

Part VI: Summary of the risk management plan

Summary of risk management plan for PROTOX (nitrous oxide/oxygen)

This is a summary of the risk management plan (RMP) for PROTOX. The RMP details important risks of PROTOX, how these risks can be minimised, and how more information will be obtained about PROTOX's risks and uncertainties (missing information).

PROTOX's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how PROTOX should be used.

I. The medicine and what it is used for

PROTOX is authorised for the treatment of short-lasting, mild to moderate pain conditions, when an analgesic effect that sets in and quickly disappears is desired and for sedation during dental surgery in anxious patients (see SmPC for the full indication). It contains nitrous oxide and oxygen at percentage of 50% each as the active substances and it is given by inhalation.

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

Important risks of PROTOX, together with measures to minimise such risks and the proposed studies for learning more about PROTOX's 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 PROTOX 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 PROTOX. 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	– Inhibition of the methionine synthase pathway (inhibition of vitamin B12) – Respiratory depression – Volume and baro effects – Drugs interactions
Important potential risks	– 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	Nitrous oxide renders vitamin B12 inactive. As consequence an impairment of the folic acid metabolism affects DNA-synthesis and cell-proliferation can be observed. An acute effect is megaloblastic anaemia. The transmethylation reaction is essential to DNA synthesis and to the maintenance of the myelin sheath by the methylation of myelin basic protein.
Risk factors and risk groups	Patients with reduced intake or uptake of vitamin B12 and/or folic acid or subject with a genetic disorder in the enzyme system involved in the metabolism of these vitamins, as well as in immunosuppressed patients.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC section 4.3 contraindication in patients with vitamin B12 or folic acid deficiency. SmPC section 4.4 PL sections: 2 and 4 The medicinal products can be administered and prescribed only by qualified persons <u>Additional risk minimisation measures:</u>

	none
--	------

Important identified risk: Respiratory depression	
Evidence for linking the risk to the medicine	There are additive effects when N2O is used in combination with other inhaled and/or intravenous anaesthetics or drugs having a central depressant action (e.g. opiates, benzodiazepines and other psychomimetics). These interactions have clear effects in clinical practice, decreasing the dose needed for the other agents combined with N2O, causing less cardiovascular and respiratory depression and increasing speed of emergence. However, if concomitant central acting agents are used the risk for pronounced sedation and depression of protecting reflexes should be acknowledged.
Risk factors and risk groups	Patients simultaneously treat with medical with a central depressant action. Newborn when the mother is treated with PROTOX during delivery.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> <i>SmPC section 4.4 and 4.5</i> PL sections: 4 The medicinal products can be administered and prescribed only by qualified persons. <u>Additional risk minimisation measures:</u> none

Important identified risk: Volume and baro effects	
Evidence for linking the risk to the medicine	This risk is well known and can occur during inhalation of nitrous oxide because the gas bubbles and enclosed gas filled spaces may expand due to the enhanced diffusivity of nitrous oxide. As consequence as baro-volumetric effects can be occurred and they can be serious and life-threatening such as pneumothorax, pneumopericardium, gas emboli. In addition the expansion of intraocular gas and the increase of middle-ear pressure, which can occur in patients receiving nitrous oxide anaesthetic, can be led to severe clinical outcome as well.
Risk factors and risk groups	Divers, surgical patients (particularly abdominal, thoracic, ear surgery), patients with extensive severe chronic lung disease (emphysema, pneumothorax, etc.).
Risk minimisation measures	<u>Routine risk minimisation measures:</u> <i>SmPC section 4.3 and 4.4</i> PL sections: 2 and 4 The medicinal products can be administered and prescribed only by

	qualified persons. <u>Additional risk minimisation measures:</u> none
--	--

Important identified risk: Drugs interactions	
Evidence for linking the risk to the medicine	There are additive effects when N2O is used in combination with other inhaled and/or intravenous anaesthetics or drugs having a central depressant action (e.g. opiates, benzodiazepines and other psychomimetics). Nitrous oxide reduces the minimum alveolar concentrations (MAC) of inhalational anaesthetics in an additive manner; an inspired concentration of 60-70% N2O is commonly used with volatile anaesthetics. Niu et al. (2017) investigated whether nitrous oxide influenced the ED50 of sevoflurane for induction of isoelectric electroencephalogram (ED50isoelectric) differently from its influence on the ED50 of sevoflurane for electroencephalogram. The main result of this study is that the ED50isoelectric of sevoflurane is significantly higher with N2O than without. Nishiyama et al. (2016) conducted a study to compare cardiac sympathetic and parasympathetic balance using heart rate variability (HRV) during induction of anaesthesia between sevoflurane and isoflurane in combination with nitrous oxide. Eventually, anaesthesia induction with isoflurane-nitrous oxide transiently increased cardiac sympathetic activity, while sevoflurane-nitrous oxide decreased both cardiac sympathetic and parasympathetic activities. The balance of cardiac parasympathetic/sympathetic activity was higher in sevoflurane anaesthesia. In addition, animal studies have shown interaction between N2O and sedative medical product. Dawson et al 2004, reported a synergistic analgesic interaction between nitrous oxide and dexmedetomidine where the analgesic action of nitrous oxide is increased by dexmedetomidine. The authors speculate that the addition of dexmedetomidine to nitrous oxide is likely to provide enhanced and more durable analgesia. Additionally, Pruhs et al (1989) reported a study where nitrous oxide increase the antianxiety effect of diazepam without increasing its sedative effect in the mouse. Regarding methotrexate, its administration is associated with frequent adverse neurological events during the treatment for acute lymphoblastic leukaemia in childhood, in particular the use of nitrous oxide contributes to methotrexate neurotoxicity: concomitant use of nitrous oxide and methotrexate is a common practice when

	performing lumbar puncture to administer intrathecal (IT) methotrexate. Forster et al. (2016) reported a case of a 12 years old girl affected by acute undifferentiated leukaemia that received IT methotrexate as part of the chemotherapy. For anaesthesia propofol was administered followed by a gaseous mix of nitrous oxide and oxygen. Four days after the 5th dose of IT methotrexate, she was presented with focal seizures rapidly progressing to generalized tonic-clonic seizures, disinhibition, severe agitation and left upper limb (LUL) weakness. MRI (T2/FLAIR and diffusion weighted) imaging on day 2 showed widespread hyperintense subcortical white matter lesions in the frontal and parietal regions with areas of restricted diffusion consistent with leukoencephalopathy. Seizure activity continued for 5 days despite maximal anticonvulsant doses of benzodiazepines and levetiracetam and the radiological changes worsened with increasing cerebral oedema and pressure effects requiring dexamethasone. She made a clinical recovery over the next 7 days but with some residual LUL weakness. Serum vitamin B12 was measured on recovery (3 weeks from the last IT methotrexate) and was low at 154 ng/L (normal range 200–1100 ng/L).
Risk factors and risk groups	Any patient in treatment with sedative medical product before PROTOX used or any patient when a concomitant sedative drug is given during the surgery. The risk of occurrence of adverse reaction linked with drug-drug interaction can be recorded in any patients simultaneously treated with methotrexate and nitrous oxide.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> <i>SmPC section 4.4 and 4.5</i> PL sections: 2 The medicinal products can be administered and prescribed only by qualified persons. <u>Additional risk minimisation measures:</u> none

Important potential risk: Occupational exposure	
Evidence for linking the risk to the medicine	Inhibition of methionine synthase by nitrous oxide is dose and duration dependent; therefore, it is plausible that environmental nitrous oxide exposure may induce an occupational risk. The majority of animal studies investigating potential effects on reproduction have used very high doses with prolonged administration, limiting the relevance of their results to the clinical setting.

	Studies in animals of doses of nitrous oxide that are consistent with occupational exposure have shown increased foetal loss and impaired postnatal development with 1,000 ppm but no effect with 500 ppm or lower when administered for the duration of pregnancy. Nitrous oxide-induced fertility problems do not occur at 1,000 ppm or lower in animals, although they have been shown to be present at 5,000 ppm in some but not all studies. The animal data suggest that doses of 500 ppm are a threshold for this toxicity. In human the reproductive toxicity of occupational exposure to nitrous oxide at levels below the OELs have not been substantiated by the available data, which unfortunately do not include prospective epidemiologic studies. In a questionnaire study attempting to address concerns about female fertility, data were sought from 7,000 dental assistants and included an estimation of their exposure to nitrous oxide as well as their time to conception. However, only 69% responded, and analysis was possible on only 459 replies because of exclusion through insufficient data or predefined criteria. From this limited data set, the authors concluded that unscavenged nitrous oxide exposure (which they estimated to exceed 1,000 ppm) for greater than 5 h per week was associated with reduced ability to conceive. Exposure to nitrous oxide in scavenged clinical settings seemed safe. Follow-up data showed that although exposure to nitrous oxide in an unscavenged setting was associated with an increased risk of spontaneous abortion, this was attributable to a group of 20 dental assistants exposed to 5–9 h of unscavenged nitrous oxide per week. Interestingly, no greater risk of spontaneous abortions occurred with unscavenged exposure beyond 10 h or after occupational exposure in scavenged settings. With the caveat that these are retrospective questionnaire data, these studies confirm the occupational safety of nitrous oxide in the scavenged workplace.
Risk factors and risk groups	Health care professional daily involved in medical practice, including anaesthesia, pain medicine, obstetrics, emergency medicine, and dentistry.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> <i>SmPC section 4.4</i> PL sections: The following information is intended for healthcare professionals only - Security Precautions. The medicinal products can be administered and prescribed only by qualified persons. <u>Additional risk minimisation measures:</u> none

Important identified risk: Negative effect on myocardial function	
Evidence for linking the risk to the medicine	Eisele's work on healthy volunteers subjected to 40% N₂O/60% O₂, when compared with 40% nitrogen control clearly, demonstrated small but statistically significant decreases in heart rate, cardiac output, and ballisto-cardiographic effects compatible with a negative inotropic effect. In addition the Evaluation of Nitrous Oxide in the Gas Mixture for Anesthesia (ENIGMA-I) trial randomized 2050 patients who underwent noncardiac surgery with N₂O-based or N₂O-free anesthesia. The study showed increased occurrence of myocardial infarction, venous thromboembolism, stroke, and death within 2 days of surgery.
Risk factors and risk groups	Heart disease and patient with heart failure and cardiac dysfunction.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> <i>SmPC section 4.3 and 4.4</i> PL sections: 2 and 4 The medicinal products can be administered and prescribed only by qualified persons. <u>Additional risk minimisation measures:</u> none

Important identified risk: Increased cerebral blood flow	
Evidence for linking the risk to the medicine	Nitrous oxide is known to increase cerebral blood flow (CBF) in animals and humans, suggesting a vasodilatory effect. However, discrepancies in the results of the studies remain due to different doses, interactions with other anaesthetic agents and potential differences between species. With the use of 50% nitrous oxide in isolation, significant increases in cerebral blood flow velocity, and decreases in cerebral vascular tone have been shown. The precise mechanism by which nitrous oxide increases CBF remains unclear. In the past, it has been suggested that the increase in CBF could be indirect, due to increases in cerebral metabolism. However, the studies using different doses, with and without the presence of other anaesthetic agents, support both direct and indirect effects of nitrous oxide on cerebral vasculature. Recent data suggest that inhalation of 50% nitrous oxide does not induce changes in global cerebral metabolism, despite some regional effects. (<i>Dashdorj et al, 2013</i>). The increase in cerebral blood flow could affect all patients subjected to nitrous oxide administration, leading to consequences that can vary from headache to cerebral edema. In the brain there is a cerebral self-regulation mechanism, capable of responding to physiological changes and pathological disorders, trying to maintain a constant cerebral blood flow. Increased flow, when associated with

	brain lesions with cerebral vessels that are fragile or more permeable to water, can cause cerebral vasodilatation and increase cerebral oedema.
Risk factors and risk groups	Administration in patients showing signs of confusion or in the presence of other signs indicating increased intracranial pressure is contraindicated.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> <i>SmPC section 4.3</i> PL sections: 2 The medicinal products can be administered and prescribed only by qualified persons. <u>Additional risk minimisation measures:</u> none

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 PROTOX.

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

There are no studies required for PROTOX.