VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Persistent pulmonary hypertension of the newborn (PPHN)

Persistent pulmonary hypertension of the newborn is a life threatening condition that occurs in up to 2 per 1000 liveborn infants.

PPHN affects mainly at-term or post-term newborns, although also present in premature infants. The rate of PPHN in newborns is not well characterized, and is probably underestimated.

Pulmonary hypertension in Heart Surgery

The mechanism of pulmonary hypertension in cardiac surgery is complex and can result from several mechanisms acting alone or in combination. These mechanisms can be present before the operation, secondary for instance from valvular heart disease.

There are no reliable data regarding the incidence and prevalence of heart surgery procedures at risk of pulmonary hypertension.

VI.2.2 Summary of treatment benefits

Nitric oxide is a medicinal gas.

Nitric oxide relaxes smooth muscles of pulmonary vessels, which then leads to vasodilation and increased oxygenation.

Nitric oxide, administered by inhalation, has a selective action on pulmonary arterial circulation because of very short half-life.

Inhaled nitric oxide is indicated, depending on countries:

In conjunction with ventilatory support and other appropriate active substances, 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 by increasing the pulmonary flow.

For the treatment of newborn infants ≥ 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension (Persistent Pulmonary Hypertension in the Newborn [PPHN]), in order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation.

VI.2.3 Unknowns relating to treatment benefits

NA.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Rebound effect: emergence or re-emergence of symptoms that were either absent or controlled while taking a medication, but appear when that same medication is discontinued, or reduced in dosage	Occurs in case of abrupt discontinuation. Outcome is favourable after reinstallement of NO therapy.	This risk is already clearly mentioned in the Product information. It can be further prevented by educational material reminding prescribers of the need of a gradual weaning
Risks associated to the medical device used to administer inhaled nitric oxide	Risk of rebound effect and loss of efficacy in case of cessation of iNO administration in case of device failure. Risk of overdosage in case of failure of monitoring devices or alarms Risk of leak	These risks are already mentioned in the Product information. They can be further prevented by educational material reminding prescribers of control checklists (pre-use checklist and periodic check) and backup materials and troubleshooting recommendations
Methaemoglobinaemia: a disorder characterized by the presence of a higher than normal level of methaemoglobin rather than haemoglobin in the blood.	Methaemoglobin has a decreased ability to bind oxygen compared to haemoglobin.	This risk is already clearly mentioned in the Product information. Its consequences can be further prevented by educational material reminding prescribers of the need to monitor methaemoglobinaemia
Off-label use in acute respiratory distress syndrome (ARDS)	The efficacy of iNO on mortality of patients suffering from ARDS has not been demonstrated. However, iNO is still used to treat ARDS.	Approved indications are already clearly listed in the Product information. This risk can be further prevented by educational material reminding prescribers of the only approved indications where favourable benefit-risk balance was demonstrated (PPHN and heart surgery) and of the lack of significant efficacy of iNO in ARDS
NO_2 formation: formation of nitrogen dioxide	Nitric oxide (NO) has a trend to transform into nitrogen dioxide (NO_2) which is irritating to the bronchi.	Control of NO and NO_2 concentrations is recommended in the Product information and in educational material.

Risk	What is known	Preventability
Pulmonary oedema in patients with pre-existing left ventricular dysfunction	In patients with dysfunction of left heart (left ventricle), inhalation of nitric oxide produces a decrease of pulmonary vascular resistance (resistance of blood flow). This is associated with an increase of pulmonary capillary wedge pressure, leading to transfer of liquid and colloid from blood capillaries through the interstitium exceeding the pumping capacity of the lymphatics.	This risk is already clearly listed in the Product information. This risk can be further prevented by educational material reminding prescribers of the risk
Acute cardiac failure with circulatory collapse in certain patient populations	Data not available	Risk of developing or aggravating cardiac failures in certain patient populations is mentioned in the Product information. This risk can be further prevented by educational material reminding prescribers of the risk

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Inhibition of platelet aggregation and increased bleeding time	Blood platelets contribute to coagulation. If their aggregation is compromised, there is a risk of bleeding. Patient at risk might be those with pre-existing bleeding disorders. Results of studies of the effect of iNO on coagulation are conflicting and not clinically relevant according to recent publications. Close control of coagulation is recommended in the Product information and in educational material.

Missing information

Risk	What is known
Combined Use with Other Vasodilators	Available data on association of nitric oxide and other vasodilators suggests additive effects on pulmonary vasodilator effects and right heart performance
Use during Pregnancy and Lactation	There are no adequate data available on the use of nitric oxide during pregnancy. The potential risk in pregnant women is unknown. It is not known whether nitric oxide is excreted in human milk.
Patients 12-17 years treated for pulmonary hypertension in conjunction with heart surgery	Clinical data supporting the suggested dose in the age range 12-17 years is limited.
Paediatric use < 34 weeks gestational age for PPHN	The data on safety and efficacy in pre-term infants < 34 weeks of gestation has not yet been established.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and

recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.
Full details on these conditions and the key elements of any educational material can be found in the Summary of Product Characteristics and in the pocket-guide distributed to healthcare professionals who use iNO.
These additional risk minimisation measures are for the following risks:
Safety concern in lay terms (medical term)

Risk minimisation measure(s)
Objective and rationale
Summary description of main additional risk minimisation measures Educational material for Healthcare Professionals under the form of a Pocket Guide distributed to all Healthcare Professionals using inhaled nitric oxide
All identified, potential risks and missing information, i.e.: Identified risks: Rebound effect Risks associated to the medical device Methaemoglobinaemia Pulmonary oedema in patients with pre-existing left ventricular dysfunction Acute cardiac failure with circulatory collapse in certain patient populations Off label use in ARDS NO_2 formation Potential risks: Platelet aggregation inhibition and increased bleeding time Missing information: Combined Use with Other Vasodilators Use during Pregnancy and Lactation Patients 12-17 years treated for pulmonary hypertension in conjunction with heart surgery Paediatric use < 34 weeks gestational age for PPHN Healthcare Professional education Objective and rationale To remind HCPs of the risks and the procedures related to their appropriate management to minimise their occurrence and/or their severity. Proposed action: HCP educational materials (Pocket Guide) to be provided to prescribing physicians

VI.2.6 Planned post authorisation development plan
Not applicable
VI.2.7 Summary of changes to the Risk Management Plan over time
Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
2.0	DEC 2011		Pocket Guide introduced
3.0	02 JUN 2014	Off label use in ARDS was added as an identified risk in version 03	Newly identified risk
3.1	21 NOV 2014	Addition as Identified risk: Heart failure or	Requested by the RMS

Version	Date	Safety Concerns	Comment
		pulmonary oedema in patients with pre-existing left ventricular dysfunction Addition as Missing Information: Combined Use with Other Vasodilators Use during Pregnancy and Lactation Patients 12-17 years treated for pulmonary hypertension in conjunction with heart surgery Paediatric use < 34 weeks gestational age for PPHN	
3.2	12 MAR 2015	Previous risk Heart failure or pulmonary oedema in patients with pre-existing left ventricular dysfunction is separated into two risks: Acute cardiac failure with circulatory collapse in certain patient populations Pulmonary oedema in patients with pre-existing left ventricular dysfunction	Requested by the RMS
3.3	10 APR 2015	VasoKinox SmPC/PIL updated First marketed dates in some countries added	
4.0	15 JAN 2016	Risk of Acute cardiac failure with circulatory collapse in certain patient populations: amended in the RMP and in the Pocket Guide	Due to insufficient data, content explaining this risk has been corrected consequently.