HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

29 May 2013

INOMAX 400 ppm mol/mol, inhalation gas

One 2-litre aluminium cylinder (CIP: 34009 565802 3 1)
One 10-litre aluminium cylinder (CIP: 34009 563402 8 6)

Applicant: LINDE HEALTHCARE

INN	Nitric oxide (NO)
ATC Code (year):	R07AX01 (Respiratory system product)
Reason for the request	**Inclusion for an extension of the indication**
List(s) concerned	**Hospital use** (French Public Health Code L.5123-2)
Indication concerned	**"INOMAX, in conjunction with ventilatory support and other appropriate active substances, is indicated 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 tissue oxygenation"**

Actual Benefit	**Substantial**
IAB	**The Committee considers that INOMAX 400 ppm mol/mol, inhalation gas, offers an improvement in actual benefit of level IV (minor IAB) in the treatment of peri- and post-operative PAHT in conjunction with heart surgery in adults and children, including newborn infants, in order to selectively decrease pulmonary artery pressure and improve right ventricular function and tissue oxygenation.**
Therapeutic use	**First-line treatment in conjunction with ventilatory support and other appropriate active substances for the treatment of PAHT in heart surgery.**
Recommendations	

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Date of the Marketing Authorisations (centralised procedure)	Initial date: 1 August 2001 Date of extension of indication in heart surgery: 17 March 2011
Prescribing and dispensing conditions/ special status	Medicinal product for hospital use only. "Prescription of nitric oxide should be supervised by a physician experienced in cardiothoracic anaesthesia and intensive care. Prescription should be limited to those cardio-thoracic and intensive care units that have received adequate training in the use of a nitric oxide delivery system. INOMAX should only be delivered according to an anaesthetist's or intensive care physician's prescription." (SPC) Nitric oxide is delivered to the patient via mechanical ventilation after dilution with an oxygen/air mixture using an approved (CE-marked) nitric oxide delivery system.

ATC Classification	2012		
	R	:	Respiratory system
	R07	:	Other respiratory system products
	R07A	:	Other respiratory system products
	R07AX	:	Other respiratory system products
	R07AX01	:	Nitric oxide (NO)

02 BACKGROUND

INOMAX 400 ppm mol/mol (nitric oxide) has Marketing Authorisation in the therapeutic management of newborn infants > 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary arterial hypertension. (AB substantial, IAB I major compared with conventional treatment, opinion of 12 December 2001).

INOMAX now has Marketing Authorisation in adults and children in conjunction with ventilatory support and other appropriate active substances for the treatment of pulmonary artery hypertension occurring during or after heart surgery.

03 THERAPEUTIC INDICATIONS

INOMAX, in conjunction with ventilatory support and other appropriate active substances, is indicated:
"- **for 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 tissue oxygenation.**

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

04 DOSAGE

“INOMAX should be used only after conventional therapeutic measures have been optimised. In clinical trials, INOMAX has been given in addition to conventional therapies in the peri-operative setting, including inotropic and vasoactive medicinal products. INOMAX should be administered under close monitoring of the haemodynamic state and the patient’s blood oxygenation. Its administration should be by the endotracheopulmonary route.

Newborns, infants, children and adolescents ages 0-17 years: the recommended starting dose for this age group is 10 ppm (parts per million). If the clinical effect obtained is insufficient, the dose may be increased up to 20 ppm. The lowest effective dose should be administered and the dose should be weaned down to 5 ppm, provided that the pulmonary artery pressure and systemic arterial oxygenation remain adequate at this lower dose.
Clinical data supporting the suggested dose in the age range 12-17 years are limited.

Adults: The starting dose recommended in adults is 20 ppm (parts per million) of inhaled gas. If the clinical effect obtained is insufficient, the dose may be increased up to 40 ppm. The lowest effective dose should be administered and the dose should be weaned down to 5 ppm, provided that the pulmonary artery pressure and systemic arterial oxygenation remain adequate at this lower dose. The effects of inhaled nitric oxide are rapid; decrease in pulmonary artery pressure and improved oxygenation are seen within 5-20 minutes. In case of insufficient response, the dose may be titrated after a minimum of 10 minutes.
Consideration should be given to discontinuation of treatment if no beneficial physiological effects are apparent after a 30-minute trial of therapy.
Treatment may be initiated at any time in the peri-operative course to lower pulmonary pressure. In clinical studies, treatment was most often initiated before stopping the extracorporeal circulation. Inhaled nitric oxide has been given for periods of up to 7 days in the peri-operative setting, but common treatment times are from 24 to 48 hours.

Weaning
Attempts to wean INOMAX should be commenced as soon as the hemodynamics have stabilised and 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 under close observation of systemic and central pressure, and then turned off. Weaning should be attempted at least every 12 hours when the patient is stable on a low dose of INOMAX. Too rapid weaning from inhaled nitric oxide therapy carries the risk of a rebound increase in pulmonary artery pressure with subsequent circulatory instability.

Paediatric population
The safety and efficacy of INOMAX in premature infants of less than 34 weeks of gestation have not yet been established. Currently available data are described in section 5.1 of the SPC but no recommendation or posology can be made.

Monitoring formation of methaemoglobin (MetHb)
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. The determination method used should make it possible to reliably distinguish between foetal haemoglobin and methaemoglobin. If the methaemoglobin level is higher than 2.5%, the INOMAX dose should be decreased and the administration of reducing medicinal products such as methylene blue should 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.

In patients undergoing heart surgery, the methaemoglobin level should be measured within one hour of the initiation of INOMAX therapy. If the fraction of methaemoglobin rises to a level that potentially compromises adequate oxygen delivery, the INOMAX dose should be decreased and the administration of reducing medicinal products such as methylene blue may be considered.

Monitoring formation of nitrogen dioxide (NO_2)
Immediately prior to each patient initiation, a proper procedure must be applied to purge the system of NO_2. The NO_2 concentration should be maintained as low as possible without exceeding 0.5 ppm. If the NO_2 concentration exceeds 0.5 ppm, the delivery system should be assessed for malfunction, the NO_2 analyser should be recalibrated, and the INOMAX and/or FiO_2 should be reduced if possible. If there is an unexpected change in INOMAX concentration, the delivery system should be assessed for malfunction and the analyser should be recalibrated."

05 THERAPEUTIC NEED

Small concentrations of exogenous nitric oxide (NO) administered by inhalation lead to relaxation of the smooth muscle cells in the pulmonary blood vessels. In subjects with high vascular resistance and elevated pulmonary artery pressure, the NO brings on pulmonary vasodilation with correction of PAHT. Based on this pharmacological effect, the use of inhaled NO was first developed in the treatment of hypoxic respiratory failure combined with pulmonary hypertension in the newborn.

In heart surgery, the onset of pulmonary arterial hypertension complicates the management of the patient and is a bad prognosis marker in morbidity and mortality terms. Fast and effective control of the pulmonary artery pressure enables right ventricular strain to be reduced. The decrease in pulmonary vascular resistance also helps improve post-operative recovery.
The usual measures for reducing the risk of an acute perioperative increase in pulmonary artery pressure include maintaining adequate oxygenation, ventilation and stress reduction.
Preventing hypoxaemia, hypercapnia and acidosis and not using medicinal products that could increase pulmonary artery pressure are additional measures to consider.
Vasodilators such as nitroglycerin or nitroprusside IV are also used off-label, but these can also affect systemic pressures. Treatment with a drug having an inotropic effect, such as milrinone, can help improve right ventricular performance and thus promote pulmonary blood flow. But the effects on the systemic circulation, which can be frequent, could compromise organ perfusion and oxygen distribution.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

Other vasodilators indicated in the event of PAHT occurring during heart surgery: none.

06.2 Other health technologies

Cardiac resuscitation measures: hyperventilation, oxygenation, alkalinisation.

NB: In addition to the cardiac resuscitation measures, management currently also calls for the off-label use of medicines for treating episodes of PAHT in heart surgery due to their vasodilating action on the pulmonary vessels (see section on Therapeutic use). These are essentially nitroglycerin, sodium nitroprusside (NITRIATE), sildenafil and the prostaglandins (epoprostenol (FLOLAN for injection) and iloprost (inhaled VENTAVIS).

◗ Conclusion

There are no relevant comparators with Marketing Authorisation in this indication.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Data concerning reimbursement or otherwise in Europe and in North America: INOMAX has been authorised using a centralised Marketing Authorisation procedure. For this reason the “hospital use only” restriction applies in all countries of the European Union.

08 ANALYSIS OF AVAILABLE DATA

The assessment of nitric oxide (INOMAX) as a vasodilator in heart surgery relies on two studies: INOT 41 study in adults and INOT 22 study in children.

In addition, the applicant has submitted literature data; only those in which nitric oxide was assessed in heart surgery and at the dosage recommended in the Marketing Authorisation will be taken into account. In these studies, the parameters assessed included, among others, haemodynamic measurements making it possible to quantify the severity of the pulmonary arterial hypertension (elevation of the central venous pressure and of the systolic, diastolic and mean pulmonary artery pressures), the vasoconstriction in the pulmonary vessels (increase in the pulmonary vascular resistance), the impact of this PAHT on heart function (decrease in the cardiac output or cardiac index) and the systemic oxygenation (decrease in the venous oxygen saturation).

In children, the data from two studies assessing the nitric oxide inhaled in preventing (off-label) PAHT episodes[1,2] are not taken into account. Another study[3] is not taken into account because its purpose was to compare the efficacy on central haemodynamic parameters of the milrinone + iNO combination with those of milrinone alone and of iNO alone. Milrinone, which is not a vasodilator but a positive inotropic agent, is not a relevant comparator. This comparison does not allow any assessment of the therapeutic added value of nitric oxide.

08.1 Efficacy

8.1.1 Available studies in adults

INOT-41 study
The aim of this study was to examine the effects of NO during the placement of a left-ventricular assist device (LVAD). The primary aim was to evaluate the usefulness of inhaled nitric oxide (iNO) in cases of acute right ventricular failure during the placement of an LVAD under extracorporeal circulation (ECC).

Methodology
Multicentre, double-blind, randomised, controlled study.
This study included patients scheduled for placement of an LVAD under ECC and presenting a pulmonary vascular resistance (PVR) ≥ 2.5 Wood units (200 dynes/sec) in the 30 days prior to the device placement. They were randomised to receive iNO 40 ppm or placebo (nitrogen).
Primary efficacy endpoint: number of patients meeting the circulatory failure criteria within a 48-hour timeframe during the course of treatment with the investigational gas. The failure criteria were defined as follows: having at least two of the following criteria for 15 minutes after complete stoppage of ECC:

- cardiac index ≤ 2.0 L/min/m^2;
- administration ≥ 20 inotropic equivalent (IE)[4];
- mean blood pressure (MAP) ≤ 55 mm Hg;
- central venous pressure (CVP) ≥ 16 mm Hg;
- percentage oxygen saturation in mixed venous blood (SvO_2) ≤ 55%;
- failure to wean off EEC at least once due to circulatory failure (not including restarting ECC to correct a bleed or other technical fault) or death.

Among the secondary endpoints: duration of mechanical ventilation.

Results:
The efficacy results were assessed in the 150 included patients (73 patients had received iNO and 77 placebo). The total number of patients meeting the failure criteria (n = 19/150, 12.7%) was small in both arms: 7 out of 73 patients (9.6%) in the iNO group versus 12 out of 77 (15.6%) in the placebo group. The difference between the two groups was not significant, p = 0.3301.
One of the secondary assessment parameters – the duration of mechanical ventilation expressed as mean time – was 2.0 days in the iNO group versus 3.0 days in the control group.

[1] Miller OI, Tang SF, Keech A., Pigott NB, Beller E, Celermajer DS. Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: a randomised double-blind study. Lancet 2000; 356(9240):1464-9.
[2] Stocker C, Penny DJ, Brizard CP, Cochrane AD, Soto R, Shekerdemian LS. Intravenous sildenafil and inhaled nitric oxide: a randomised trial in infants after cardiac surgery. Intensive Care Med 2003; 29:1996-2003.
[3] Cai J, Su Z, Shi Z, Zhou Y, Xu Z, Xu Z, et al. Nitric oxide and milrinone: combined effect on pulmonary circulation after Fontan-type procedure: a prospective, randomized study. Ann Thorac Surg 2008; 86:882-8.
[4] Possible inotropic agent: 10 µg/kg/min dopamine, dobutamine, enoximone or amrinone equivalent to 10 IE; 0.1 µg/kg/min epinephrine or norepinephrine equivalent to 10 IE; 1 µg/kg/min milrinone equivalent to 15 IE; 0.1 U/min vasopressin equivalent to 10 IE.

Conclusion: It has not been possible with this study to demonstrate any difference in circulatory failure between iNO and placebo in cases of acute right ventricular failure during LVAD placement under extracorporeal circulation. This study may have lacked power, given the small number of failures observed in both groups.

Summary of literature data presented with nitric oxide:
The studies in question evaluated the effect of various vasodilators (including nitric oxide) on the haemodynamic parameters (mean values) continuously recorded in patients undergoing or having just undergone heart surgery and having pulmonary arterial hypertension (PAHT). The methodology used in these studies (lack of any calculation of the number of subjects required to test for a difference between treatments evaluated on one or more endpoints after a predetermined period of time) does not allow a comparison to be made of the results for the parameters between the groups, which makes it impossible to determine the effect size.

Study by Fattouch et al.[5]
The aim of this study was to compare the haemodynamic efficacy of post-operative inhaled NO, inhaled prostacyclin and intravenous sodium nitroprusside (control group) in 58 patients with mitral valve stenosis and high PVR (> 250 dynes – sec/cm^5) after mitral valve surgery.

Methodology
Double-blind, randomised, controlled study.
Patients were randomly assigned to one of the following three groups:
- inhaled prostacyclin: 0.3 ml/min
- inhaled NO: 20 ppm
- intravenous nitroprusside: 2.5 to 25 ng/kg/min (control group).
Administration of these medicinal products started 5 minutes before the end of extracorporeal circulation and was continued in ICU.

Criteria evaluated:
- circulatory: mean pulmonary artery pressure (MPAP) and pulmonary vascular resistance (PVR). The data were collected at 6 different time-points, before anaesthesia, during and after surgery. The treatment duration was 30 minutes
- time to extubation and time spent under artificial ventilation.

Results:
In the two groups – iNO (21 patients) and prostacyclin (19 patients) – the MPAP and PVR decreased relative to their baseline values ($p < 0.05$) and the fall in the PAP was maintained throughout the study, which was not observed in the control group (18 patients).
In the iNO and prostacyclin groups, an increase in the cardiac indices and in the right ventricular ejection fraction was also noted with respect to the values on inclusion.
Patients under iNO or under prostacyclin were more readily weaned off extracorporeal circulation than those in the control group ($p < 0.04$) and were intubated on average for a shorter time and their stay in ICU was shorter than those in the control group:
- duration of intubation: 18 hours in the inhaled prostacyclin group and 20 hours in the inhaled NO group versus 31 hours in the control group, $p = 0.03$.
- stay in ICU: 10 days in the inhaled prostacyclin group and 9 days in the inhaled NO group versus 14 hours in the control group, $p = 0.02$.

Conclusion: The results presented do not permit any comparison of haemodynamic efficacy in adults between the three groups after mitral valve surgery. These data suggest that there has been an improvement in the management of patients receiving prostacyclin or inhaled nitric oxide (iNO) compared with those receiving nitroprusside. In addition, compared with the group receiving

[5] Fattouch K, Sbraga F, Sampognaro R, Bianco G, Gucciardo M, Lavalle C, et al. Treatment of pulmonary hypertension in patients undergoing cardiac surgery with cardiopulmonary bypass: a randomized, prospective, double-blind study. J Cardiovasc Med 2006;7:119-23.

nitroprusside, patients receiving inhaled NO or prostacyclin were able to be weaned off extracorporeal circulation more quickly, were intubated for a shorter time and spent less time in ICU. However, these results need to be interpreted with caution given the methodology used: lack of a primary endpoint, multiplicity of criteria assessed, constant repetition of measurements on the haemodynamic criteria and small patient numbers.

Study by Solina et al.[6]

The aim of the study was to compare the efficacy and adverse effects of inhaled nitric oxide (two possible dosages) with those of milrinone (IV) on the circulatory parameters at the end of extracorporeal circulation after heart surgery.

Methodology
Randomised controlled study.
Forty-five (45) adult patients undergoing heart surgery and with pulmonary arterial hypertension were randomised to receive milrinone IV (inotropic agent), 20 ppm or 40 ppm iNO. The randomised patients were distributed among the 3 groups before the operation:
- Those in the milrinone group (n = 15) received a bolus injection of milrinone (50 µg/kg) 15 minutes before the end of extracorporeal circulation. Milrinone was maintained at 0.5 µg/kg/min in the operating theatre and for the first 24 hours in ICU.
- Those in the NO group were randomised to receive either 20 ppm NO (n = 15) or 40 ppm NO (n = 15) at the end of extracorporeal circulation (restoration of pulmonary arterial circulation). Administration of NO was maintained for the first 24 hours in ICU.

Criteria evaluated: haemodynamic parameters evaluated 8 times in 24 hours, including: right ventricular ejection fraction, blood pressure, pulmonary vascular resistance (PVR), cardiac index, heart rate, systemic vascular resistance (SVR). The doses of vasopressor used in each of the three groups were recorded.

Results:
Mean bypass duration was 120 minutes. The treatments evaluated were administered over 24 hours.
No difference between the groups was observed in the following parameters: PVR, cardiac index, heart rate, SVR.
On arrival in ICU, the mean blood pressure was higher in the group receiving NO 20 ppm than in the other two groups. On the other hand, the right ventricular ejection fraction was higher in the iNO 40 ppm group (40%) than in the milrinone (30%) and iNO 20 ppm (33%) groups, $p < 0.05$. Moreover, patients in the milrinone group had to be given more phenylephrine (vasopressor) than those in the iNO groups (20 and 40 ppm alike) during their stay in ICU ($p < 0.05$).

Conclusion: In patients with pulmonary arterial hypertension after heart surgery, the administration by inhalation of 40 ppm NO was observed to have a more favourable effect on the right ventricular ejection fraction than the 20 ppm dose or milrinone. But the comparison to milrinone, an agent used mainly for its positive inotropic action, is of little relevance. Besides, in light of the methodology used, these results need to be interpreted with caution: open-label study, lack of any primary endpoint, multiplicity of criteria assessed, repetition of the measurements carried out and small patient numbers.

Study by Rajek et al.[7]

The aim of this study was to compare inhaled NO and prostaglandin E1 (PGE1) administered intravenously in terms of a reduction in PVR in adult patients undergoing heart transplantation.

[6] Solina A, Papp D, Ginsberg S, Krause T, Grubb W, Scholz P, et al. A comparison of inhaled nitric oxide and milrinone for the treatment of pulmonary hypertension in adult cardiac surgery patients. J Cardiothorac Vasc Anesth 2000;14:12-7.

[7] Rajek A, Pernerstorfer T, Kastner J, Mares P, Grabenwoger M, Sessler DI, et al. Inhaled nitric oxide reduces pulmonary vascular resistance more than prostaglandin E1 during heart transplantation. Anesth Analg 2000; 90:523-30.

Methodology
Randomised controlled study.
Sixty-eight (68) patients undergoing heart transplantation were included: 34 patients in the PGE1 group at a starting dose of 8 ng/kg/min, increasing in stages to 16 ng/kg/min, then to 24 ng/kg/min, and 34 in the iNO group, with the NO administered at a starting concentration of 4 ppm, increasing by stages to a maximum concentration of 24 ppm.

Criteria evaluated:
- among the haemodynamic criteria: PVR, MPAP and systemic vascular resistance
- stoppage of ECC.

Results
The treatment lasted 6 hours.

PVR and MPAP: No results are available for the comparisons between the two groups, knowing that the values were similar between the two treatment groups 6 hours after the end of surgery.
However, immediately after the end of extracorporeal circulation, a reduction of about 50% was observed in the PVR and about 30% in the MPAP in the iNO group, but there was no further variation in these two parameters until 6 hours after surgery. In the PGE1 group, the PVR decreased by about 10% and the MPAP by about 16% immediately after extracorporeal circulation was stopped. Moreover, the pulmonary vasodilation obtained in the iNO group was not accompanied by any fall in the systemic vascular resistance.

Stoppage of ECC: All patients in the iNO group were successfully weaned off ECC after 6 hours, whereas 6 patients in the PGE1 group could not be weaned off it due to a high PVR and right ventricular failure ($p = 0.03$). It is interesting to note that in seven of the patients in the iNO group, the attempted fast suspension of treatment resulted in an increased PVR and in a reduction in the mixed venous blood oxygen saturation and in the cardiac output. The iNO concentration was therefore subsequently gradually reduced over a maximum period of 48 hours.

Conclusion: These data suggest that stopping extracorporeal circulation is easier to achieve when the patients undergoing heart transplantation are receiving inhaled NO rather than intravenous prostacyclin. These results need to be interpreted with caution in light of the methodology used: open-label study, lack of a primary endpoint, multiplicity of criteria evaluated, repetition of the measurements carried out and small patient numbers.

Study by Schmid[8]
The aim of this study was to compare the haemodynamic effect of three vasodilators – inhaled NO, prostaglandin E1 (PGE1) or nitroglycerin (NTG) – administered to adult patients with severe PAHT after heart surgery.

Methodology
Randomised, controlled, crossover study.
The patients included had PAHT defined by values for PAP > 30 mm Hg and/or PVR > 300 dynes.sec/cm^{-5}. Successively they were given inhaled NO (40 ppm), intravenous prostaglandin E1 (PGE1: 0.1 µg/kg/min) and nitroglycerin (NTG: 3 to 5 µg/kg/min).

Criteria evaluated:
Evaluation of central haemodynamics (including PVR, mean PVR/SVR ratio, PAP, MAP, SVR, cardiac index, etc.) 15 to 20 min after administration of the vasodilator. A minimum of 20 min after stopping the vasodilator was required for the variables to return to baseline, these values being taken for reference prior to the administration of the next vasodilator.

[8] Schmid ER, Burki C, Engel MH, Schmidlin D, Tornic M, Seifert B. Inhaled nitric oxide versus intravenous vasodilators in severe pulmonary hypertension after cardiac surgery. Anesth Analg 1999; 89:1108-15.

Results:
This study included 14 adult patients.
The three vasodilators reduced the pulmonary vascular resistances (PVR) to a similar extent, p = 0.003.
However, it seems that systemic vasodilator effects were observed, especially in the PGE1 and NTG groups, while the vasodilator effect obtained with iNO may have been more selective, because the mean arterial pressure (MAP) and the systemic vascular resistances (SVR) showed little variation in this group and the mean PVR/SVR ratio decreased in the iNO group while remaining unchanged in the PGE1 and NTG groups.
The cardiac index increased in the iNO and PGE1, but in the NTG group.
The right ventricular ejection fraction increased only in the PGE1 group.

Conclusion: This study suggests that in adult patients with severe PAHT after heart surgery, administration of vasodilator (NO by inhalation, NTG or PGE1 by the intravenous route) helps reduce pulmonary vascular resistances. It seems that the vasodilator effect after administration of NO has little systemic effect. In light of the methodology used, these results need to be interpreted with caution: open-label study, lack of a primary endpoint, multiplicity of criteria evaluated, repetition of the measurements carried out and small patient numbers.

Study by Winterhalter et al.[9]
The aim of this study was to compare haemodynamic efficacy after administration by inhalation of two vasodilators (iloprost and NO) in cases of PAHT occurring during heart surgery following stoppage of extracorporeal circulation.

Methodology
Randomised, controlled study.
Included patients were due to undergo heart surgery and had a PAHT defined by PAP ≥ 26 mm Hg before the operation at rest, after induction of anaesthesia and at the end of extracorporeal circulation. They received iloprost 20 µg for 4 to 6 minutes (n = 23) or iNO 20 ppm (n = 23) immediately after extracorporeal circulation was stopped.

Among the criteria evaluated: pulmonary artery pressure (PAP) and pulmonary vascular resistances (PVR), cardiac output.

Results:
In this study, 46 patients were included. The two vasodilators caused a reduction in the PAP and PVR and an increase in cardiac output 30 minutes after administration. However, iloprost was more effective than iNO in reducing the PVR (p = 0.013) and MPAP (p = 0.0006) and further reduced the cardiac output (p = 0.002). This difference in favour of iloprost was also observed in the cardiac output 90 minutes after administration of the two vasodilators (p = 0.002).

Conclusion: This study suggests that in patients with PAHT after extracorporeal circulation has been stopped for heart surgery, iloprost and iNO administered by inhalation allow a reduction in the PVR and PAP and an increase in the cardiac output. This effect seems to have been greater under iloprost than under nitric oxide (NO). In light of the methodology used, these results need to be interpreted with caution: open-label study, lack of a primary endpoint, multiplicity of criteria evaluated, repetition of the measurements carried out and small patient numbers.

8.1.2 Available studies in children

Study conducted with INOMAX: **INOT 22 study**

[9] Winterhalter M, Simon A, Fischer S, Rahe-Meyer N, Chamtzidou N, Hecker H, et al. Comparison of inhaled iloprost and nitric oxide in patients with pulmonary hypertension during weaning from cardiopulmonary bypass in cardiac surgery: a prospective randomized trial. J Cardiothorac Vasc Anesth 2008; 22:406-13.

The aim of this study was to compare the number of patients with reversible (vasoreactive) PAHT according to whether they were receiving adjuvant therapy with O_2 alone, NO alone, or combined O_2 + inhaled NO. The results indicate that the NO + O_2 combination helped obtain a more powerful pulmonary vasodilation than oxygen alone or NO alone.
But evaluation of the reactivity of the pulmonary vascular system carried out during cardiac catheterisation in children with PAHT is not transferable to the situation of an episode of PAHT during or after heart surgery in the course of acute pulmonary vasodilator testing does not permit these results to be transferred during heart surgery. Only the safety results are presented for information purposes.

Summary of the literature data

Study by Goldman et al.[10]
The aim of this study was to compare the effects of two vasodilators (inhaled NO and prostacyclin IV) in cases of post-operative PAHT following heart surgery.

Methodology
Randomised, controlled, crossover study.
The included children (aged from 3 days to 12 months) with severe PAHT following heart surgery received 20 ppm NO for 10 minutes or prostacyclin IV (20 ng/kg/min) for 10 minutes, then vice versa.

Endpoints: haemodynamic parameters (including PAP, SBP).

Results:
The data for 13 children are available.
PAP showed a greater reduction in the iNO group [28.5 ± 2.9 mm Hg] than in the prostacyclin group [35.4 ± 2.1 mm Hg], $p < 0.05$. The MPAP/SBP ratio was reduced by more in the inhaled NO group (0.46 ± 0.04) than in the prostacyclin group (0.68 ± 0.05), $p < 0.01$.

Conclusion: In cases of PAHT episodes following heart surgery, administration of inhaled nitric oxide was more effective, and its effect was more selective as a vasodilator of pulmonary arteries, than prostacyclin IV. But in light of the methodology used, these results need to be interpreted with caution: open-label study, lack of a primary endpoint, multiplicity of criteria assessed and a small patient population.

Study by Day et al.[11]
The aim of this study was to determine whether inhaled NO reduces the incidence of attacks of pulmonary arterial hypertension in comparison with conventional treatment in children with congenital heart disease following corrective surgery or heart transplantation.

Methodology
Randomised, controlled study.
Children who had a systolic pulmonary artery pressure (sPAP) at least 50% higher than the systemic arterial systolic pressure immediately after surgery were randomised to receive either iNO 20 ppm (n = 20) or conventional treatment (n = 20) combining hyperventilation, oxygenation and alkalinisation (control group).

Endpoint: number of episodes of pulmonary hypertension (PAHT).

Results:

[10] Goldman AP, Delius RE, Deanfield JE, Macrae DJ. Nitric oxide is superior to prostacyclin for pulmonary hypertension after cardiac operations. Ann Thorac Surg 1995; 60:300-5.
[11] Day RW, Hawkins JA, McGough EC, Crezee KL, Orsmond GS. Randomized controlled study of inhaled nitric oxide after operation for congenital heart disease. Ann Thorac Surg 2000;69:1907-12.

The data for 38 children are available.
The number of PAHT episodes was three in the inhaled NO group and four in the control group, a non-significant difference.

Conclusion: Administration by inhalation of nitric oxide did not significantly reduce the occurrence of episodes of pulmonary arterial hypertension in comparison with conventional treatment in children following surgery for congenital heart disease. The study lacked power to be able to demonstrate a difference, given the small number of events that occurred and the small study population.

08.2 Adverse effects

8.2.1 Data from the available clinical studies

In adults:

- Study conducted with INOMAX (INOT 41): the safety results were assessed in 137 patients (of the 150 included). No difference was discernible as regards the incidence or severity of adverse effects between the iNO group and the placebo group.

Literature data:
- Rajek study: Cardiac output, heart rhythm, mean arterial pressure, right atrial pressure and pulmonary capillary pressure showed no difference between the groups. Seven (7) patients required prolonged suspension of iNO over 48 hours; two patients in the iNO group (and one patient in the PGE1 group) developed systemic infections and died in the first month.
- Schmid study: The median methaemoglobin levels rose from 0.64% to 1.06% in the iNO group, with a maximum methaemoglobin level of 1.55%. NO_2 levels of 2.4 ppm (95% CI [1.8-4.2]) were detected. In one patient, the peak NO_2 was 6.4 ppm.
- Winterhalter study: No major side effects were reported.

In children
- Study conducted with INOMAX (INOT 22): four patients had adverse effects. These adverse effects included bradycardia, low cardiac output syndrome, ST-segment elevation in the ECG, reduced O_2 saturation, pulmonary hypertension and hypotension. Two deaths were considered to be treatment-related. There were four non-fatal serious adverse effects. Treatment had to be stopped in two patients. Given the small patient numbers, it was not possible to determine whether there was any difference in the risk of serious side effects between the two groups.

Literature data:
- Miller Study: The overall mortality rate was 6.5% (8/124): surgical complications in the immediate post-operative period (one death); low cardiac output (two deaths) and sepsis (three deaths). Beyond 7 days, there were two deaths (one in each group) from suspected pneumothorax-related PAHT. During the study (< 8 days), 6% of the patients, five in the placebo group and two in the iNO group, needed rescue therapy with iNO due to a PAHT episode.
The methaemoglobin level remained below 3.4% and the NO_2 level below 2.1 ppm in all the children.
- Day study: Maximum methaemoglobin values increased slightly more in the iNO group (1.4% + 0.1%) than in the control group (1.1% + 0.1%, p = 0.023). There were no other iNO-related adverse events.
- Goldman study: There were four deaths. In one patient in the iNO group, a transient 8% increase was noted in the methaemoglobin level.

8.2.2 Data from the SPC

According to the SPC:
- INOMAX administration should not be discontinued abruptly as it may result in an increase in pulmonary artery pressure (PAP) and/or worsening of blood oxygenation (PaO2) due to a rebound effect. 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 transferred 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.

- Formation of methaemoglobin: A large portion of nitric oxide for inhalation is absorbed systemically. The end medicinal products of nitric oxide that enter the systemic circulation are predominantly methaemoglobin and nitrate. The concentrations of methaemoglobin in the blood should be monitored.

- Formation of NO_2: nitric oxide (NO_2) rapidly forms in gas mixtures containing nitric oxide and oxygen (O_2), which can cause an inflammatory reaction and airway damage. The dose of nitric oxide should be reduced if the NO_2 concentration exceeds 0.5 ppm.

- Effects on platelets: There has been no evidence of any increase in bleeding complications in randomised controlled trials in term and near-term neonates with hypoxic respiratory failure. Regular monitoring of haemostasis and measurement of bleeding time is recommended during the administration of INOMAX for more than 24 hours to patients with functional or quantitative platelet anomalies, a low coagulation factor or receiving anticoagulation treatment.

08.3 Summary & discussion

Clinical study results
The assessment of inhaled nitric oxide (iNO) – INOMAX – in episodes of pulmonary arterial hypertension during and after cardiac surgery is based on the results of two clinical studies, one in randomised adults versus placebo in double-blind mode (INOT 41) and the other in newborn babies (INOT 22 performed in the framework of a diagnostic test prior to heart surgery) and on literature data.

In adults, the incidence of failures during placement of a left-ventricular assist device with extracorporeal circulation and the mean duration of mechanical ventilation were no different under iNO or placebo. This study lacks power in view of the small number of failures observed in the two groups. These results suggest that their use should not therefore be considered except in combination with an inotropic agent or another vasodilator.
In children it is not possible on the basis of the data to come to any conclusion about the therapeutic value of iNO during or after heart surgery.

Controlled and randomised studies carried out in small patient populations suggest that iNO might be as effective as other vasodilators used off-label (nitroprusside IV, epoprostenol, inhaled iloprost, sildenafil IV) in reducing pulmonary artery pressure and pulmonary vascular resistances and thus improving tissue oxygenation and right ventricular function.

The two risks to take into account are that of rebound in cases of abrupt discontinuation of nitric oxide delivery and that of methaemoglobinaemia, which is rare but does need to be carefully monitored.

The available data, both in adults and in children, offer low levels of proof, and it is impossible on the basis of this data to draw any firm conclusions as regards any difference with respect to other vasodilators used (off-label) either as concerns the haemodynamic parameters or as concerns the morbidity and mortality in these clinical situations.

Principal areas of debate with regard to the data:

1) Methodology: The studies presented are methodologically of poor quality: very small patient populations, lack of a primary endpoint, multiplicity of evaluated criteria – non-clinical for the most part, no double-blind mode.

2) Transferability and data to be collected: The effect of inhaled nitric oxide in the treatment of episodes of PAHT is not well-established and its impact on morbidity and mortality associated with the occurrence of these episodes is not established in heart surgery, either in adults or in children.

09 THERAPEUTIC USE

INOMAX (nitric oxide) does have Marketing Authorisation and is widely used in adults and children in the treatment of episodes of PAHT during and after heart surgery to prevent episodes of right ventricular failure. In clinical trials, it was used perioperatively in conjunction with conventional therapies comprising inotropic and vasoactive medicines. It should be administered with close supervision of the haemodynamic status and blood oxygenation and it should only be used after conventional therapeutic resources have been optimised. Treatment duration is usually between 24 and 48 hours. Abrupt discontinuation of treatment should be avoided.

The clinical benefit of INOMAX compared with other vasodilators for reducing the occurrence and the complications associated with the onset of PAHT episodes during heart surgery[12] are not supported by studies with a high level of evidence. However, in the available studies, inhaled nitric oxide does have a favourable haemodynamic effect (reducing pulmonary pressures and pulmonary vascular resistances) in cases of PAHT in heart surgery, in adults as well as children. It improves heart function and can help facilitate stopping extracorporeal circulation and mechanical ventilation. It could also help reduce the intake of medicinal products with an inotropic effects.[13] Its vasodilator effect is perhaps more selective with regard to the pulmonary arteries, even bringing about a limited reduction in systemic blood pressure. Besides, its medical use is well established and is based in particular on European[14] and American[15] guidelines, which recommend nitric oxide for the treatment of episodes of PAHT and for preventing episodes of right ventricular failure during and after heart surgery, the appearance of which carries with it a worsening prognosis.

Other vasodilators are also used (cf. guidelines and expert consensus documents referred to above), off-label. They can have effects on the systemic circulation likely to compromise organ perfusion and oxygen distribution to the tissues.

[12] Griffiths M. J. D., Evans T. Drug therapy: inhaled nitric oxide therapy in adults. N Engl J Med 2005;353:2683-95.
[13] MacKnight B, Martinez EA, Simon BA. Anesthetic management of patients with pulmonary hypertension. Semin Cardiothorac Vasc Anesth 2008;12(2):91-6.
[14] Germann P, Braschi A, Della RG, Dinh-Xuan AT, Falke K, Frostell C, et al. Inhaled nitric oxide therapy in adults: European expert recommendations. Intensive Care Med 2005;31(8):1029-41.
[15] McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol 2009;53(17):1573-619.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

- *Heart surgery with extracorporeal circulation (ECC) can be complicated by an episode of PAHT during the immediate perioperative period.* Severe PAHT with a pulmonary artery pressure close or equal to the systemic arterial pressure is a serious complication of heart surgery. These PAHT episodes during and after heart surgery can thus significantly increase morbidity and mortality.
- *INOMAX is regarded as a preventive treatment for right heart failure and as a cure for acute post-operative PAHT episodes in heart surgery.*
- *INOMAX is a first-line treatment in conjunction with ventilatory support and other treatments for peri- and post-operative PAHT episodes in cardiac surgery.*
- Public health benefit:

  Although a PAHT episode occurring during or after heart surgery is a serious complication and is accompanied by considerable morbidity and mortality, the clinical situations in which its use is justifiable are rare. The public health burden is therefore small.

  In light of the available data, it is not expected that nitric oxide (INOMAX) will have any additional impact on morbidity and mortality in heart surgery. The impact on quality of life or on the organisation of care is not documented (it could however reduce the number of days spent in ICU).

  The transferability of the available data is not guaranteed, based on the clinical data currently available (small patient numbers, study methodology).

  In sum, it is not anticipated that nitric oxide (INOMAX) will offer any public health benefit in heart surgery either in adults or in children.
- *In heart surgery, inhaled nitric oxide has hitherto been used off-label.* The assessment of the efficacy/adverse effects ratio is based on clinical experience gained off-label and on several publications; it is high in adults and in children.
- *There is no medicinal alternative (whose use has been validated by a Marketing Authorisation) in this indication.*

Taking account of these points, the Committee considers that the actual benefit of INOMAX is substantial in this indication.

The Committee recommends inclusion on the list of medicines approved for hospital use in the indication "in conjunction with ventilatory support and other appropriate active substances for the treatment of peri- and post-operative pulmonary hypertension in conjunction with heart surgery in adults and children, including newborn infants, in order to selectively decrease pulmonary artery pressure and improve right ventricular function and tissue oxygenation" and at the dosages given in the Marketing Authorisation.

010.2 Improvement in actual benefit

The Committee considers that INOMAX 400 ppm mol/mol, inhalation gas, offers an improvement in actual benefit of level IV (minor IAB) in the treatment of peri- and post-operative PAHT in conjunction with heart surgery in adults and children, including newborn infants, in order to selectively decrease pulmonary artery pressure and improve right ventricular function and tissue oxygenation.

010.3 Target population

The target population for INOMAX 400 ppm mol/mol, inhalation gas, is defined by infants, children and adults having peri- and post-operative episodes of pulmonary arterial hypertension in heart surgery.

Estimate
In France, there are 500 to 550 heart surgery interventions per million inhabitants and per year,[16] i.e. between 33,000 and 36,000 interventions per year. Around 80% of the interventions are under extracorporeal circulation.

There are currently no data that will allow us to estimate the number of patients having PAHT episodes during heart surgery. Between 8000 and 10,000 patients/year could receive INOMAX for the treatment of an episode of pulmonary arterial hypertension during the course of heart surgery (expert opinion).

Conclusion: The target population for INOMAX is unquantifiable. According to the opinion of experts, 8000 to 10,000 patients/year could be involved.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging
Appropriate for the prescription conditions according to the indication, dosage and treatment duration.

[16] SROS IDF 2010, source Rapport Chir Card APHP