VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Respiratory Distress Syndrome (RDS) is the main cause of respiratory illness in premature infants and it is caused by an insufficient production of a substance called “lung surfactant”. This substance works by reducing surface tension and prevents the air sacs of the lungs from collapsing and so makes normal breathing possible..

When there is a lack of surfactant production in the lungs, this can then lead to problems with breathing, fatigue and a reduced capacity in the newborn’s lungs: this deficiency will result in progression of the illness and lead to injury to the lung sacs. These sacs will then become replaced with scar- like tissue.

RDS has been reported to affect 24,000 infants annually in the USA (approximately 1 infant in 6,800 of the population), where there are approximately 1,000 reported deaths annually for those infants with RDS. **(1)** There are several risk factors for RDS in newborn infants, and these include the gestational age; the infant’s birth weight; elective and emergency caesarean section; if the newborn’s sex is male and the mother’s age. **(2)**

The rate of infant deaths in England and Wales in 2011 has been recorded as 4.1 deaths per 1,000 live births **(3).**

VI.2.2 Summary of treatment benefits

The mainstay treatment for infant RDS (respiratory distress syndrome is a breathing disorder that affects premature infants). is the administration of natural lung surfactant substances. These substances contain surfactant associated proteins that have properties to lower surface tension preventing collapse of the lung’s air sacs.

A report of the published information on clinical studies using Lung Surfactants has been published. This report concerns six studies which have looked at the use of surfactant preparations in newborns who have either been diagnosed with RDS or in those newborns where a deficiency of lung surfactant has been identified. **(5)**

In these clinical studies, the administration of surfactant to newborns has been demonstrated to be effective in reducing the risk of lung injury and chronic lung disease, and increasing overall survival rates. The authors of the report concluded the importance of providing early surfactant treatment to newborn babies who are receiving assisted ventilation.

Curosurf®, which is an extract of natural porcine lung surfactant, is administered to premature infants with, or who are at risk of, RDS. It is also administered to premature infants where there is evidence of a deficiency of surfactant.

Prior to authorisation approximately 3,500 infants were treated with Curosurf®. In total six randomised clinical studies were conducted

Administration of Curosurf® with the new method LISA:

Curosurf® administration using the method LISA (less invasive surfactant administration) via a thin tube (catheter) during CPAP (continuous positive airway pressure is a treatment that uses mild air pressure to keep the airways open) was evaluated during this research study. The aim was to compare the efficacy and the safety in the short and in the long time duration after the administration of Curosurf® with the new method LISA to the conventional one.

A total of 213 premature infants , recruited from 13 German neonatal intensive care units, were put into the treatment groups randomly to either the LISA group (108 premature infants) or the control group (105 premature infants). Notably, this study enrolled extremely premature infants who might greatly benefit from avoidance (bronchopulmonray dysplasia <BPD>) lung injury induced by a prolonged mechanical ventilation (using a machine that supplies oxygen to help with breathing), especially in the first days of life. This should improve the child's breathing function by reducing inflammation to the lungs and allowing sufficient oxygen to be taken- up. Results of this study showed that the LISA method was not inferior to the conventional method of Curosurf® administration in terms of survival without BPD in extremely premature infants.
More importantly, the LISA method was superior to the control method in increasing survival without major complications and in reducing the frequency of other morbidities (degradations of the health) associated with prematurity (leakage of air from alveoli into the pulmonary interstitium< air leak syndrome> and bleeding in brain <intrventricular hemorrhage >). Lower incidence of the aforementioned morbidities is of particular clinical importance because it might reduce the probability of lifelong disabilities.

VI.2.3 Unknowns relating to treatment benefits

Curosurf® was first marketed as a medicine for use in preterm infants for the treatment of RDS in November 1992. Since that date of its first marketing, it has been demonstrated to be an effective medicine to be administered to preterm infants diagnosed with RDS.

VI.2.4 Summary of safety concerns

Important identified risks

Table VI.2.4 1: Important identified risks

Risk	What is known	Preventability
Whole-body inflammation state (sepsis)	It is a typical complication of prematurity disease, since in newborn infants, there is a deficiency of protein substances that act as antibodies. Sepsis is a major cause of death and other complications in preterm infants despite the use of antibiotic treatments. It can occur in between 20% to 40% of all pre term infants.	Yes, by a prompt diagnosis and effective preventative treatment with antibacterial and antifungal medicines.
Bleeding in the brain (intracranial haemorrhage)	Bleeding in the brain is a typical complication of prematurity disease, and can increase the risk of death or neurodevelopmental damages in those infants. It occurs in between 2.3% and 19% of very low birth weight (VLBW) infants.	Yes. In the antenatal period, steroid medicines have been reported to provide protection against the development of bleeding in the brain. It is recommended that the ventilator is correctly adjusted after instillation to avoid any peaks in the arterial blood flow. Diagnostic ultrasound tests should be taken at different times to get more precision for identifying risk factors for bleeding in the brain in order to try to avoid this risk.
Slowing of the heart beat (bradycardia)	In bradycardia, there is a slowing of the heartbeat, usually to less than 80 beats per minute for a premature baby. It often follows episodes where breathing has either stopped or is very shallow. It can be caused by a high rate of surfactant infusion or by the placing of a feeding tube.	Yes by preterm infants undergoing continuous cardiorespiratory monitoring in the neonatal intensive care unit to detect any episodes of a slowing of the heartbeat. This will enable prompt nursing action. The most common method to prevent these episodes in preterm newborns is through manual stimulation.

Risk	What is known	Preventability
Lowering of blood pressure (hypotension)	Low blood pressure is common amongst infants of VLBW. It has been shown to occur in between 24% to 45% of these infants.	Yes. Avoiding taking other medicines that cause low blood pressure can prevent the occurrence of these episodes.
Neonatal chronic lung disease (Bronchopulmonary dysplasia)	It is a typical complication of prematurity disease, mainly in premature infants with LBWs and who received prolonged treatment with a ventilator for RDS. It is distinguished by inflammation and scarring in the lungs.	Yes. Mechanical ventilation, supplemental oxygen, careful control of fluids.
Bleeding from the lungs (Pulmonary haemorrhage)	Bleeding from the lungs is a rare complication for RDS associated with prematurity. Small preterm infants are particularly likely to experience this condition. Several reasons to explain this condition have been proposed and these include: pressure changes in the air sacs within the lungs; fragile blood vessels as a result of prematurity; and a susceptibility to bleeding conditions and possible harmful effect on the cell membranes in preterm infants, caused following treatment with surfactants.	The preventability of this risk occurring is unknown.
Collapsed lung (Pneumothorax)	It is a typical complication of prematurity associated with an high mortality rate.	Yes, by identifying those babies at highest risk by measuring the percentage of oxygen in the first 12 hours of life.
Increased amount of oxygen in the body (Hyperoxia)	If preterm infants are exposed to large concentrations of oxygen this can cause damage to the developing lung, resulting in chronic lung disease and can lead to injuries to the brain in these infants, leading to death.	To diligently control the delivery of supplemental oxygen and monitoring of SaO2 by oximetry.
Blue colour of skin or gums, caused by too little oxygen (Cyanosis neonatal)	This discolouration of skin or gums is often found in newborns particularly around	Yes. Adequate supplementation of inspired oxygen in preterm infants together with monitoring

Risk	What is known	Preventability
	the extremities; however, it is important to rule out any risk of infection. If this discolouration is more widespread this may suggest a serious disease requiring urgent medical evaluation.	of oximetry.
Stopping of breathing (Apnoea)	For premature newborns this occurs in the range of 0.5-12 per 10,000 of the population. Apnoea lasting more than 20 seconds can lead to severe consequences, mainly neurodevelopmental.	Spontaneously breathing infants can be treated with intravenous Caffeine Citrate to prevent apnoea.
Insufficient oxygen in the blood (oxygen saturation decreased)	This decrease in oxygen in premature infants is most likely associated with a lack of surfactant although other factors such as rapid breathing and pneumonia in the newborn.	Yes. Supplements of oxygen to the inspired air with monitoring of oximetry to avoid hyperoxia and hypoxia.
Abnormal reading of the brain activity (abnormal electroencephalogram)	By instilling surfactants, this may cause there to be changes in the patterns of readings of the brain.	Potentially by administering the surfactant from an aerosol, as this might have less significant effects on blood pressure and the blood supply to the brain.
Complication with placement of the tubes into the lungs (Endotracheal intubation complication)	Sometimes on rare occasions, the tube can become obstructed or blocked by mucus and require replacing.	This is not predictable as it occurs on rare occasions, mainly if pulmonary secretions are copious before the surfactant administration.

Important potential risks

Risk	What is known	Preventability
Complication linked the instillation of Curosurf with the LISA method: Slowing of the heartbeat (bradycardia), stopping of breathing (Apnoea) and Insufficient oxygen in the blood (oxygen saturation decreased)	By administering Curosurf® with LISA method, slowing of the heartbeat, stopping of breathing and insufficient oxygen in the blood were more frequently observed than the administration with the conventional method.	-The most common method to prevent slowing heartbeat in preterm newborns is through a manual stimulation. -Supplements of oxygen to the inspired air with monitoring of oximetry to avoid insufficient oxygen blood. -Spontaneously breathing infants can be treated with intravenous caffeine to prevent stopping of breathing.

Important missing information

During the programme for the development of the medicine and the subsequent period of marketing following its authorisation, no important missing information that would impact on the safety of Curosurf® has been identified.

VI.2.5 Summary of additional risk minimisation measures by safety concern

No additional risk minimisation measures other than the ongoing safety monitoring activities for Curosurf® are required.

VI.2.6 Planned post authorisation development plan

None.

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
01	30 April 2012	All ADRs in section 4.8 of the SPC are considered important identified risk.	First version of the EU-RMP.
02	18 April 2013	No safety concerns added or removed.	RMP moved to the new format, according to GVP, Module V, for the renewal in Estonia.
03	November 2015	Changes in the list of important identified risks Risks linked to the administration of Curosurf® with the LISA method (*Bradycardia, apnea and oxygen saturation decreased)* added .	RMP updated for the LISA-variation procedure.
	June 2016	-Deletion of endotracheal intubation complications from the list of important identified risks further to the request made by the RMS. -Use in patients with hepatic impairment was added as missing information following a request made by the RMS -Changes in the public summary section by using a lay language	Update following requests made by health authorities
	September 2016	-Endotracheal intubation complication was added in the list of important identified risks following a a reevaluation made by the RMS -Deletion of the missing information use in patients with hepatic impairment following a reevaluation made by the RMS.	Update following requests made by health authorities
	October 2016	-TheCM- NL disagree with adding << *Endotracheal intubation complication, Pneumothorax and pulmonary haemorrhage*>> and requested for removing them from the RMP.	Update following requests made by the NL health authorities