Reports, which will initially be submitted at 6 monthly intervals. The PSURs will include information on adverse reaction reports (including reports of device failure), clinical trials and the published literature, and are anticipated to further increase our knowledge of the unfavourable effects of NO.

**Benefit-Risk Balance**

The benefit-risk balance for the use of inhaled NO in pulmonary hypertension peri- and post heart surgery, although based primarily on publications, is considered positive in adults since no major safety or efficacy considerations have been identified and the use presents itself as an extension to currently well established use for pulmonary hypertension in Intensive Care. In the case of the paediatric population the supporting data does not appear as robust making a positive benefit risk balance difficult. However, in the absence of robust information we are left with the choice of non-approval of a paediatric indication for a potentially life-saving drug due to lack of data in age groups in which the drug is less frequently used, or a more pragmatic approach. Overall the latter appears preferable as:

- The proposed posology in children (initiation at 10 ppm, titration between 5-20 ppm based upon response) is generally based on the available data. Although the lower dose (5 ppm) does not appear to have been employed in the key paediatric studies it is in the effective range on the basis of available physiological data and is a “non-toxic” dose.
- Cardiac surgery in children is principally performed in younger children for whom the proposed posology is well supported by Miller’s and Cai’s studies
Physicians administering NO are likely to be conversant with the principle of titration to effect and the risks of NO therapy particularly circulatory compromise secondary to lowered pulmonary vascular resistance and methaemoglobinaemia both of which are detailed in the SPC.

The SPC statement regarding the limited clinical data in 12-17 year olds should alert physicians to the possibility that the proposed posology may be ineffective in this age group.

Taking the above into account, the risk benefit balance for INOmax, in conjunction with ventilatory support and other appropriate agents as part of the treatment of peri- and post-operative pulmonary hypertension in adults and children in conjunction to heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation, is considered positive.

The following indication wording is therefore agreed for section 4.1 of the SmPC (additions highlighted):

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

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

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

### 3. Conclusion

On 20 January 2011 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet and the introduction of an Annex 127a.

The PSUR reporting cycle for INOmax shall be increased to 6-monthly intervals.