HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

04 December 2013

KINOX 225 ppm mol/mol, medicinal gas, compressed

5 l cylinder (CIP: 34009 572 212 3 2)
20 l cylinder (CIP: 34009 572 214 6 1)

KINOX 450 ppm mol/mol, medicinal gas, compressed

5 l cylinder (CIP: 34009 572 223 5 2)
20 l cylinder (CIP: 34009 572 224 1 3)

APPLICANT: AIR LIQUIDE SANTE FRANCE

INN	Nitric oxide
ATC code (2013)	R07AX01 (nitric oxide)
Reason for the review	**Extension of indication**
List concerned	**Hospital use** (French Public Health Code L.5123-2)
Indication concerned	**"KINOX is indicated for the treatment of perioperative and postoperative pulmonary hypertension in adults and newborn infants, infants, children and adolescents, aged 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**
Improvement in Actual Benefit	**The Committee finds that like INOMAX 400 ppm mol/mol, inhalation gas, KINOX 225 and 450 ppm mol/mol, medicinal gas, provides an improved actual benefit of level IV (minor IAB) in the treatment of perioperative and postoperative PH in heart surgery in adults and children, including newborn infants, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and tissue oxygenation.**
Therapeutic Use	**First-line treatment in conjunction with assisted ventilation and other appropriate treatments for treating PH in heart surgery.**
Recommendations	

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (national procedure)	Initial MA of 30 July 2004 in the treatment of newborn infants of gestational age ≥ 34 weeks, with hypoxic respiratory failure associated with clinical or echocardiographic signs of pulmonary hypertension: Corrective Marketing Authorisation of 05 November 2012 in the extension of indication in the treatment of perioperative and postoperative pulmonary hypertension in conjunction to heart surgery.
Prescribing and dispensing conditions / special status	List I Medicinal product reserved for hospital use.

ATC Classification	2004 R Respiratory system R07 Other respiratory system products R07A Other respiratory system products R07AX Other respiratory system products R07AX01 Nitric oxide

02 BACKGROUND

The opinion concerns an application for inclusion of the proprietary medicinal product KINOX (nitric oxide) on the list of medicines approved for hospital use in an extension of indication. Presently, KINOX has an MA in adults and children, in association with assisted ventilation and other appropriate treatments for treating pulmonary hypertension occurring during or after heart surgery.

As a reminder, KINOX (nitric oxide) also has an MA for treating newborn infants from gestational age >34 weeks with hypoxic respiratory failure associated with clinical or echocardiographic signs of pulmonary hypertension (substantial AB, KINOX shares the major IAB (level I) of INOMAX, Opinion of 16 March 2005).

03 THERAPEUTIC INDICATIONS

"KINOX is indicated:

- **for the treatment of perioperative and postoperative pulmonary hypertension in adults and newborn infants, infants, children and adolescents, aged 0-17 years in conjunction to heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and tissue oxygenation.**

- in association with assisted ventilation and other appropriate treatments in the treatment of newborn infants of gestational age ≥ 34 weeks, with with hypoxic respiratory failure associated with clinical or echocardiographic signs of pulmonary hypertension, in order to improve oxygenation and avoid extracorporeal membrane oxygenation (ECMO). "

04 DOSAGE

"Pulmonary hypertension in the context of heart surgery:

KINOX should only be used by prescription from an anaesthesiologist or intensive care specialist. KINOX should be used only after conventional treatments have been optimised. NO treatment may be initiated at any time point in the perioperative course to lower pulmonary vascular pressure.
In clinical trials, inhaled nitric oxide was used as an add on to the conventional treatments used in the perioperative course, comprising inotropic and vasoactive medicines. KINOX should be administered under close monitoring of patient haemodynamics, pulmonary pressure and blood oxygenation.
Treatment may be initiated at a dose of 20 ppm, which will then be lowered according to the clinical response to seek the lowest effective dose between 2 and 20 ppm. In adults, the dose may be increased up to 40 ppm if the lower dose has not provided sufficient clinical effects, but this dose should be decreased as soon as haemodynamic conditions and systemic arterial oxygenation permit it.
The effects of inhaled nitric oxide are rapid; decrease in pulmonary artery pressure and improved oxygenation are seen within 5-20 minutes of administration.
Treatment should not be continued if no beneficial physiological effects are apparent after 30 minutes.

Weaning:
Weaning from inhaled NO treatment should begin as soon as haemodynamic status is stabilised conjointly with respiratory assistance and inotropic treatment. Inhaled nitric oxide treatment should be discontinued gradually and incrementally with close monitoring of pulmonary arterial pressure. Administration will be gradually reduced to a dose of 1 ppm, which will be maintained for 30 minutes while monitoring pulmonary arterial pressure, before it is discontinued. Weaning should be attempted at least every 12 hours when the patient's clinical status is stable at a low KINOX dose. If weaning is too rapid, there is a risk of a sudden increase in pulmonary arterial pressure and destabilisation of the haemodynamic status (rebound effect). In the event of a rebound effect, KINOX should be administered once again at the initial dosage of 5 ppm and a new attempt at weaning will be considered after 12 to 24 hours.

Monitoring of treatment:
Nitrogen dioxide (NO_2) can form rapidly in gaseous mixtures containing nitric oxide and oxygen (O_2), which may cause an inflammatory reaction and airway lesions. The concentrations of nitric oxide and nitrogen dioxide inhaled must be measured continuously in the inspiratory circuit near to the patient using the appropriate certified equipment (medical device with CE marking). The concentration of NO_2 in the inhaled air must remain as low as possible. For the patient's safety, alert thresholds during treatment must be set: nitric oxide ± 2 ppm of dose to use, NO_2: 1 ppm. If the NO_2 concentration exceeds 1 ppm, the nitric oxide dose must be reduced immediately. Immediately prior to each treatment initiation, if the NO_2 concentration exceeds 0.5 ppm, the nitric oxide and/or $Fi0_2$ should be reduced as much as possible, after ruling out any administration system malfunction. With ventilators in sequential discontinuous flow mode, monitoring of spirometry helps detect a significant increase in the KINOX flow rate if any difference between the insufflated volume and the expired volume appears. "

05 THERAPEUTIC NEED

In heart surgery, the occurrence of pulmonary hypertension complicates patient care and is a marker for a poor prognosis in terms of morbidity and mortality. 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.

In subjects with high vascular resistance and elevated pulmonary artery pressure, NO induces pulmonary vasodilation with correction of PH. On the basis of this pharmacological effect, the use of inhaled NO (iNO) was first developed in the treatment of hypoxic respiratory failure associated with pulmonary hypertension in newborn infants. INOMAX (inhaled nitric oxide) also obtained a Marketing Authorisation for treatment of PH crises in heart surgery.
Vasodilators such as nitroglycerin or nitroprusside IV are also used off-label, but these can also affect systemic pressures. Treatment with a medicinal product having an inotropic effect, such as milrinone, can help improve right ventricular performance and thus promote pulmonary blood flow. However, the effects on the systemic circulation, which are frequent, could compromise organ perfusion and oxygen distribution.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

NAME (INN) *Company*	Indication	Date of opinion	AB	IAB (Wording)
INOMAX (nitric oxide) **Linde Healthcare**	indicated in association with assisted ventilation and other treatments for perioperative and postoperative 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. "	29/05/2013	Substantial	IAB IV (minor)

*pharmacotherapeutic category

06.2 Other health technologies

Cardiac resuscitation measures: hyperventilation, oxygenation, alkalinisation.

NB: In addition to cardiac resuscitation measures, management currently also calls for the off-label use of medicines for treating episodes of PH 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

INOMAX (nitric oxide) is a relevant comparator in this indication.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	REIMBURSEMENT	
	YES/NO If not, why not	Population(s) That of the Marketing Authorisation or restricted
Belgium	NO (not applicable)	
Spain	YES	
Portugal	YES	
Italy	YES	

08 ANALYSIS OF AVAILABLE DATA

The assessment of KINOX as a vasodilator in heart surgery relies on a study conducted in children. The efficacy of nitric oxide (iNO) was compared with that of placebo in prevention of postoperative PH. Although off-label, the results of this study will be presented for information purposes. No study was presented in adults in this indication for KINOX.
In addition, the company presented literature data. Only those where nitric oxide was evaluated in heart surgery and at the dosage recommended by the Marketing Authorisation will be considered. In these studies, the endpoints included haemodynamic measurements to assess the extent of the PH (elevation of central venous pressure and systolic, diastolic and mean pulmonary arterial pressure), vasoconstriction of the pulmonary vessels (increase in pulmonary vascular resistance), impact of this PH on cardiac function (decreased cardiac output or index) and systemic oxygenation (decreased venous oxygen saturation).

08.1 Efficacy

8.1.1 Study in children

Macrae study (ALS-1-97-P-301, 1999)
The primary aim of this study was to evaluate the relative reduction in pulmonary hypertension after preventive use of small concentrations of nitric oxide versus placebo (N_2) after corrective surgery for congenital heart malformations.

Study design
Placebo-controlled, randomised, double-blind, multicentre study. This study included patients at high risk of postoperative arterial hypertension following corrective surgery for left-to-right shunt lesions or obstruction of pulmonary venous drainage. The patients were randomised to receive 5 ppm of iNO or placebo (nitrogen) on arrival in the ICU and at most 30 minutes after surgery. The patients were evaluated after 30 minutes, 3 h, 6 h, 12 h, 24 h and then every 12 h, until the first appearance of a serious PH episode, requiring treatment, or until extubation (48 h or 4 days, depending on the type of surgical procedure).

Primary efficacy endpoint:
Percentage of patients without PH episode at 48 h.

The secondary endpoints include:
Duration of gas inhalation, duration of intubation and duration of stay in the ICU.

Results in the ITT population:
The results were evaluated in 219 patients included (106 patients received iNO and 113 placebo), with a mean age of 5 months.

Primary efficacy endpoint:
The percentage of patients alive at 48 h without a PH episode was no different between the two groups (87.7% in the iNO group versus 85.8% in the placebo group), p=0.7.

Secondary endpoints:
- The mean duration of inhalation was shorter in the placebo group (35.5±24.6 hours) than in the iNO group (45.1±28.6 hours, p<0.01).
- The mean duration of intubation was significantly shorter in the placebo group (4.3±4.1 days) than in the iNO group (5.1±4.8 days, p<0.03).
- The mean duration of stay in the ICU was significantly shorter in the placebo group (7.4±7.5 days) than in the iNO group (9.7±13.3 days, p<0.04).

Conclusion: this study did not show a difference in terms of efficacy between iNO and placebo in preventing postoperative PH crises after corrective surgery for congenital heart defects. Note that while the necessary number of subjects to include was calculated at 275 patients, only 219 could be included.

Literature data in children

The following Goldman et al.[1] and Day et al.[2] studies were already presented to the Transparency Committee during the assessment of INOMAX, another nitric oxide-based proprietary medicinal product with an MA for the same indication. As a reminder, the conclusions drawn from the following studies were:

- Goldman et al. study: this study aimed to compare the effects of two vasodilators (inhaled NO or IV prostacyclin) in postoperative PH after heart surgery. In cases of PH after heart surgery, the administration of inhaled nitric oxide was more effective and had a more selective effect as a pulmonary artery vasodilator than IV prostacyclin. However, these results should be interpreted with caution due to the methodology: open-label study, no primary efficacy endpoint, multiple endpoints evaluated and small number of subjects.
- Day et al. study: this study aimed to determine whether inhaled NO reduced the incidence of pulmonary hypertension crises compared with conventional treatment in children with congenital heart disease after a corrective surgical procedure or heart transplant. Inhaled administration of nitric oxide did not significantly reduce the occurrence of pulmonary hypertension crises compared with conventional treatment in children after a surgical procedure for a congenital heart defect. The study lacked power to prove a difference, given the small number of events that occurred and the small number of subjects.

NOTE

The Russell et al.[3] study was not considered due to the use of iNO at a dosage not validated by the Marketing Authorisation. The Miller et al.[4] and Stocker et al.[5] studies were not considered due to the use of iNO in an off-label indication. The Khazin et al.[6] and Cai et al.[7] studies were not considered due to the comparison of iNO with milrinone and the combination of milrinone + iNO. Milrinone is an agent used for its inotropic action; therefore this comparison is not very relevant. The Morris et al.[8] study results will not be commented on due to the small number of subjects.

8.1.2 Available adult studies (literature data)

The Fattouch et al.,[9] Solina et al.,[10] Rajek et al.,[11] Schmid et al.[12] and Winterhalter et al.[13] studies were also considered by the Committee during the assessment of INOMAX. As a reminder, the following conclusions were drawn from these studies:

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[1] 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.

[2] 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.

[3] Russell I.A. et al. The effects of inhaled nitric oxide on postoperative pulmonary hypertension in infants and children undergoing surgical repair of congenital heart disease. Anesth Analg. 1998;87:46-51.

[4] Miller O.I. et al. Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: a randomised double-blind study. Lancet.2000;356:1464-9.

[5] Stocker et al. Intravenous sildenafil and inhaled nitric oxide: a randomised trial in infants after cardiac surgery. Intensive Care Med. 2003;29:1996-2003.

[6] Khazin V *et al.* Milrinone and Nitric oxide: combined effect on pulmonary artery pressures after cardiopulmonary bypass in children. J of cardiothorac vascular Anesth. 2004;18:156-9.

[7] Cai J et al. Nitric oxide in conjunction with milrinone better stabilized pulmonary haemodynamics after Fontan procedure. Artificial Organs. 2008;32:864-869

[8] Morris K. et al. Comparison of hyperventilation and inhaled nitric oxide for pulmonary hypertension after repair of congenital heart disease. Crit Care Med.2000;28:2974-8.

[9] 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.

- Fattouch et al. study: this study aimed to compare the haemodynamic efficacy of postoperative use of inhaled NO, inhaled prostacyclins and IV sodium nitroprusside (control group) in 58 patients with mitral valve stenosis and high PVR (> 250 dynes s/cm5) after mitral valve surgery. The results do not permit comparing the haemodynamic efficacy among the three groups after mitral valve surgery. The data suggest an improvement in the treatment of patients receiving inhaled prostacyclin or nitric oxide (iNO) compared with those receiving nitroprusside. In addition, compared with the group receiving 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. Nevertheless, these results should be interpreted with caution due to the methodology: no primary efficacy endpoint, multiple endpoints evaluated, repetition of measurements on haemodynamic criteria and small number of subjects.
- Solina et al. study: the objective was to compare the efficacy and adverse effects of inhaled nitric oxide (two possible dosages) with those of milrinone (IV) on haemodynamic parameters at the end of extracorporeal circulation after heart surgery. In patients with pulmonary hypertension after heart surgery, a favourable effect of inhaled administration of 40 ppm of NO on the right ventricular ejection fraction was observed compared with those receiving 20 ppm of NO or milrinone. However, the comparison with milrinone, an agent used mainly for its positive inotropic action, is of little relevance. Furthermore, these results should be interpreted with caution due to the methodology: open-label study, no primary efficacy endpoint, multiple endpoints evaluated, repeated measurements and small number of subjects.
- Rajek et al. study: this study aimed to compare inhaled NO and prostaglandin E1 (PGE1 administered by IV) in terms of reducing PVR in adult patients undergoing heart transplant. The data suggest that extracorporeal circulation is more easily discontinued in patients receiving inhaled NO rather than IV prostaglandin E1 during heart transplant. These results should be interpreted with caution due to the methodology: open-label study, no primary efficacy endpoint, multiple endpoints evaluated, repeated measurements and small number of subjects.
- Schmid et al. study: 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 PH after heart surgery. This study suggests that in adult patients with severe PH after heart surgery, the administration of a vasodilator (inhaled NO or IV NTG or PGE1) reduced pulmonary vascular resistance. It seems that the vasodilator effect after administration of iNO has little systemic effect. These results should be interpreted with caution due to the methodology: open-label study, no primary efficacy endpoint, multiple endpoints evaluated, repeated measurements and small number of subjects.
- Winterhalter et al. study: the objective was to compare the haemodynamic efficacy after inhaled administration of two vasodilators (iloprost and NO) in PH occurring during heart surgery after discontinuing extracorporeal circulation. This study suggests that, in patients with PH after discontinuing extracorporeal circulation for heart surgery, inhaled iloprost and NO reduce PVR and PAP and increase cardiac output. This effect seems to have been greater with iloprost than with nitric oxide (NO). These results should be interpreted with caution due to the methodology: open-label study, no primary efficacy endpoint, multiple endpoints evaluated, repeated measurements and small number of subjects.

[10] 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.
[11] 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.
[12] 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.
[13] 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.

New study presented: **Khan et al. study**[14]
This is a comparative, randomised, crossover study. The efficacy of iNO was compared with that of prostacyclin (PGI2i) in patients with PH and/or right ventricular dysfunction and/or hypoxaemia during heart or lung transplant. The primary efficacy endpoint was mean pulmonary arterial pressure (PAP). The results are available in 25 out of 32 patients randomised. No difference was demonstrated on this endpoint between the two groups.

NOTE
The Radovancevic et al.[15] study was not considered due to the use of iNO at a dosage not validated by the Marketing Authorisation. The Kieler-Jensen[16] (N = 13) and Argenziano et al.[17] (N=11) study results will not be commented on due to the small number of subjects.

In conclusion, the available data for KINOX (and INOMAX) in adults and children suggest that iNO has an efficacy similar to other vasodilators used off-label (injected nitroprusside, epoprostenol, inhaled iloprost, injected sildenafil) to reduce pulmonary arterial pressure and pulmonary vascular resistance and therefore improve tissue oxygenation and right ventricle function; the data therefore do not demonstrate a difference relative to these vasodilators.

08.2 Adverse effects

8.2.1 Macrae study (ALS-1-97-P-301)

The safety results were evaluated in 219 patients. No difference was revealed between the iNO group and the placebo group relative to the incidence and severity of adverse events, haemodynamic parameters, blood gas and respiratory parameters. A total of 9 deaths (iNO group = 3 deaths, placebo group = 6 deaths) and 19 serious adverse events (iNO group = 9 SAE, placebo group = 10 SAE) were observed during the study period and the 30-day follow-up period. No link was established between the use of KINOX and the occurrence of these events according to the investigators.

8.2.2 Pharmacovigilance data

The company provided the latest periodic safety update report (PSUR) covering the period from 05/05/2008 to 04/05/2012.
According to this report, an additional notice was added:
- section 4.3 "Contraindications" of the SPC: "hypersensitivity to nitric oxide",
section 4.5 "Interaction with other medicinal products and other forms of interaction": "Available data suggest additive effects of inhaled nitric oxide and other vasodilators acting by the cGMP or cAMP systems (phosphodiesterase inhibitors, prostacyclin, PGI_2etc.), on pulmonary arterial pressure and right ventricular performance. Therefore, these products should be used with caution during treatment with inhaled nitric oxide. Moreover, a possible synergy between the platelet anti aggregation effects of KINOX and prostacyclin and its analogues is suggested by experimental data. "

[14] Khan T.A. et al. A prospective, randomized, crossover pilot study of inhaled nitric oxide versus inhaled prostacyclin in heart transplant and lung transplant recipients. J Thorac Cardiovasc Surg. 2009;138:1417-24.
[15] Radovancevic B et al. Nitric oxide versus prostaglandin E1 for reduction of pulmonary hypertension in heart transplant candidates. J Heart Lung Transplant. 2005;24:690-5.
[16] Kieler-Jensen N, Lundin S, Ricksten SE. Vasodilator therapy after heart transplantation: effects of inhaled nitric oxide and intravenous prostacyclin, prostaglandin E1, and sodium nitroprusside. J Heart Lung Transplant. 1995;14:436-43.
[17] Argenziano M et al. Randomized, double-blind trial of inhaled nitric oxide in LVAD recipients with pulmonary hypertension. Ann Thorac Surg. 1998;65:340-5.

8.2.3 SPC data

Blood and lymphatic system disorders

- Methaemoglobinaemia:

Newborn infants have a reduced activity of MetHb-reductase and are therefore exposed to a higher risk of developing methaemoglobinaemia. The appearance of methaemoglobinaemia > 5% has been observed despite the administration of appropriate concentrations of nitric oxide. The risk of methaemoglobinemia is increased in cases of G6PD and methaemoglobin reductase deficiency. The concentration of methaemoglobin in the blood should be monitored.

- Inhibition of platelet aggregation:

Bleeding time may be increased by inhibition of platelet aggregation. Regular monitoring of haemostasis and measurement of bleeding time is recommended during the administration of KINOX for more than 24 hours to patients with functional or quantitative platelet anomalies, a low coagulation factor or receiving anticoagulation treatment.

Cardiovascular disorders

- Rebound effect:

Rebound reactions such as intensified pulmonary vasoconstriction and hypoxaemia after sudden withdrawal of inhaled nitric oxide therapy have been described, precipitating cardiovascular collapse. Increasing FiO_2 and/or restarting treatment with inhaled nitric oxide should be considered. Weaning from inhaled nitric oxide should be done with caution.

Respiratory, thoracic and mediastinal disorders

- Inflammatory reaction and lesions of the respiratory system:

Nitrogen dioxide (NO_2) can form rapidly in gaseous mixtures containing nitric oxide and oxygen (O_2), which may cause an inflammatory reaction and airway lesions. Animal data suggest increased sensitivity to infection of the airways during exposure to small amounts of NO_2. The dose of nitric oxide administered should be reduced if the NO_2 concentration exceeds 0.5 ppm.

08.3 Summary & discussion

KINOX (inhaled nitric oxide, iNO) in the treatment of perioperative and postoperative pulmonary hypertension in heart surgery was evaluated in a randomised, placebo-controlled, double-blind clinical trial in children (Macrae) and on literature data.

In children, iNO (KINOX) was no different than placebo for the prevention of PH crises after heart defect surgery.

The literature data, in adults and children, do not change conclusions of the evaluation of KINOX (iNO) in the treatment of perioperative and postoperative PH crises in terms of safety and efficacy. As a reminder, it was concluded that:
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 consider are rebound if nitric oxide is suddenly discontinued, and methaemoglobinaemia, which is rare but must be subject to close monitoring.

Available data, both in adults and in children, are weak and do not demonstrate a difference relative to the other vasodilators used (off-label) both for haemodynamic parameters and for morbidity and mortality treating peri-and post-heart surgery PH episodes.

The main points for discussion of the data are the same as for the evaluation of INOMAX:

1) Methodology: the studies presented are of poor methodological quality, in particular: very small number of subjects, no primary efficacy endpoints, multiple non-clinical endpoints evaluated and, most often, lack of double blinding.

2) Transferability and data to be collected: the effect of inhaled nitric oxide to treat PH is poorly established and the impact on morbidity and mortality associated with PH episodes has not been established in heart surgery, in either adults or children.

09 THERAPEUTIC USE

Inhaled nitric oxide (KINOX) has Marketing Authorisation and is widely used in adults and children in the treatment of perioperative and postoperative PH in conjunction with heart surgery, to prevent 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 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 KINOX, like that of INOMAX, compared with other vasodilators to reduce the occurrence and complications related to PH episodes during heart surgery[18] is not supported by studies with a high level of evidence. However, in the available studies, inhaled nitric oxide had a favourable haemodynamic effect (reduced pulmonary pressure and pulmonary vascular resistance) in PH in heart surgery, both in adults and children. It improves heart function and can help facilitate discontinuing extracorporeal circulation and mechanical ventilation. It also permits reducing administration of medicines with inotropic effect.[19] Its vasodilator effect would be more selective with regard to the pulmonary arteries, bringing about in particular a limited reduction in systemic blood pressure. Further, its medical use is well established, particularly based on European[20] and American[21] recommendations that advocate nitric oxide to treat PH and prevent perioperative and postoperative right ventricular failure during heart surgery, the occurrence of which leads to a poorer prognosis.
Other vasodilators are also used (see recommendations 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.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

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

[18] Griffiths M. J. D., Evans T. Drug therapy: inhaled nitric oxide therapy in adults. N Engl J Med 2005; 353: 2683-95.
[19] MacKnight B, Martinez EA, Simon BA. Anesthetic management of patients with pulmonary hypertension. Semin Cardiothorac Vasc Anesth 2008;12(2):91-6.
[20] Germann P, Braschi A, Della RG, nh-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.
[21] 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.

010.1 Actual benefit

◗ Heart surgery with extracorporeal circulation can be complicated by a PH crisis in the immediate perioperative period. Severe PH with a pulmonary artery pressure close or equal to the systemic arterial pressure is a serious complication of heart surgery. These PH episodes during and after heart surgery can thus significantly increase morbidity and mortality.
◗ KINOX is a preventive therapy for right heart failure and a curative therapy for acute postoperative PH in heart surgery.
◗ KINOX is a first-line medicine, in combination with assisted ventilation and other treatments for perioperative and postoperative PH in heart surgery.

◗ Public health benefit

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

Given the available data, KINOX is not expected to have an additional impact on morbidity or 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 all, it is not expected that KINOX will benefit public health in heart surgery in adults and children.

◗ In heart surgery, inhaled nitric oxide has been used off-label to date. Evaluation of the efficacy/adverse effects ratio is based on clinical experience acquired during off-label use and several publications; it is substantial in adults and children.
◗ There is a treatment alternative: INOMAX, another medicine based on iNO.

Consequently, the Committee considers that the actual benefit of KINOX 225 and 450 mol/mol, medicinal gas, is substantial in this indication.

The Committee renders a favourable opinion for inclusion on the list of medicines approved for hospital use in the indication "in association with assisted ventilation and other appropriate treatments for perioperative and postoperative pulmonary hypertension in heart surgery in adults and children, including newborn infants, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and tissue oxygenation" and at the dosages in the Marketing Authorisation.

010.2 Improvement in actual benefit (IAB)

The Committee considers that like INOMAX 400 ppm mol/mol, inhalation gas, KINOX 225 and 450 ppm mol/mol, medicinal gas, provides an improved actual benefit of level IV (minor IAB) in the treatment of perioperative and postoperative PH in heart surgery in adults and children, including newborn infants, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and tissue oxygenation.

010.3 Target population

The target population for KINOX 225 and 450 ppm mol/mol, medicinal gas, is defined by newborn infants, children and adults with perioperative and postoperative pulmonary hypertension in heart surgery.

Estimate
In France, there are 500 to 550 heart surgeries per million inhabitants per year,[22] or between 33,000 and 36,000 procedures 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 PH episodes during heart surgery. Between 8000 and 10,000 patients/year may receive KINOX for treatment of a pulmonary hypertension episode during heart surgery (expert opinion).

Conclusion: the KINOX target population may not be quantified. According to expert opinion, 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.

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