

Part VI: Summary of the risk management plan

Summary of risk management plan for LEVIOXAP 50%/50% v/v gas medicinale compresso

This is a summary of the risk management plan (RMP) for LEVIOXAP 50%/50% v/v gas medicinale compresso. The RMP details important risks of LEVIOXAP 50%/50% v/v gas medicinale compresso, and how these risks can be minimised.

LEVIOXAP 50%/50% v/v gas medicinale compresso's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how LEVIOXAP 50%/50% v/v gas medicinale compresso should be used.

I. The medicine and what it is used for

LEVIOXAP 50%/50% v/v gas medicinale compresso is indicated in adults and children older than 1 month for the treatment of short-term pain conditions of mild to moderate intensity when rapid analgesic onset and offset effects are wanted and for sedation during dental surgery in anxious patients. It contains nitrous oxide and oxygen as active substances and it is given via inhalation.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of LEVIOXAP 50%/50% v/v gas medicinale compresso, together with measures to minimise such risks are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed-including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of LEVIOXAP 50%/50% v/v gas medicinale compresso are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of LEVIOXAP 50%/50% v/v gas medicinale compresso. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	<ul style="list-style-type: none"> • Inhibition of the methionine synthase pathway (inhibition of vitamin B12) • Respiratory depression • Volume and baro effects • Drugs Interactions
Important potential risks	<ul style="list-style-type: none"> • Occupational exposure • Negative effect on myocardial function • Increased cerebral blood flow
Missing information	None

II.B Summary of important risks

Important identified risk: Inhibition of the methionine synthase pathway (inhibition of vitamin B12)	
Evidence for linking the risk to the medicine	The information about inhibition of the methionine synthase pathway (inhibition of vitamin B12) is presented in the scientific conclusion of PSUSA-10572-201706 , SmPC and in published studies from literature public domain.
Risk factors and risk groups	<p>Patients with pre-existing disorders affecting vitamin B12 levels and/or folates, like megaloblastic anaemia, a vegetarian diet, untreated vitamin B12 deficiency, Biermer anaemia, Crohn's disease, known deficiency of enzyme or substrate belonging to the metabolic pathway of the synthesis of methionine are at higher risk of experiencing toxicity related to vitamin B12 inactivation. Patients concomitantly administered with methotrexate are at higher risk of haematological toxicity/neurotoxicity due to the interaction of methotrexate with the folate system.</p> <p>The prolonged and/or frequent exposure to nitrous oxide increases the risk of B12 inactivation related toxicity, especially in healthcare professional for occupational exposure.</p>
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u></p> <p>As reported in section 4.2 of the product SmPC, LEVIOXAP 50%/50% v/v gas medicinale compresso can be administered for up to 6 hours without haematological monitoring in patients with no risk factors. Special precautions should be taken when working with nitrous oxide. Nitrous oxide should be administered by personnel with knowledge of its use according to local guidelines.</p> <p>As reported in section 4.3 of the SmPC and related PIL sections, the product administration is contraindicated in patients with diagnosed but untreated vitamin B12 or folic acid deficiency or diagnosed genetic disorder of the enzyme system involved in metabolism of these vitamins.</p> <p>As reported in section 4.4 of the product SmPC and related sections of the PIL, hematological monitoring and referral to a hematologist is recommended while treating patients with nitrous oxide/oxygen combination. The haematological evaluation must include an assessment regarding the megaloblastic alteration of red blood cells and the hypersegmentation of neutrophils. Neurological toxicity can occur without anemia or macrocytosis and with normal vitamin B12 levels.</p>

	<p>As reported in section 4.5 of the SmPC and related PIL sections, considering the effects of methotrexate on folates metabolism, patients concomitantly administered with methotrexate and N₂O containing medicinal products may experience an enhanced effect. Moreover, the combination use should be limited in time due to the interference between nitrous oxide and folate metabolism via Vitamin B12.</p> <p>The risk-related ADRs, including megaloblastic anaemia, leukopenia, polyneuropathy, paraparesis, myelopathy, myeloneuropathy, neuropathy and subacute degeneration of the spinal cord are reported in section 4.8 of the product SmPC and related PIL section together with the indication that substitution treatment should be considered in all cases where vitamin B12 or folate deficiency may be suspected or where signs or symptoms of nitrous oxide-triggered effects on methionine synthesis have arisen.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>Nitrous oxide should always be administered in the presence of medical personnel, who decide whether the medicine can be administered and the appropriate dose, in structures that allow cardio-respiratory emergency resuscitation.</p> <p><u>Additional risk minimisation measures:</u></p> <p>No additional risk minimisation measures.</p>
<p>Important identified risk: Respiratory depression</p>	
<p>Evidence for linking the risk to the medicine</p>	<p>The information about respiratory depression is presented in the SmPC and in published studies from literature public domain.</p>
<p>Risk factors and risk groups</p>	<p>In the absence of comorbid diseases N₂O generally has limited effects on ventilator and cardiovascular function and causes less respiratory depression than the volatile anesthetic agents. Patients affected by pulmonary diseases, difficult breathing and needing respiration of pure oxygen and neonates are at increased risk. The use of high doses of nitrous oxide may be more likely to be associated with respiratory depression.</p>
<p>Risk minimisation measures</p>	<p><u>Routine risk minimisation measures:</u></p> <p>As reported in section 4.2 of the product SmPC and related PIL section, LEVIOXAP 50%/50% v/v gas medicinale compresso should only be administered by personnel with knowledge of its use. Its administration should only occur under supervision of, and with instruction from, personnel familiar with the equipment and its effects. LEVIOXAP 50%/50% v/v gas medicinale compresso should only be</p>

	<p>administered when the possibility of oxygen supplementation and equipment for resuscitation are readily available.</p> <p>As reported in section 4.3 of the SmPC and related PIL section, nitrous oxide administration is contraindicated in patients affected by pneumothorax, pneumopericardium, severe emphysema and gas embolism.</p> <p>As reported in section 4.4 of the SmPC and related PIL section, when a constant flow of the gas mixture is used, the risk of pronounced sedation, unconsciousness and effects on protective reflexes, e.g. regurgitation and aspiration, should be considered.</p> <p>The gas mixture should be stored and used only in areas/rooms where the temperature exceeds 0°C. At lower temperatures the gas mixture can separate and result in administration of a hypoxic gas mixture.</p> <p>Use of LEVIOXAP 50%/50% v/v gas medicinale compresso is not recommended in neonates. Nitrous oxide may cause in rare cases respiratory depression in the neonate. The neonate should be checked for possible respiratory depression when LEVIOXAP 50%/50% v/v gas medicinale compresso is used during childbirth.</p> <p>Due to the rapid wash-out dilution, a decrease of the alveolar oxygen concentration, diffusion hypoxia, might occur. This can be prevented by oxygen supplementation.</p> <p>As reported in section 4.9 of the SmPC and related PIL section, if the patient becomes cyanotic during use of LEVIOXAP 50%/50% v/v gas medicinale compresso, treatment must immediately be discontinued and pure oxygen should be supplied, assisted ventilation may be required. Overdose of nitrous oxide and or hypoxic gas mixture can occur if the equipment is exposed to cold, below -5°C. This can result in separation of the gas mixture, and consequently an excessively high nitrous oxide concentration can be supplied from the equipment with a risk of a hypoxic gas mixture being supplied.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>Nitrous oxide should always be administered in the presence of medical personnel, who decide whether the medicine can be administered and the appropriate dose.</p> <p><u>Additional risk minimisation measures:</u></p> <p>No additional risk minimisation measures.</p>
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Important identified risk: Volume and baro effects	
Evidence for linking the risk to the medicine	The information about volume and baro effects is presented in the SmPC and in published studies from literature public domain.
Risk factors and risk groups	The risk groups are represented by patients affected by underlying diseases like pneumothorax, pneumopericardium, severe emphysema, gas embolism, decompression sickness, following cardiopulmonary bypass with heart lung machine or coronary bypass without heart lung machine, recent intraocular gas injection (e.g. SF6, C3F8), severely dilated gastrointestinal tract.
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u></p> <p>As reported in section 4.2 of the product SmPC and related sections of the PIL, Administration via endotracheal tubes is not recommended. If the product is to be used in patients breathing through an endotracheal tube, the administration should only be done by health care personnel skilled in the delivery of anaesthesia.</p> <p>As reported in section 4.3 of the product SmPC and related sections of PIL, the product administration is contraindicated in patients affected by underlying diseases like pneumothorax, pneumopericardium, severe emphysema, gas embolism, decompression sickness, following cardiopulmonary bypass with heart lung machine or coronary bypass without heart lung machine, recent intraocular gas injection (e.g. SF6, C3F8), severely dilated gastrointestinal tract.</p> <p>The risk-related ADRs, including feeling of pressure in the middle ear, bloating, increased volume of gas in the intestines are reported in section 4.8 of the product SmPC and related PIL section.</p> <p>Information about pharmacodynamic properties of nitrous oxide is reported in section 5.2 of the SmPC.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>Nitrous oxide should always be administered in the presence of medical personnel, who decide whether the medicine can be administered and the appropriate dose, in structures that allow cardio-respiratory emergency resuscitation.</p> <p><u>Additional risk minimisation measures:</u></p> <p>No additional risk minimisation measures.</p>

Important identified risk: Drugs Interactions	
Evidence for linking the risk to the medicine	The information about drug interactions is presented in the SmPC and in published studies from literature public domain.
Risk factors and risk groups	Risk groups include patients concomitantly taking nitrous oxide/oxygen with opiates, benzodiazepines, barbiturates, other anesthetics, methotrexate, bleomycin, amiodarone, furadantin and similar antibiotics, agents toxic to the lung such as paraquat.
Risk minimisation measures	<p><u>Routine risk minimisation measures:</u></p> <p>As reported in section 4.5 of the product SmPC and related PIL sections, the nitrous oxide component of LEVIOXAP 50%/50% v/v gas medicinale compresso interacts in an additive manner with inhaled anaesthetics and/or other active substances with effects on the central nervous system (e.g. opiates, benzodiazepines and other psychomimetics). If concomitant central acting agents are used the risk for pronounced sedation and depression of protecting reflexes should be acknowledged.</p> <p>LEVIOXAP 50%/50% v/v gas medicinale compresso enhances the inhibiting effect of methotrexate on methionine synthase and folic acid metabolism.</p> <p>The pulmonary toxicity associated with active substances such as bleomycin, amiodarone, furadantin and similar antibiotics may be exacerbated by inhalation of increased concentrations of oxygen.</p> <p>High oxygen fraction may potentiate pulmonary toxicity caused by exposure to agents such as paraquat which are toxic to the lung.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>Nitrous oxide should always be administered in the presence of medical personnel, who decide whether the medicine can be administered and the appropriate dose, in structures that allow cardio-respiratory emergency resuscitation.</p> <p><u>Additional risk minimisation measures:</u></p> <p>No additional risk minimisation measures.</p>
Important potential risk: Occupational exposure	
Evidence for linking the risk to the medicine	The information about occupational exposure is presented in the SmPC and in published studies from literature public domain.

<p>Risk factors and risk groups</p>	<p>The risk group is represented by healthcare professional who are exposed to nitrous oxide through occupational exposure.</p>
<p>Risk minimisation measures</p>	<p><u>Routine risk minimisation measures:</u></p> <p>As reported in section 4.2 of the product SmPC and related sections of the PIL, nitrous oxide should be administered by personnel with knowledge of its use according to local guidelines. In dentistry, the use of a double mask is recommended, alternatively, a nasal mask or nasobuccal mask with adequate scavenging/ventilation is used.</p> <p>As reported in section 4.4 of product SmPC and related sections of the PIL, areas in which LEVIOXAP 50%/50% v/v gas medicinale compresso is used should be adequately ventilated and/or equipped with scavenging equipment in order that the concentration of nitrous oxide in ambient air is below set national hygienic limit values; according to TWA (time weight average), the mean value over a working day and STEL (short term exposure limit) mean value during shorter exposure, national set values must always be followed.</p> <p>As reported in section 4.6 of product SmPC and related sections of the PIL, animal studies at low concentration of nitrous oxide ($\leq 1\%$) suggest that there is a slight alteration in male or female fertility (see section 5.3).</p> <p>The potential risk associated to chronic work place exposure cannot be ruled out.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>Personnel must be properly trained and updated on the use of nitrous oxide that must be administered with appropriate equipment, in well-ventilated rooms suitable for ensuring immediate air exchange, with ventilation systems that do not allow excessive concentrations of gas in the ambient air and using, for example, the so-called "Double masks" ("active" nasal masks), particularly recommended for dental operations.</p> <p><u>Additional risk minimisation measures:</u></p> <p>No additional risk minimisation measures.</p>
<p>Important potential risk: Negative effect on myocardial function</p>	
<p>Evidence for linking the risk to the medicine</p>	<p>The information about negative effect on myocardial function is presented in the SmPC and in published studies from literature public domain.</p>

<p>Risk factors and risk groups</p>	<p>Risk groups include patients affected by pulmonary hypertension, cardiovascular diseases and reduced cardiac performance. The effects on cardiovascular system seem to be concentration-dependent.</p>
<p>Risk minimisation measures</p>	<p><u>Routine risk minimisation measures:</u></p> <p>As reported in section 4.3 of the product SmPC and related sections of PIL, the product administration is contraindicated in patients with heart failure or cardiac dysfunction (e.g. after cardiac surgery) in order to avoid the risk of further deterioration in heart function.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>Nitrous oxide should always be administered in the presence of medical personnel, who decide whether the medicine can be administered and the appropriate dose, in structures that allow cardio-respiratory emergency resuscitation.</p> <p><u>Additional risk minimisation measures:</u></p> <p>No additional risk minimisation measures.</p>
<p>Important potential risk: Increased cerebral blood flow</p>	
<p>Evidence for linking the risk to the medicine</p>	<p>The information about increased cerebral blood flow is presented in the SmPC and in published studies from literature public domain.</p>
<p>Risk factors and risk groups</p>	<p>Patients affected by intracranial complications are at increased risk.</p>
<p>Risk minimisation measures</p>	<p><u>Routine risk minimisation measures:</u></p> <p>As reported in section 4.3 of the product SmPC and related sections of PIL, the product administration is contraindicated in case of head injury and in patients presenting signs of confusion or in some other way showing signs of increased intracranial pressure.</p> <p><u>Other routine risk minimisation measures beyond the Product Information:</u></p> <p>Nitrous oxide should always be administered in the presence of medical personnel, who decide whether the medicine can be administered and the appropriate dose, in structures that allow cardio-respiratory emergency resuscitation.</p> <p><u>Additional risk minimisation measures:</u></p> <p>No additional risk minimisation measures.</p>

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies, which are conditions of the marketing authorisation or specific obligation of LEVIOXAP 50%/50% v/v gas medicinale compresso.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for LEVIOXAP 50%/50% v/v gas medicinale compresso.



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Risk Management Plan

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