Public Assessment Report

Decentralised Procedure

Neophyr 225 ppm mol/mol Medicinal Gas, Compressed
Neophyr 450 ppm mol/mol Medicinal Gas, Compressed
Neophyr 1000 ppm mol/mol Medicinal Gas, Compressed

UK licence no: PL 35326/0001-3
UK/H/3968/001-3/E01

Applicant: SOL SPA
LAY SUMMARY

On the 11 January 2012, Austria, Belgium, Germany, Italy, Luxemburg, the Netherlands and the UK granted SOL SpA Marketing Authorisations (licences) for the medicinal products Neophyr 225 ppm mol/mol, 450 ppm mol/mol and 1000 ppm mol/mol medicinal gas, compressed (UK/H/3968/001-3/DC). These are prescription-only medicines.

Neophyr is a medicinal gas, compressed, consisting of a mixture of gases that contains 225 ppm, 450 ppm or 1000 ppm mol/mol of nitric oxide.

Neophyr must be administered exclusively by healthcare professionals and it is only for strict hospital use. Neophyr is indicated in the following conditions:

- Newborn babies with lung failure associated with high blood pressure in the lungs, a condition known as hypoxic respiratory failure. When inhaled, this gas mixture can improve the flow of blood through the lungs, which may help to increase the amount of oxygen that reaches the baby’s blood
- Newborn babies, babies, children, teenagers 0-17 years and adults with high blood pressure in the lungs, connected with heart surgery. This gas mixture can improve heart function and increase the flow of blood through the lungs.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of using Neophyr 225 ppm mol/mol, 450 ppm mol/mol and 1000 ppm mol/mol medicinal gas, compressed outweigh the risks.

After a national phase, licences were granted in the UK on 16 February 2012. This was followed by a repeat-use procedure (UK/H/3968/001-3/E01) in Bulgaria, Ireland and Romania, which concluded successfully on 23 January 2013.
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Module 1

Information about initial procedure

| Product Name | Neophyr 225 ppm mol/mol medicinal gas, compressed  
|             | Neophyr 450 ppm mol/mol medicinal gas, compressed  
|             | Neophyr 1000 ppm mol/mol medicinal gas, compressed |
| Type of Application | Bibliographic (well-established use), Article 10a |
| Active Substance | Nitric oxide |
| Form | Medicinal gas, compressed |
| Strength | Nitric oxide 225ppm mol/mol  
|           | Nitric oxide 450ppm mol/mol  
|           | Nitric oxide 1000ppm mol/mol |
| MA Holder | SOL SpA  
|           | Via Borgazzi 27 – 20900 Monza  
|           | ITALY |
| Reference Member State (RMS) | UK |
| Concerned Member States (CMS) | UK/H/3968/001-3/DC: Austria, Belgium, Germany, Italy, Luxembourg and The Netherlands  
|           | UK/H/3968/001-3/E01: Bulgaria, Ireland, Romania |
| Procedure Numbers | UK/H/3968/001-3/DC  
|                   | UK/H/3968/001-3/E01 |
| End of Procedure | UK/H/3968/001-3/DC (Day 210): 11 January 2012  
|                   | UK/H/3968/001-3/E01 (Day 90): 23 January 2013 |
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling

Neophyr
225 ppm mol/mol
Medicinal gas, compressed
Nitric oxide

A 15-litre gas cylinder filled to 150 bar supplies 1500 l of gas at a pressure of 1 bar at 15°C
A 18-litre gas cylinder filled to 150 bar contains about 1.7 kg of gas
Keep out of the reach and sight of children
Reserved for Medicinal Use

Neophyr 225 ppm mol/mol contains nitric oxide
225 ppm mol/mol In nitrogen. Also contains nitrogen.

For inhalation use
Read the package leaflet before use.
Childhood: The dosage of 20 ppm should never be exceeded. Therefore, the gas content of this cylinder must be diluted at least 11.25 times.
Adults: The dosage of 40 ppm should never be exceeded. Therefore, the gas content of this cylinder must be diluted at least 5.63 times.

For hospital use only
Marketing Authorisation Number PL36225/0003
Marketing Authorisation Holder
SOL SpA
Via Enrico in 27
23800 Monza (Italy)

Special storage conditions
All regulations concerning handling of compressed cylinders must be followed. Storage is supervised by specialists at the hospital.
Cylinders are to be stored in well-ventilated rooms or in ventilated sheds where they are protected from rain and direct sunlight. The cylinders must be stored at a temperature between -10 and +50°C.
Protect the cylinders from shocks, falls, oiling and flammable materials, moisture, sources of heat or ignition.

Storage in the pharmacy department
The gas cylinders should be kept in a site designated exclusively for medicinal gas storage that is well ventilated, clean and under lock and key. This place should house a separate, special facility for the storage of nitric oxide gas cylinders.

Storage in medical department
The cylinder should be placed in an area with appropriate equipment to ensure that the cylinder is held vertically.
When the gas cylinder is empty, do not dispose of it. Empty gas cylinders will be collected by the supplier.
Neophyr 450 ppm mol/mol contains nitric oxide.
450 ppm mol/mol in nitrogen. Also contains nitrogen.

For inhalation use:
Read the package leaflet before use.
Children: The dosage of 20 ppm should never be exceeded. Therefore, the gas content of this cylinder must be diluted at least 25.5 times.
Adults: The dosage of 30 ppm should never be exceeded. Therefore, the gas content of this cylinder must be diluted at least 15.25 times.

For hospital use only;
Marketing Authorisation Number PL35230/2002
Marketing Authorisation Holder
SOL Spa
via Borgata 27
20052 Monza (Italy)

Special storage conditions:
All regulations concerning handling of pressurised cylinders must be followed. Storage is supervised by specialists at the hospital.
Cylinders are to be stored in well-ventilated rooms or in ventilated sheds where they are protected from rain and direct sunlight. The cylinders must be stored at a temperature between -10 and +50°C.
Protect the cylinders from shocks, falls, oxidizing and flammable materials, moisture, sources of heat or ignition.

Storage in the pharmacy department:
The gas cylinders should be kept in a place designated exclusively for medicinal gas storage that is well-ventilated, clean and under lock and key. This place should house a separate, special facility for the storage of nitric oxide gas cylinders.

Storage in medical department:
The cylinder should be placed in an area with appropriate equipment to ensure that the cylinder is held vertically. When the gas cylinder is empty, do not dispose of it. Empty gas cylinders will be collected by the supplier.

Keep out of the reach and sight of children.
Reserved for Medicinal Use.

DCPAR_Neophyr 225, 450 & 1000 ppm mol/mol medical gas compressed
UK/H/3968/001-3/E01
Neophyr 1000 ppm mol/mol

Medicinal gas, compressed
Nitric oxide

A 10-liter gas cylinder filled to 160 bar supplies
1000 l of gas at a pressure of 1 bar at 15°C
A 10-liter gas cylinder filled to 160 bar contains
about 1.77 kg of gas

Keep out of the reach and sight of children
Reserved for Medicinal Use

Neophyr 1000 ppm mol/mol contains nitric oxide.
1000 ppm mol/mol is nitrogen.
Also contains nitrogen.

For inhalation use
Read the package leaflet before use.
Children: The dosage of 20 ppm should never be exceeded. Therefore, the gaseous content of this
cylinder must be diluted at least 50 times.
Adults: The dosage of 40 ppm should never be exceeded. Therefore, the gaseous content of this
cylinder must be diluted at least 25 times.

For hospital use only
Marketing Authorisation
Number PL35326/0001
Marketing Authorisation Holder
SOL Spa
Via Colombo 27
20060 Monza (Italy)

Special storage conditions
All regulations concerning handling of pressurised cylinders must be followed. Storage is supervised by
specialists at the hospital.
Cylinders are to be stored in well-ventilated rooms or in ventilated shelves where they are protected from rain
and direct sunlight. The cylinders must be stored at a temperature between -10 and +40°C.
Protect the cylinders from shocks, falls, cracking and flammable materials, moisture, sources of heat or ignition.

Storage in the pharmacy department
The gas cylinders should be kept in a place designated exclusively for medicinal gas storage that is well ventilated,
clean and under lock and key. This place should house a separate, special facility for the storage of nitric oxide gas
cylinders.

Storage in medical department
The cylinder should be placed in an area with appropriate equipment to ensure that the cylinder is held vertically.
When the gas cylinder is empty, do not dispose of it. Empty gas cylinders will be collected by the supplier.
Module 5

Scientific discussion during initial procedure

I INTRODUCTION

On 11 January 2012, Austria, Belgium, Germany, Italy, Luxemburg, the Netherlands and the UK agreed to grant Marketing Authorisations (MAs) to SOL SpA for the medicinal products Neophyr 225 ppm mol/mol, 450 ppm mol/mol, 1000 ppm mol/mol Medicinal Gas, compressed. The MAs were granted via a Decentralised Procedure (DCP), with the UK as Reference Member State (UK/H/3968/01-3/DC). After the national phase, MAs were granted in the UK on 16 February 2012 (PL 35326/0001-3).

On 23 January 2013, MAs were subsequently granted in Romania, Bulgaria and Ireland via a Mutual Recognition Procedure, with the UK as Reference Member State (UK/H/3968/01-3/E01).

The applications were submitted as abridged, bibliographic applications, for an active of well-established use, according to Article 10a of Directive 2001/83/EC, as amended.

These products are prescription-only medicines.

These products contain the active substance nitric oxide. Nitric oxide is a compound produced by many cells of the body. It relaxes vascular smooth muscle by activating guanylate cyclase and increasing intracellular levels of cyclic guanosine 3’,5’-monophosphate, which then leads to vasodilation. When inhaled, nitric oxide produces selective pulmonary vasodilation.

Nitric oxide is administered by inhalation by special devices approved for clinical use, mostly in intubated patients during mechanical ventilation, under control of approved monitoring, continuously measuring NO and NO₂.

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

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

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

No new non-clinical or clinical efficacy studies were necessary for these applications, which is acceptable given that these were bibliographic applications for products containing an active of well-established use. Bioequivalence studies are not necessary to support these bibliographic applications.
The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation holder (MAH) has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well-established.

The MAH has provided a satisfactory Environmental Risk Assessment (ERA). These applications have been submitted under well-established use; it is not expected that the environmental exposure to nitric oxide will increase following the marketing approval of the proposed products.
# II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Neophyr 225 ppm mol/mol medicinal gas, compressed  
Neophyr 450 ppm mol/mol medicinal gas, compressed  
Neophyr 1000 ppm mol/mol medicinal gas, compressed |
| Name(s) of the active substance(s) (INN) | Nitric oxide |
| Pharmacotherapeutic classification (ATC code) | R07 AX 01 Other respiratory system products |
| Pharmaceutical form and strength(s) | Medicinal gas, compressed |
| Reference numbers for the Decentralised/Mutual Recognition Procedure | UK/H/3968/001-3/DC  
UK/H/3968/001-3/E01 |
| Reference Member State | United Kingdom |
| Member States concerned | UK/H/3968/01-03/DC: Austria, Belgium, Germany, Italy, Luxemburg and The Netherlands  
UK/H/3968/001-3/E01: Bulgaria, Ireland, Romania |
| Marketing Authorisation Number(s) | PL 35326/0001-3 |
| Name and address of the authorisation holder | SOL SpA  
Via Borgazzi 27 – 20900 Monza  
ITALY |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

Nitric Oxide

rINN name: Nitric Oxide
Chemical name: Nitric Oxide
Molecular formula: NO
Molecular weight: 30.01 g/mol

Structure
N = O

General properties
Description: A colourless gas which turns brown when exposed to air.
Solubility in water: At 20 °C and at a pressure of 101 kPa, 1 volume dissolves in about 21 volumes of water.

The active substance, nitric oxide, is the subject of a European Pharmacopoeia (EP) monograph.

Information has been provided covering the manufacture and control of nitric oxide.

Manufacture
Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

Nitric oxide has a simple molecular formula. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for all working standards. Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with inhaled gases.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.
DRUG PRODUCT

Description and Composition

The proposed product is a colourless, odourless compressed medicinal gas. The product is formulated to contain 0.225ml nitric oxide in 999.775ml of nitrogen; 0.450ml nitric oxide in 999.65ml of nitrogen and 1ml nitric oxide in 999ml in nitrogen respectively.

A 10 litre gas cylinder filled to 150 bar supplies 1500 L of gas at a pressure of 1 bar at 15°C.

Other ingredients consist of pharmaceutical excipients, nitrogen. An appropriate justification for the inclusion of this excipient has been provided. Nitrogen shows compliance with its Ph Eur monograph. A satisfactory Certificate of Analysis for nitrogen has been provided. The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in, or used in the manufacturing process for the proposed product. Furthermore, no genetically modified organisms are used in the manufacture of nitrogen.

Pharmaceutical development

The applicant has provided a suitable product development section. As previously indicated, the drug product is composed of nitric oxide (active substance) and nitrogen (as excipient). General information regarding the physical properties of both substances has been presented.

The applicant has stated that nitric oxide has been in use in human health care for more than 10 years and can therefore be concluded as a well established use product. Efficacy and safety are justified based on bibliographical evidence.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted on 3 batches of each strength and are satisfactory. The validation data demonstrated consistency of the manufacturing process.

Finished Product Specification

Finished product specifications are provided for both release and shelf-life, and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and adequately validated, as appropriate. Satisfactory batch analysis data are provided. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

Container-Closure System

The finished products are licensed for marketing in gas cylinders with a capacity of 10L. A 10 L gas cylinder filled to 150 bar contains about 1.77kg of gas. Aluminium alloy cylinders have a white painted body and a turquoise-painted shoulder. They are equipped with a stainless steel residual valve with a specific ISO 5145 (2004) type outlet connector.

The cylinders conform to the requirement set out in the current Carriage of Dangerous Goods and the Transportable Pressure Equipment Regulations 2004 control these cylinders. All cylinders used for Medical Oxygen are designed and tested to conform to these regulations.
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with EU legislation.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been approved with the following storage information: “All regulations concerning handling of pressurised cylinders must be followed”, “Storage is supervised by the specialists at the hospital”, “Cylinders are to be stored in well-ventilated rooms or in ventilated sheds where they are protected from rain and direct sunlight”, “The cylinders must be stored at a temperature between -10 and +50°C” and “Protect the cylinders from shocks, falls, oxidising and flammable materials, moisture, sources of heat or ignition”. For information on how to store the product in the pharmacy and medical departments and transportation of the gas cylinder please refer to Section 6.4 of the SmPC.

**Quality Overall Summary**

A satisfactory quality overall summary is provided and has been prepared by an appropriately qualified expert. The *curriculum vitae* of the expert has been provided.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**

The SmPC, PIL and labelling are pharmaceutically acceptable. Colour mock-ups of the labelling and PIL have been provided.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test show that the patients/users are able to act upon the information that is contains.

**MAA Forms**

The MAA form is pharmaceutically satisfactory.

**Conclusion**

There are no objections to the approval of Neophyr 225 ppm mol/mol, 450 ppm mol/mol and 1000 ppm mol/mol medicinal gas, compressed from a pharmaceutical point of view.

**III.2 NON-CLINICAL ASPECTS**

The pharmacodynamic, pharmacokinetic and toxicological properties of nitric oxide are well-known. Therefore, no further studies are required and the applicant has provided none.

**ENVIRONMENTAL RISK ASSESSMENT**

A satisfactory environmental risk assessment has been submitted. It was not possible to obtain a LogKow value for this gas however, a discussion on the potential of nitric oxide for persistence, bioaccumulation and toxicity has been provided.

In the environment, nitric oxide is not expected to be mobile in soil; it rapidly converts in air to nitrogen dioxide, and forms nitrous acid in water. Nitric oxide does not bio-accumulate. Although over-exposure to nitric oxide may cause harm to both the terrestrial and aquatic environment, the risk of an accidental release of this gas mixture to the environment is negligible.
The overall PECsurfacewater is well below the threshold triggering a phase II assessment; therefore no phase II risk assessment is required. The applicant concludes that as there are no other environmental concerns apparent, it is assumed that the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients.

The potential for extraction and leaching of materials from valves and gaskets, etc, and any degradation of the non-metallic components in the wetted area of the container in contact with the gas from a non-clinical perspective in line with the Guideline on Medicinal Gases: Pharmaceutical Documentation (Including Recommendation on Non-Clinical Safety Requirements for Well Established Medicinal Gases) (CPMP/QWP/1719/00) have been satisfactorily addressed.

The SmPC includes appropriate precautionary and safety measures that should be taken regarding the environmental release from use in patients, and disposal of unused products or waste materials derived from such products.

NON-CLINICAL OVERVIEW
The non-clinical overall summary was written by a suitably qualified person and is satisfactory. The curriculum vita of the expert has been provided.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
The SmPC is satisfactory from a non-clinical viewpoint

There are no objections to the approval of Neophyr 225 ppm mol/mol, 450 ppm mol/mol and 1000 ppm mol/mol medicinal gas compressed from a non-clinical point of view.

III.3 CLINICAL ASPECTS

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

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

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

POSOLOGY AND METHOD OF ADMINISTRATION
Prescription of nitric oxide should be supervised by a physician experienced in neonatal intensive care.

Full details concerning the posology are provided in the SmPC.

TOXICOLOGY
The toxicology of nitric oxide is well-known. No new data have been submitted and none are required for this type of application.

**CLINICAL PHARMACOLOGY**
The clinical pharmacology of nitric oxide is well-known. No novel pharmacodynamic or pharmacokinetic data are supplied or required for this application.

**Pharmacokinetics**
Nitric oxide gas is administered by inhalation and is absorbed by the lung. The major metabolic pathway of inhaled NO is that the inhaled gas combines with haemoglobin forming nitrosyl-haemoglobin from which nitrites and nitrates are generated. In the presence of oxygen there is a rapid oxidation of nitrosyl-haemoglobin into methemoglobin and the subsequent reduction by methemoglobin reductase into ferrous haemoglobin and nitrate. The nitrite and nitrate are then transferred to the serum and the greater part of the nitrate is excreted into the urine through the kidney. The pulmonary vasodilatation of NO is selective. The half-life of NO in vivo is only a few seconds. Age and hepatic impairment do not affect the pharmacokinetics of NO. In renal impairment clearance of metabolites may be impaired.

**Pharmacodynamics**
The pharmacodynamics of nitric oxide is well established, both therapeutically and as a substance endogenous within the body. It is involved in the regulation of the cardiovascular, nervous and immune systems. Its effect on the vascular endothelium is carefully balanced with calcium to maintain vascular tone. It does this by its action on guanylate cyclise, leading to vascular smooth muscle relaxation and also causing platelet inhibition. It binds with the haem moiety of guanylate cyclise and activating the enzyme. The enzyme then triggers off the production of cyclic GMP from GTP, which activates a cascade of intracellular events which culminate in the reduction of smooth muscle tone.

This effect can also be triggered exogenously with the use of inhaled nitric oxide gas, as it has direct access to the pulmonary vasculature. After inhalation the nitric oxide diffuses quickly across the alveolar-capillary membrane into the subjacent smooth muscle of the pulmonary vessels. Here it activates soluble guanylate cyclise. This has the same effect as above and therefore causes relaxation of the vascular smooth muscle, therefore relieving the pulmonary hypertension present. If withdrawal is too rapid rebound pulmonary hypertension can occur. *In vitro* data suggest that inactivation or downregulation of endothelial NO synthase during inhaled NO therapy may be one of the potential mechanisms for rebound pulmonary hypertension.

Platelet adhesion and aggregation are inhibited by both endogenous and exogenous NO. The effects of NO on platelets are mediated predominantly via cGMP-PKG pathway.

**Clinical efficacy**
Treatment of newborns with hypoxic respiratory failure associated with pulmonary hypertension:
A number of studies have now been conducted in this field. Early pilot studies showed that inhaled nitric oxide increased systemic oxygenation in severely hypoxic children with persistent pulmonary hypertension (Roberts et al. 1992, Kinsella et al. 1992).
Multiple multicentre studies then confirmed this. Three large trials have confirmed efficacy and safety. One demonstrated in 235 neonates that lower rates of death and ECMO use were seen in subjects treated with NO when the two end points were combined. There were also statistically and clinically significant reductions in PaO2 and alveolar-arterial oxygen gradient.

A second study in 186 term and preterm infants showed similar results, with the ECMO rate being statistically significantly lower in those treated with NO. Deaths were numerically lower but the small numbers of deaths in the study meant that this was not statistically significant.

A third study in 248 subjects also demonstrated similar results, with decreased ECMO rates and also combined death/ECMO end points shown in those treated with NO. Deaths on their own did not decrease in a statistically significant level.

Other, supporting studies supported the findings from these studies.

One showed a rise in systemic oxygenation of nearly half. It also showed that the increase in oxygen levels was inversely proportional to the levels of hypoxia before treatment and that in 75% of infants breathing nitric oxide the increased systemic oxygen concentrations were maintained (Roberts et al. 1997).

A study looking at outcomes after nitric oxide therapy showed that 76.4% of children studied survived. Oxygenation indices, arterial alveolar oxygen tension ratio and the alveolar arterial oxygen gradient were all significantly improved (Chotigeat et al. 2007).

Another study followed 248 neonates over 1 year, however it showed no differences between the control group and the inhaled nitric oxide group on deaths, pulmonary disease levels, supplemental oxygen requirements, developmental delay or neurological signs (Clark et al. 2003).

Most causes of hypoxic respiratory failure with pulmonary hypertension do respond to this type of treatment, although it is well established that nitric oxide does not work in patients with congenital diaphragmatic hernia.

Treatment of perioperative and postoperative pulmonary hypertension: Nitric oxide has been used in both adults and children perioperatively and postoperatively when pulmonary hypertension occurs.

The applicant has presented a number of studies and retrospective reviews to provide data for the indication.

One study showed that inhaled prostacyclin and NO (20 pm) are effective in the treatment of postoperative pulmonary hypertension in patients with mitral valve stenosis undergoing mitral valve surgery. Both drugs improved cardiac output and reduce mean pulmonary arterial pressure, pulmonary vascular resistance, and trans-pulmonary gradient. Both inhaled treatments are superior to nitroprusside.

Another study showed that inhaled NO and prostacyclin is effective in the postoperative treatment of pulmonary hypertension. Both inhaled treatments are superior to nitroprusside
with respect to treatment pulmonary hypertension. Compared to nitroprusside, both inhaled treatments were superior with regards to time of weaning, intubation time and intensive care unit stay.

Another study showed that inhaled NO immediately after surgery in patients with mitral stenosis and severe pulmonary hypertension improves haemodynamics and may have short-term clinical benefits.

Another study showed that inhaled NO can blunt release of markers of myocardial injury and antagonise left ventricular subclinical dysfunction during and immediately after cardiopulmonary bypass.

Another study demonstrated that inhaled NO improved arterial oxygenation and caused a significantly shorter period of mechanical ventilation.

Another study showed that inhaled NO and prostaglandin i.v. decreased pulmonary vascular resistance and increased cardiac index.

Another study demonstrated that inhaled NO compared with milrinone lead to lower heart rates, higher right ventricular ejection fraction, and a lower requirement for treatment with vasopressor agents.

Another study showed that inhaled NO and iloprost both reduced pulmonary artery pressure and pulmonary vascular resistance immediately after weaning from cardiopulmonary bypass. In a direct comparison of the 2 substances, iloprost was found to be significantly more effective.

Studies in adult patients undergoing heart transplant or LVAD insertion:
One study showed that post-transplant inhaled NO significantly reduced right ventricular stroke work and pulmonary vascular resistance.

Another study showed that inhaled NO induces significant reductions in mean pulmonary artery pressure and increases in LVAD flow in LVAD recipients with elevated pulmonary vascular resistance.

Another study showed that inhaled NO and prostacyclin is equally effective in reducing the pulmonary artery pressure and central venous pressure, and increasing cardiac index and venous oxygen saturation in a cohort of heart transplant and lung transplant recipients.

Another study demonstrated that inhaled NO at a dose of 20 ppm significantly reduced pulmonary capillary wedge pressure and pulmonary vascular resistance. Another showed that prostaglandin E1 and inhaled NO have comparable dilatory effects in pulmonary hypertension.

Another study showed that NO inhalation (4 ppm) causes selectively reduction of pulmonary vascular resistance and pulmonary artery pressure immediately after heart transplantation. Inhaled NO aided weaning from cardiopulmonary bypass more successfully than prostaglandin E1.

Studies in children undergoing cardiac surgery for congenital heart disease:
One study showed that the application of combined inhaled NO and milrinone were more effective in lowering pulmonary vascular resistance compared to either drug alone. In addition, the combined application had significant shorter time on ventilation.

Another had different findings, showing that NO did not substantially improve pulmonary haemodynamics and gas exchange immediately after operation for congenital heart disease. Nitric oxide also failed to significantly decrease the incidence of pulmonary hypertensive crises.

Another study showed that inhaled NO resulted in a lower pulmonary arterial pressure compared to prostacyclin.

Another study showed that infants at high risk of pulmonary hypertension, routine use of inhaled NO (10 ppm for a maximum of 7 days) after congenital heart surgery can lessen the risk of pulmonary hypertensive crises and shorten the postoperative course with no adverse effects.

Another study showed that inhaled NO and hyperventilation are both effective at lowering pulmonary artery pressure and pulmonary vascular resistance in children with pulmonary hypertension after repair of congenital heart disease. However, the selective action of inhaled NO on the pulmonary circulation offers advantages over hyperventilation because a decrease in cardiac output and an increase in systemic vascular resistance are undesirable in the postoperative period.

Another study showed that inhaled NO selectively reduced pulmonary artery pressures in paediatric patients who developed pulmonary hypertension immediately after cardiopulmonary bypass and surgical repair.

Another study showed that inhaled NO (20 ppm) and i.v. sildenafil lowered PVRI. Sildenafil also lowered systemic blood pressure.

Dosing and administration:
Most of the studies described above use the already licensed dosing of 2-40ppm of nitric oxide. No information has been provided to support use of higher doses and it is known that the risk of methaemoglobinaemia and elevated nitric dioxide levels is significantly greater over 40ppm.

Nitric oxide needs to be withdrawn in a slow, step-wise manner to avoid rebound pulmonary hypertension, increased right to left shunting and a decrease in oxygenation.

Administration is by ventilation after dilution in an air/oxygen mixture and that direct intratracheal administration is to be avoided.

Clinical safety
Safety and Adverse events:

Controlled studies have included 325 patients on NO doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on inhaled NO, a result adequate to exclude NO mortality being more than 40% worse than placebo.
From all controlled studies, at least 6 months of follow-up is available for 278 patients who received inhaled NO and 212 patients who received placebo. Among these patients, there was no evidence of an adverse effect of treatment on the need for rehospitalisation, special medical services, pulmonary disease, or neurological sequelae.

Data on nitrogen dioxide, a toxic by-product formed when nitric oxide interacts with oxygen, shows that formation is minimal in the circumstances in which it is used (Sokol et al. 1999).

Two studies showed that overall neurological development seems not to be affected by administration of nitric oxide in term or near-term infants (Konduri et al. 2007, Mestan et al 2005). Some differences in favour of placebo were seen when measuring psychomotor development indices in one study (Konduri et al. 2007). However, the other study did show that nitric oxide seemed protective against abnormal neurodevelopment outcomes (Mestan et al 2005).

One study examined 36 children for circulatory, respiratory or neurological disorders via a variety of methods over the long term. Nearly half had visible chest x-ray changes, a quarter was on bronchodilators, 4 had congenital heart disease with pulmonary hypertension and 1 had psychomotor abnormalities (Gothberg et al. 2000).

A retrospective review of notes in a paediatric intensive care unit showed up no adverse events that required intervention beyond reduction of the nitric oxide concentration (Ryan and Tobias 2007).

Adults:
**Precautions:**

A number of studies have established that nitric oxide is of no benefit in premature infants of less than 34 weeks gestation (Kinsella et al. 2004, Barrington and Finer 2007). It is also well established that nitric oxide does not give any benefit (and there are some indications of

It is well established that discontinuation of nitric oxide must be performed in a slow, step wise manner.

Haemostasis and platelet function need to be monitored as nitric oxide has been shown in both animals and humans to inhibit platelet function and can increase bleeding time. Therefore monitoring is recommended (Weinberger et al. 2001, Beghetti et al. 2003, Gries et al. 2003).

Nitrogen dioxide formation is a well established event when nitric oxide is administered with oxygen. Nitrogen dioxide causes an inflammatory reaction and airway lesions and therefore levels should be routinely monitored (Cuthbertson et al. 1997).

Methaemoglobin levels must be monitored as it is a concern, especially in neonates who have reduced levels of methaemoglobin reductase activity (Bloch et al. 2007, Taylor et al. 2001).

**Interactions:**
Nitric oxide donors (such as sodium nitroprusside and nitroglycerine) should not be used in conjunction with nitric oxide as they could lead to unacceptable levels of methaemoglobinemia.

Phosphodiesterase inhibitors (such as sildenafil and dipyridamole) have been shown to enhance the effect on pulmonary vascular resistance and reduce the nitric oxide requirements in some studies (Cavallaro et al. 2008, Preston et al. 2005, Lepore et al. 2005). However they have been shown to lead to systemic hypertension and impaired oxygenation in other studies (Stocker et al. 2003).

In vitro studies have shown that nitric oxide has an inhibitory effect on surfactant (Lee et al. 2005, Salinas et al. 2003, Bhandari et al. 2002). However, these effects have not yet been born out in clinical use.

**Overdose:**
The largest risks in overdose are the elevations in nitrogen dioxide and methaemoglobin. The nitrogen dioxide will cause acute lung injury, whilst methaemoglobinemia will cause a reduction in oxygen carriage. Treatments are symptomatic and reduction in nitric oxide concentrations delivered. If methaemoglobin levels are not reduced by this then IV vitamin C, methylene blue or even blood transfusion should be considered (Persinger et al. 2002, do Nascimento et al. 2008, Alapat and Zimmerman 2008).

**Expert Report**
A satisfactory clinical overall summary is provided, and has been prepared by an appropriately qualified physician. The *curriculum vitae* of the expert has been provided.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPCs and PIL are medically acceptable. The labelling is medically acceptable and in-line with current requirements.
MAA form
The MAA forms are medically satisfactory.

Conclusion
There are no objections to approval of Neophyr 225 ppm mol/mol, 450 ppm mol/mol and 1000 ppm mol/mol medicinal gas, compressed from a clinical point of view.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Neophyr 225 ppm mol/mol, 450 ppm mol/mol and 1000 ppm mol/mol medicinal gas, compressed are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
No new data are submitted and none are required for applications of this type.

The published literature supports the efficacy of this product in the proposed indications. The safety and efficacy of nitric oxide are well-known. The presented evidence for well-established use of the active substance is sufficient.

The literature review identifies no new safety issues or concerns. The safety profile of nitric oxide is well-known.

PRODUCT LITERATURE
The SmPCs and PILs are acceptable, and consistent with those for the reference product. The labelling is acceptable and in-line with current requirements.

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Nitric oxide is an active substance of well-known safety and efficacy. Extensive clinical experience with nitric oxide is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

The following table lists some non-safety updates to the Marketing Authorisation for this product that have been approved by the MHRA since the product was first licensed. The table includes updates that are detailed in the annex to this PAR. This is not a complete list of the post authorisation changes that have been made to this Marketing Authorisation.

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>18/04/2013</td>
<td>IB</td>
<td>To introduce a new Pharmacovigilance System Master File (PSMF) to replace the Detailed Description of the Pharmacovigilance System (DDPS). To also update the Risk Management Plan (RMP) in line with the new pharmacovigilance legislation. In addition, to change the frequency of submission of the Periodic Safety Update Report (PSUR) from 3 years to 6 months for the first 2 years and then annually for the next 3 years, with subsequent renewal.</td>
<td>Approved 18/07/2013</td>
</tr>
<tr>
<td>14/03/2013</td>
<td>IB</td>
<td>To update sections 4.1, 4.2 and 5.1 of the SPC to remove an indication which is patent protected in the UK. As a consequence, the PIL has also been updated.</td>
<td>Approved 02/05/2013</td>
</tr>
<tr>
<td>14/01/2014</td>
<td>IB</td>
<td>To update sections 4.1, 4.2, 4.4 and 5.1 of the SPC to re-include an indication for which the patent has now expired in the UK. As a consequence, the PIL has also been updated.</td>
<td>Approved 21/02/2014</td>
</tr>
</tbody>
</table>
Annex 1

Reference:  
PL 35326/0001- 0008  
PL 35326/0002- 0009  
PL 35326/0003- 0009

Product:  
Neophyr 1000 ppm mol/mol medicinal gas, compressed  
Neophyr 450 ppm mol/mol medicinal gas, compressed  
Neophyr 225 ppm mol/mol medicinal gas, compressed

Marketing Authorisation Holder: SOL SpA  
Active Ingredient: Nitric Oxide

Reason  
To introduce a Pharmacovigilance System Master File (PSMF) to replace the Detailed Description of the Pharmacovigilance System (DDPS). To also update the Risk Management Plan (RMP) in line with the new pharmacovigilance legislation. In addition, to change the frequency of submission of the Periodic Safety Update Report (PSUR) from 3 years to 6 months for the first 2 years, and then annually for the next 3 years, with subsequent renewal.

Supporting evidence  
The applicant has provided a Summary of the PSMF to replace the DDPS and has confirmed that the PSMF is permanently available for inspection and that a copy of the PSMF will be provided to the National Competent Authorities/European Medicines Agency within 7 days upon request. The PSMF is located either at the site in the EU where the main pharmacovigilance activities of the MAH are performed, or at the site where the Qualified Person for Pharmacovigilance (QPPV) operates. The applicant has also confirmed that the QPPV resides and operates in the EU. The applicant has also submitted an updated RMP.

Evaluation  
The PSMF and updated RMP are satisfactory. The change in frequency/date of submission of the PSUR has been agreed by CHMP/CMDh, as set out in the European Union Reference Date (EURD) list.

Conclusion  
The PSMF and updated RMP, and the change in the frequency of the submission of the PSUR can be approved.

Decision: Approved on 18/07/2013
Annex 2

Reference:

PL 35326/0001- 0007
PL 35326/0002- 0007
PL 35326/0003- 0007

Product:

Neophyr 1000 ppm mol/mol medicinal gas, compressed
Neophyr 450 ppm mol/mol medicinal gas, compressed
Neophyr 225 ppm mol/mol medicinal gas, compressed

Marketing Authorisation Holder: SOL SpA
Active Ingredient: Nitric Oxide

Reason
As the indications currently listed on the SPC are patent protected in the UK, variations were submitted to update sections 4.1, 4.2, 4.4 and 5.1 of the SPC to modify the first indication and completely remove the second indication, in order to commercialise the product in the UK without patent infringement. As a consequence, the PIL has also been updated.

Supporting evidence
Amended SPC fragments and an amended PIL have been submitted.

Evaluation
The updated SPC fragments and PIL are satisfactory.

Conclusion
The updated SPC fragments and PIL can be approved.

Decision: Approved on 02/05/2013
Annex 3

Reference: PL 35326/0001-0015
            PL 35326/0002-0016
            PL 35326/0003-0016

Product: Neophyr 1000 ppm mol/mol medicinal gas, compressed
          Neophyr 450 ppm mol/mol medicinal gas, compressed
          Neophyr 225 ppm mol/mol medicinal gas, compressed

Marketing Authorisation Holder: SOL SpA
Active Ingredient: Nitric Oxide

Reason
As the patent for the indications originally listed on the SPC has now expired, variations were submitted to update sections 4.1, 4.2, 4.4 and 5.1 of the SPC to re-instate the original wording for the first indication and to re-include the second indication that was previously deleted.

As a consequence, the PIL has also been updated.

Supporting evidence
The data supporting the indications were assessed during the assessment of the original Marketing Authorisation applications, which were approved on 16 February 2012. No further clinical or non-clinical data were submitted with these variation applications and none were required. As the patent for the indications has now expired in the UK, the SPC fragments and PIL have been amended accordingly.

Evaluation
The updated SPC fragments and PIL are satisfactory.

Conclusion
The updated SPC fragments and PIL can be approved.

Decision: Approved on 21/02/2014