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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

INOmax

Nitric Oxide

Procedure No.: EMEA/H/C/000337/A45/0019

CHMP assessment report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	INOmax
INN (or common name) of the active substance(s):	Nitric Oxide
MAH:	INO Therapeutics AB
Currently approved Indication(s)	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.
Pharmaco-therapeutic group (ATC Code):	Other respiratory system products R07 AX
Pharmaceutical form(s) and strength(s):	400 ppm mol/mol inhalation gas

I. INTRODUCTION

On 25 January 2008 the MAH submitted 7 completed paediatric studies for nitric oxide, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for INOmax and that there is no consequential regulatory action.

II. SCIENTIFIC DISCUSSION

II.1 Information on the pharmaceutical formulation used in the clinical study(ies)

Nitric oxide (NO) is the active component of endothelium-derived relaxing factor. Exogenous inhaled NO acts selectively on the pulmonary circulation. In smooth muscle cells, NO activates soluble guanylate cyclase to form cyclic GMP, which in turn promotes a calcium dependent relaxation. It has little systemic effect because of its short half-life caused by inactivation by binding to haemoglobin, rapid oxidation and the interaction with free radicals.

INOmax 400 ppm contains the active drug substance, nitric oxide, formulated as a series of dilutions in nitrogen. It is delivered to the patient via mechanical ventilation after dilution with an air/oxygen mixture using approved (CE-marked) ventilators and delivery devices.

The current indication is for the treatment, in conjunction with ventilatory support and other appropriate agents, 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. The maximum recommended dose is 20 ppm decreasing to 5 ppm within 4-24 hours provided arterial oxygenation is adequate at lower dose. The 20 ppm dose should not be exceeded. In the pivotal clinical trials, the starting dose was generally 20 ppm.

II.2 Clinical aspects

1. Introduction

The MAH submitted reports for the following studies:

-INOT 12 “Phase III open study of INO 346-404 using AW-ME01 in the treatment of neonates with hypoxic respiratory failure and associated pulmonary hypertension”

-Clark et al 2003 “Low-Dose nitric oxide therapy for persistent pulmonary hypertension:1-Year follow-up”

-NINOS Follow-up 2000 “Inhaled nitric oxide in term and near-term infants: neurodevelopmental follow up of the Neonatal Inhaled Nitric Oxide Study Group”

-Van Meurs 2005 “Inhaled nitric oxide for premature infants with severe respiratory failure”

-Ballard 2006 “Inhaled nitric oxide in preterm infants undergoing mechanical ventilation”

-Schreiber et al 2003 “Inhaled nitric oxide in premature infants with the respiratory distress syndrome”

-Kinsella et al 2006 “Early inhaled nitric oxide therapy in premature newborns with respiratory failure”

1. **Clinical study(ies)**

Studies in term or near term infants

INOT 12 “Phase III open study of INO 346-404 using AW-ME01 in the treatment of neonates with hypoxic respiratory failure and associated pulmonary hypertension”

- **Description**

This is a small 10 patient open study evaluating efficacy and safety for the use of INOmax in Japanese term or near term neonates with hypoxic respiratory failure and associated pulmonary hypertension.

- **Methods**

- Objective(s)

To assess the safety and efficacy of the study drug INO 346-404 in term or near-term Japanese newborns with hypoxemia and persistent pulmonary hypertension of the newborn and compare these responses to that reported previously in domestic and overseas trials amongst similar infants (CINRGI study, INOT 01/02 study, NINOS study and the Japanese Neonate NO Inhalation Therapy Research Group).

The performance characteristics of AW-ME01 NO delivery device in delivering constant, precise doses of the drug were evaluated.

- Study population /Sample size

10 evaluable patients enrolled, one non-evaluable patient enrolled

- Treatments

The study drug was administered in the following sequence:

1) Administration began by introduction of 20 ppm of INO 346-404 into the inspiratory limb of the respiratory path via AW-ME01. If the PaO2>60 mmHg or SpO2 >92% at least four hours after the start of administration, then the dose of INO 346-404 was lowered to 5 ppm.

2) The FiO2 was then lowered, as clinically indicated, while the INO 346-404 was maintained at 5 ppm until the PaO2>70 mmHg with the FiO2 between 0.4 and 0.6.

3) When the subject was confirmed to be clinically stable, INO 346-404 administration was gradually decreased and then terminated. At the discretion of the treating physician, the FiO2 could be raised by 0.1 prior to ending the study gas.

Patients were maintained on INO 346-404 until their FiO2 ≤0.5 ± 0.1 with a PaO2 >70 mmHg at which time the treatment gas was incrementally decreased. Before discontinuation of study gas, the FiO2 could be increased by 0.1 for 1 hour.

- Outcomes/endpoints

Efficacy:

Primary endpoints:
1) Changes from baseline in the oxygenation index (OI) at 30 minutes and 24 hours after the start of INO 346-404

2) Study device evaluation of the comparison of set NO concentration and the actual delivered NO concentration as well as the amount of NO2 delivered to the patient

Secondary endpoints:
1) Changes from baseline in the arterial to alveolar partial pressure of oxygen (a/A) ratio at 30 minutes and 24 hours after the start of INO 346-404

2) Changes from baseline in the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO2/FiO2) at 30 minutes and 24 hours after the start of INO 346-404

Safety:
1) Blood methemoglobin levels
2) Delivered NO2 concentration
3) Mortality rate
4) Adverse events

- **Results**

Efficacy

Eleven patients were enrolled, one of whom had an undiagnosed congenital heart defect and was subsequently dropped from the analysis of the trial. Patients were all ≥34 week gestation infants with normal birth weights. They had very severe hypoxemic respiratory failure as demonstrated by the mean oxygenation index (OI) of 35.5 cm H2O/ mmHg.

Initiation of INO 346-404 therapy lead to a rapid, statistically significant (p = 0.002) drop in the OI by 30 minutes after initiating therapy that was sustained through 24 hours (p-value = 0.004). The OI fell by over 21 cm H2O/ mmHg in the first half-hour and fell over 29 cm H2O/mmHg by 24 hours, falls that changed the classification of the infant from “critical” to “mild” respiratory failure. A similar, dramatic improvement was seen in the secondary endpoints of oxygenation, the a/A and PaO2/FiO2 ratios.

Compared to previous overseas and domestic trials of inhaled nitric oxide in comparable patients, the current patients had similar drops in oxygenation index but larger improvements in their a/A and PaO2/FiO2 ratios.

The AW-ME01 delivery system accurately and constantly delivered the precise dose of INO 346-404 selected by the treating physician and this was not associated with clinically concerning levels of nitrogen dioxide.

Safety

This therapy was associated with no episodes of methemoglobinemia (all value were <2%) nor with elevated nitrogen dioxide levels (all values were <0.5 ppm). All reported adverse events were expected among these critically ill infants and in no case were they assessed by the treating physician as being related to the therapy itself. Monitoring of renal and liver function tested showed no evidence of any deleterious impact that INO 346-404 had on the kidneys or liver. Similarly, there were no apparent detrimental effects on any of the measured hematologic assessments.

Assessor's comments
This study in Japanese term or near term neonates with hypoxic respiratory failure showed similar effects to those seen in previous trials in similar populations from Europe and USA. There was a significant improvement in oxygenation with no new safety signals identified.

Clark et al 2003 "Low-Dose nitric oxide therapy for persistent pulmonary hypertension: 1-Year follow-up"

- **Description**

The results on the in-hospital outcomes of 248 neonates who were >34 weeks' gestational age and were randomised to receive low-dose inhaled nitric oxide or placebo have been previously reported. Extracorporeal membrane oxygenation was used in 78 (64%) neonates in the control group and in 48 (38%) neonates in the inhaled nitric oxide group (p=0.001). This is now the 1-year follow up study.

- **Methods**

  - Objectives

The purpose of this study was to report on the 1 year outcome of neonates treated with inhaled nitric oxide compared to a group of neonates who did not receive nitric oxide.

  - Study population /Sample size

248 neonates born after more than 34 weeks' gestation were studied, who were 4 days old or less, required assisted ventilation, and had an oxygenation index of ≥25. These neonates were required to have clinical or echocardiographic evidence of pulmonary hypertension without structural heart disease. Neonates were not eligible for the study if extracorporeal membrane oxygenation was urgently needed for refractory hypotension (mean blood pressure <35 Torr) or profound hypoxemia (partial pressure of arterial oxygen <30 Torr); or if they had a lethal congenital anomaly, significant bleeding diathesis, active seizures, or a history of severe asphyxia.

- **Results**

Of the 248 neonates twenty-four (10%) died before 1 year of age. There was no difference in mortality between the two groups (11% in the control group and 9% in the inhaled nitric oxide group). Of the 224 surviving infants, the parents or guardians of 201 (90%) children were contacted. There were no intergroup differences in the numbers of patients reported as requiring medications for pulmonary disease (14% in the control group and 14% in the inhaled nitric oxide group) or the need for supplemental oxygen (1% in the control group and 0% in the inhaled nitric oxide group). The number of neonates reported to have an abnormal neurological examination or developmental delay was also similar in both groups (14% in the control group and 19% in the inhaled nitric oxide group).

Assessor's comments
This study showed that the use of nitric oxide in term and near term infants with hypoxic respiratory failure that was shown previously to reduce the need for ECMO was not associated with an increase of adverse outcomes at 1 year.

NINOS Follow-up 2000 "Inhaled nitric oxide in term and near-term infants: neurodevelopmental follow up of the Neonatal Inhaled Nitric Oxide Study Group"

- **Description**

In this study patients of the original NINOS study were followed up for 2 years. Neurodevelopmental assessments were conducted at 18 months and 24 months of age.

- **Methods**

  - Objectives

The purpose of this study was to report on the 2 year neurodevelopmental outcome of term or near term neonates treated with inhaled nitric oxide (the original study was part of the dossier for the initial application for marketing authorisation for INOmax).

- **Results**

A total of 235 infants were enrolled in the original trial. There were 36 deaths, 20 of 121 infants in the control group and 16 of 114 infants in the INO-treated group. Of the 199 surviving infants, 173 (86.9%) were seen for follow-up (88 members of the control group and 85 members of the INO-treated group), and 135 infants were normal (69 [79.3%] members of the control group and 66 [77.6%] members of the INO-treated group).

Twenty-two infants had sensorineural hearing loss (12 members of the control group and 10 members of the INO-treated group). Moderate to severe cerebral palsy occurred in 13 infants (7 infants in the control group and 6 infants in the INO-treated group). Mental developmental index scores (87 ± 18.7 in the control group vs 85 ± 21.7 in the INO-treated group) and psychomotor developmental index scores (93.6 ± 17.5 in the control group vs 85.7 ± 21.2 in the INO-treated group) were not different. A total of 29.6% of the control group compared with 34.5% of the INO-treated group had at least one disability. Infants with congenital diaphragmatic hernia, enrolled in a separate but parallel trial, had similar outcomes with a higher incidence of sensorineural hearing loss.

Assessor's comments
This study showed that the use of nitric oxide in term and near term infants with hypoxic respiratory failure was not associated with an increase in neurodevelopmental, behavioural, or medical abnormalities at 2 years of age.

Studies in premature infants

Van Meurs 2005 "Inhaled nitric oxide for premature infants with severe respiratory failure"

- **Description**

This was a multicenter, randomized, blinded, controlled trial to determine whether inhaled nitric oxide reduced the rate of death or bronchopulmonary dysplasia in premature infants with severe respiratory failure.

- **Methods**

420 neonates, born at less than 34 weeks of gestation, with a birth weight of 401 to 1500 g, and with respiratory failure more than four hours after treatment with surfactant were randomly assigned to receive placebo (simulated flow) or inhaled nitric oxide (5 to 10 ppm). Infants with a response (an increase in the partial pressure of arterial oxygen of more than 10 mm Hg) were weaned according to protocol. Treatment with study gas was discontinued in infants who did not have a response.

- **Primary and secondary hypotheses**

The primary hypothesis was that administration of inhaled nitric oxide to neonates at less than 34 weeks of gestation, with a birth weight of 401 to 1500 g, and with severe respiratory failure would reduce the incidence of bronchopulmonary dysplasia or death (defined as death before discharge to home or within 365 days among hospitalized infants).

The secondary hypotheses were that inhaled nitric oxide would not increase the incidence of grade 3 or 4 intraventricular hemorrhage or periventricular leukomalacia, and that it would decrease the number of days of assisted ventilation and oxygen use, the length of hospitalization, and the incidence of threshold retinopathy of prematurity.

- **Results**

The rate of death or bronchopulmonary dysplasia was 80 percent in the nitric oxide group, as compared with 82 percent in the placebo group (relative risk, 0.97; 95 percent confidence interval, 0.86 to 1.06; P=0.52), and the rate of bronchopulmonary dysplasia was 60 percent versus 68 percent (relative risk, 0.90; 95 percent confidence interval, 0.75 to 1.08; P=0.26).

There were no significant differences in the rates of severe intracranial hemorrhage or periventricular leukomalacia. Post hoc analyses suggest that rates of death and bronchopulmonary dysplasia are reduced for infants with a birth weight greater than 1000 g, whereas infants weighing 1000 g or less who are treated with inhaled nitric oxide have higher mortality and increased rates of severe intracranial hemorrhage.

Assessor's comments
This study showed that the use of nitric oxide in premature infants with respiratory failure did not decrease the rates of death or bronchopulmonary dysplasia.

Ballard 2006 "Inhaled nitric oxide in preterm infants undergoing mechanical ventilation"

- **Description**

This was a multicenter, randomized, blinded, placebo-controlled trial of inhaled nitric oxide at 21 centers involving infants with a birth weight of 1250 g or less who required ventilatory support between 7 and 21 days of age.

- **Methods**

The trial was conducted at 21 infant intensive care units. Infants were randomised to either nitric oxide or placebo and initially received 20 ppm of study gas for 48 to 96 hours, and the doses were subsequently decreased to doses of 10, 5, and 2 ppm at weekly intervals, with a minimum treatment duration of 24 days.

- **Primary and secondary hypotheses**

The primary hypothesis was that administration of inhaled nitric oxide to infants would increase survival without bronchopulmonary dysplasia at 36 weeks of postmenstrual age (primary outcome).

Secondary outcomes included the duration of oxygen therapy and the duration of hospitalisation. In addition, the need for hospitalisation and respiratory support, including mechanical ventilation, continuous positive airway pressure, and oxygen supplementation at 40, 44, 52, and 60 weeks of postmenstrual age was prospectively evaluated.

- **Results**

Among 294 infants receiving nitric oxide and 288 receiving placebo birth weight (766 g and 759 g, respectively), gestational age (26 weeks in both groups), and other characteristics were similar.

The rate of survival without bronchopulmonary dysplasia at 36 weeks of postmenstrual age was 43.9 percent in the group receiving nitric oxide and 36.8 percent in the placebo group (P = 0.042). The infants who received inhaled nitric oxide were discharged sooner (P = 0.04) and received supplemental oxygen therapy for a shorter time (P = 0.006).

There were no short-term safety concerns.

Assessor's comments
In this study the authors concluded that prolonged inhaled nitric oxide therapy that is initiated between 7 and 21 days of age in preterm infants undergoing mechanical ventilation significantly improved survival without BPD without short-term effects.

This is in contrast with what is seen in other trials involving premature infants, were differences in survival rates or survival without BPD were not seen.

Schreiber et al 2003 "Inhaled nitric oxide in premature infants with the respiratory distress syndrome"

- **Description**

This was a randomized, double-blind, placebo-controlled trial of inhaled nitric oxide during the first week of life on the incidence of chronic lung disease and death in premature infants who were undergoing mechanical ventilation for respiratory distress syndrome.

- **Methods**

Infants were randomly assigned to receive inhaled nitric oxide (10 ppm on day 1, followed by 5 ppm for six days) or inhaled oxygen placebo for seven days. The infants were further randomly assigned in each group to receive intermittent mandatory or high-frequency oscillatory ventilation.

- **Primary hypothesis**

The primary hypothesis was that inhaled nitric oxide would decrease the incidence of chronic lung disease and death among premature infants who were undergoing mechanical ventilation. The primary outcome measure was defined as death or chronic lung disease (among surviving infants).

- **Results**

A total of 207 premature infants were enrolled. In the group given inhaled nitric oxide, 51 infants (48.6 percent) died or had chronic lung disease, as compared with 65 infants (63.7 percent) in the placebo group (relative risk, 0.76; 95 percent confidence interval, 0.60 to 0.97; P=0.03). There was no significant difference between the nitric oxide and placebo groups in the overall incidence of intraventricular hemorrhage and periventricular leukomalacia (33.3 percent and 38.2 percent, respectively), but the group given inhaled nitric oxide had a lower incidence of severe intraventricular hemorrhage and periventricular leukomalacia (12.4 percent vs. 23.5 percent; relative risk, 0.53; 95 percent confidence interval, 0.28 to 0.98; P=0.04). The type of ventilation had no significant effect on the outcome.

Assessor's comments
In this study inhaled nitric oxide treatment was initiated during the first week of life. The authors concluded that use of inhaled nitric oxide in premature infants with respiratory distress syndrome decreases the incidence of chronic lung disease and death

This is in contrast with what is seen in other trials involving premature infants, were differences in survival rates or survival without BPD were not seen.

Kinsella et al 2006 "Early inhaled nitric oxide therapy in premature newborns with respiratory failure"

- **Description**

This was a study on the safety and efficacy of early, low-dose, prolonged therapy with inhaled nitric oxide in premature infants with respiratory failure.

- **Methods**

This was a multicenter, randomized trial involving 793 newborns who were 34 weeks of gestational age or less and had respiratory failure requiring mechanical ventilation. Newborns were randomly assigned to receive either inhaled nitric oxide (5 ppm) or placebo gas for 21 days or until extubation, with stratification according to birth weight (500 to 749 g, 750 to 999 g, or 1000 to 1250 g).

- **Primary and secondary outcomes**

The primary efficacy outcome was a composite of death or bronchopulmonary dysplasia at 36 weeks of postmenstrual age. Secondary safety outcomes included severe intracranial hemorrhage, periventricular leukomalacia, and ventriculomegaly.

- **Results**

Overall, there was no significant difference in the incidence of death or bronchopulmonary dysplasia between patients receiving inhaled nitric oxide and those receiving placebo (71.6 percent vs. 75.3 percent, P = 0.24). However, for infants with a birth weight between 1000 and 1250 g, as compared with placebo, inhaled nitric oxide therapy reduced the incidence of bronchopulmonary dysplasia (29.8 percent vs. 59.6 percent); for the cohort overall, such treatment reduced the combined end point of intracranial hemorrhage, periventricular leukomalacia, or ventriculomegaly (17.5 percent vs. 23.9 percent, P = 0.03) and of periventricular leukomalacia alone (5.2 percent vs. 9.0 percent, P = 0.048). Inhaled nitric oxide therapy did not increase the incidence of pulmonary hemorrhage or other adverse events.
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Assessor's comments
In this study inhaled nitric oxide treatment was continued for 21 days or until the infants were extubated. The authors concluded that among premature newborns with respiratory failure, low-dose inhaled nitric oxide did not reduce the overall incidence of bronchopulmonary dysplasia, except among infants with a birth weight of at least 1000 g, but it did reduce the overall risk of brain injury. Some benefit was seen in the larger infants weighing more than 1000 g.

2. Discussion on clinical aspects

The first study (INOT 12) in Japanese term or near term neonates with hypoxic respiratory failure showed similar effects to those seed in previous trials in similar populations from Europe and USA. There was a significant improvement in oxygenation with no new safety signals identified.

Follow up studies
The studies by Clark et al and the follow up NINOS study followed the development of children who were treated in the neonatal period for hypoxic respiratory failure with nitric oxide at 1 year and 2 years of age respectively. These studies showed no adverse outcome in terms of medical or neurodevelopmental outcomes.

Premature infant studies
A number of published studies were submitted. Although there were methodological differences in the trials, all were conducted in premature neonates with respiratory distress syndrome.

The studies by Ballard et al and Schreiber et al showed improvement in bronchopulmonary dysplasia. The study by Kinsella et al showed no reduction in the overall incidence of bronchopulmonary dysplasia apart from infants with birth rate of at least 1000 g. As far as brain injury was concerned, the study by Shreiber showed no difference overall but lower incidence in severe brain injury in babies treated with nitric oxide. The study by Kinsella et al showed reduction of the overall risk of brain injury.

Due to these conflicting results, there is no indication from the data submitted at present that premature infants with respiratory distress syndrome would benefit from treatment with nitric oxide.

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The study in Japanese term or near term infants with hypoxic respiratory failure, supports what is already known, that treatment with nitric oxide is beneficial in this group of patients.

However, the evidence of efficacy and safety in the premature infant population is conflicting at present, therefore an indication for treatment of premature infants with respiratory distress syndrome cannot be supported.

- **Recommendation**

☒ **Fulfilled –**

No further action required

IV. ADDITIONAL CLARIFICATIONS REQUESTED

Not applicable