SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Protoxan 50 % / 50 %, medicinal gas, compressed

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each cylinder contains: Nitrous oxide (medicinal N_2O) 50 % v/v and oxygen (medicinal O_2) 50 % v/v - 170 bar (15 ºC).

3. PHARMACEUTICAL FORM

Medicinal gas, compressed.
Colourless and odourless gas.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Protoxan is indicated for the treatment of short-term pain conditions of mild to moderate intensity when rapid analgesic onset and offset effects are wanted.

Protoxan is indicated in children aged more than 1 month, adolescents and adults

4.2. Posology and method of administration

Special precautions must be taken when working with nitrous oxide. Nitrous oxide should be administered according to local regulations.

Posology

The administration of Protoxan should start shortly before the analgesic effect is required. The analgesic effect is seen after 4-5 breaths and reaches its maximum in 2-3 minutes. The administration of Protoxan should continue throughout the painful process, or as long as the analgesic effect is desired. Following discontinuation of the administration/inhalation, the effects wear off quickly within a few minutes.

Paediatric population
The safety and efficacy of Protoxan in children younger than 1 month has not been established.

Method of administration
Protoxan is administered via inhalation in spontaneously breathing patients via a face mask. Administration of Protoxan is governed by the patient’s breathing. By holding the mask tightly around the mouth and nose and breathe through the mask, it opens a "demand valve" and Protoxan flows from the cylinder and is administered to the patient through the airways. Absorption occurs in the lungs.

To reduce the risk of aspiration associated with the combination of a sedative effect and increased risk for nausea and vomiting (see section 4.4), local institutional guidelines for fasting before anaesthetic procedures should be followed.

In odontology, the use of a double mask is recommended; alternatively, a nasal or oral-nasal mask with adequate scavenging / ventilation is used.

Administration via endotracheal tubes is not recommended. If Protoxan is used in patients breathing through an endotracheal tube, the application must be made only by health care personnel skilled in the delivery of anaesthesia.

According to the individual pain relieving reaction in the patient, additional analgesics may be required.

Protoxan should be administered only by personnel with knowledge of its use. Administration of Protoxan should only occur under the supervision and instruction of personnel familiar with the equipment and its effects. Protoxan should only be administered when the possibility of oxygen supplementation and equipment for resuscitation is readily available.

Ideally, the patient should hold the mask through which Protoxan is administered. The patient should be instructed to hold the mask to his/her face and breathe normally. This is an additional safety measure to minimize the risk of overdose. If for any reason the patient receives more Protoxan than is necessary and wakefulness becomes affected, the patient will drop the mask and administration will cease. By breathing ambient air, the effect of Protoxan rapidly wears off and the patient will regain consciousness.

Protoxan should preferably be used in patients able to understand and follow instructions about the use of the equipment and the mask. In children or other patients who are unable to understand and follow the instructions, Protoxan might be administered under the supervision of competent medical personnel who can help them keep the mask in place and actively monitor the administration. In such cases, Protoxan may be administered with a constant gas flow. Due to the increased risk of the patient becoming markedly sedated and unconscious, this form of administration should however, only take place under controlled conditions. Continuous gas flow should be used only in the presence of competent personnel and with equipment available to manage the effects of the more pronounced sedation/decreased level of consciousness. The potential risk of possible inhibition of protective airway reflexes should be acknowledged and preparedness to secure the airway and assist ventilation available whenever constant flow is used.

When the administration is ended, the patient should be allowed to recover under calm and controlled conditions, for around 5 minutes, or until the patient’s degree of alertness / consciousness has recovered satisfactorily.

Protoxan can be administered for up to 6 hours without haematological monitoring in patients with no risk factors (see section 4.4). Nitrous oxide should not be given more frequently than every 4 days.

4.3. Contraindications

When Protoxan is inhaled, the gas bubbles (gas emboli) and the gas-filled cavities may expand due to the increased ability of nitrous oxide to diffuse. Thus, Protoxan is contraindicated in the following conditions:

- In patients with signs or symptoms of pneumothorax, pneumopericardium, severe emphysema, gas embolism or head injury.
- Following deep sea diving with risk of decompression sickness (bubbles of nitrogen).
- Following cardiopulmonary bypass with heart lung machine or coronary bypass without heart lung machine.
- In patients who have recently received an intraocular injection of gas (eg. SF_6, C_3F_8, C_2F_6) until the gas in question is completely absorbed, because the gas may increase the pressure / volume and therefore result in blindness.
- In patients with severe dilatation of the gastrointestinal tract.

Protoxan is also contraindicated:

- In patients with heart failure or cardiac dysfunction (eg. after cardiac surgery) in order to avoid the risk of further deterioration in heart function.
- In patients showing signs of confusion, changed cognitive function or other signs that could be related to increased intracranial pressure as nitrous oxide may further increase the intra-cranial pressure.
- In patients with decreased level of consciousness or impaired ability to cooperate and follow instructions because of the risk that further sedation from the nitrous oxide, may affect natural protective reflexes.
- In patients with diagnosed but untreated vitamin B12 or folic acid deficiency or genetic disorder of the enzyme system involved in the metabolism of these vitamins.
- In patients with facial injury where the use of face masks may present difficulties or risks.

4.4. Special warnings and precautions for use

Protoxan should only be administered by competent personnel with access to adequate resuscitation equipment (see section 4.2).

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.

The potential of drug abuse should be acknowledged.

Warnings
Nitrous oxide affects vitamin B12 and folate metabolism. Inhibits methionine synthase which contributes to the conversion of homocysteine to methionine. Inhibition of this enzyme affects/reduces the formation of thymidine which is an important part of the formation of DNA. Inhibition of the formation of methionine by nitrous oxide may cause defects and reduced formation of myelin, and therefore damage to the spinal cord. The effect on DNA synthesis is one of the probable reasons for the influence of nitrous oxide in the formation of blood and fetal damage seen in animal studies.

Reduced fertility in medical and paramedical personnel has been reported after repeated exposure to nitrous oxide in inadequately ventilated rooms. It is not currently possible to confirm or exclude the existence of any causal connection between these cases and exposure to nitrous oxide. It is important that the content of nitrous oxide in the ambient air is kept as low as possible and below the nationally set limit value.

The areas where Protoxan is used should be ventilated and / or equipped with scavenging equipment to keep the concentration of nitrous oxide in ambient air 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.

The gas mixture should be stored and used only in areas / rooms where the temperature exceeds -5 °C. At lower temperatures the gas mixture can separate and result in administration of a hypoxic gas mixture.

Protoxan can be used in children who can follow instructions on how to use the equipment. In the treatment of younger children or other patients who are unable to follow instructions, the use of constant gas flow may be required. Continuous gas-flow should be applied only by medical personnel trained in the use of the gas, with equipment available to secure the airway and for provision of assisted ventilation (see also section 4.2.).

Special precautions for use
Nitrous oxide can affect vitamin B12 and folate metabolism, therefore, Protoxan should be used with caution in patients at risk, ie, patients with reduced intake or uptake of vitamin B12 and / or folic acid, or a genetic disorder in the system of enzymes involved in the metabolism of these vitamins as well as in immunosuppressed patients. If necessary, substitution treatment with vitamin B12/folic acid should be considered.

Continuous administration for periods longer than 6 hours must be done with caution because of the possible risk of clinical manifestations from the inhibitory effects on methionine synthase. Prolonged continuous use or recurrent use should be accompanied by haematological monitoring to minimize the risk of potential side effects.

Due to its content of nitrous oxide, Protoxan can increase the pressure in the middle ear and other air-filled cavities (see also section 4.3.).

In patients taking other medicinal products affecting the central nervous system, e.g. derivatives of benzodiazepines and / or morphine, concomitant administration of Protoxan may result in increased sedation, and therefore, can affect breathing, circulation and protective reflexes. If Protoxan is to be used in such patients, this should take place under the supervision of appropriately trained personnel (see section 4.5).

Repeated administration or exposure to nitrous oxide may lead to addiction. Caution should be excercised in patients with a known history of substance abuse or in healthcare professionals with occupational exposure to nitrous oxide.

Nitrous oxide causes inactivation of vitamin B12, which is a co-factor of methionine synthase. Folate metabolismo is consequently interfered with and DNA synthesis is impaired following prolonged administration of Nitrous Oxide. Prolonged or frequent use of Nitrous oxide may result in megaloblastic marrow changes, myeloneuropathy and subacute combined degeneration of the spinal cord. Nitrous oxide should not be used without close clinical supervision and haematological monitoring. Specialist advice should be sought from a haematologist in such cases.

Haematological assessment should include assessment for megaloblastic change in red cells and hypersegmentation of neutrophils. Neurological toxicity can occur without anaemia or macrocytosis and with vitamin B12 levels in the normal range. In patients with undiagnosed subclincial deficiency of vitamin B12, neurological toxicity has occured after single exposures to Nitrous Oxide during anaesthesia.

After discontinuing Protoxan administration, the patient should recover under proper supervision until the potential risks resulting from the use of Protoxan have subsided and the patient has recovered satisfactorily. The recovery of the patient should be assessed by healthcare personnel.

After cessation of Protoxan administration, nitrous oxide rapidly diffuses from the blood into the alveoli. 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.

Paediatric population

The safety and efficacy of Protoxan in children younger than 1 month has not been established.

4.5. Interaction with other medicinal products and other forms of interaction

Interaction with other medicinal products

The nitrous oxide component of Protoxan interacts additively with inhaled anesthetics and / or other active substances with effects on the central nervous system (eg. opiates, benzodiazepines and other psychomimetic). If other agents acting on the central nervous system are used the risk for pronounced sedation and depression of protecting reflexes should be acknowledged (see section 4.4).

Protoxan enhances the inhibitory effect of methotrexate on methionine synthase and the metabolism of folic acid.

Pulmonary toxicity associated with active substances such as bleomycin, amiodarone, and nitrofurantoin and similar antibiotics may be exacerbated by inhalation of increased concentrations of oxygen.

Other forms of interaction
The nitrous oxide component of Protoxan causes inactivation of vitamin B12 (a co-factor for the synthesis of methionine), which interferes with the metabolism of folic acid. Thus, DNA synthesis is impaired after prolonged use of nitrous oxide. These disturbances may lead to megaloblastic bone marrow changes and possibly polyneuropathy and / or subacute combined degeneration of the spinal cord (see also section 4.8). Therefore, the administration / application of Protoxan must be for a limited time (see also sections 4.2 and 4.4).

4.6. Fertility, pregnancy and lactation

Pregnancy
The nitrous oxide component of Protoxan may interfere with the metabolism of vitamin B12 / folic acid (see section 4.4).

The inhibition of methionine synthase may cause adverse effects during early stages of pregnancy. There are no adequate data from use of Protoxan in pregnant women to determine the potential harmful effects on embryonic / foetal human.

Animal studies have shown that high concentrations or prolonged exposure during particular stages of pregnancy can induce teratogenic effects (see section 5.3). The potential risk for humans is unknown.

Therefore, it is recommended to avoid the use of Protoxan during the first two trimesters of pregnancy. Protoxan can be used during the later stages of pregnancy, third trimester and delivery. When Protoxan is used close to delivery, newborns should be supervised for possible adverse effects.

Lactation
Protoxan can be used during the breast-feeding period, but should not be used during breast-feeding itself.

4.7. Effects on ability to drive and use machines

The nitrous oxide component of Protoxan has effects on cognitive and psychomotor functions.
It is rapidly eliminated from the body after brief inhalation and adverse psychometric effects are rarely evident 20 minutes after the administration has stopped while its influence on the cognitive capabilities can persist for several hours.

When used as the sole analgesic/sedative agent, driving and use of complex machinery is not recommended for at least 30 minutes after cessation of the administration of Protoxan and until the patient has returned to their initial mental status as judged by the attending healthcare professional.

4.8. Undesirable effects

Megaloblastic anaemia and leukopenia have been reported following prolonged or repeated exposure to Protoxan. Neurological effects such as polyneuropathy and myelopathy have been reported after exceptionally high and frequent exposure.

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.

Other analgesic therapies should be considered in patients showing signs of vitamin B12/folate deficiency.

The undesirable effects listed are derived from public domain scientific medical literature and post marketing safety surveillance.

	Common (≥1/100 to <1/10)	***Uncommon (≥1/1,000 to <1/100)***	***Very rare (<1/10,000)***	***Not known (cannot be estimated from the available data)***
Blood and lymphatic system disorders				Megaloblastic anaemia, leukopenia.
Psychiatric disorders				Psychosis, anxiety, confusion.
Nervous system disorders	Vertigo, dizziness, light headaches, euphoria.	Severe fatigue.	Polyneuropathy, paraparesis, myelopathy.	Headache. Generalised seizures. Addiction, myeloneuropathy, neuropathy, subacute degeneration of the spinal cord.
Ear and labyrinth disorders		Feeling of pressure in the middle ear.		
Gastrointestinal disorders	Nausea, vomiting.	Bloating, increased volume of gas in the intestine.		
Respiratory, thoracic and mediastinal disorders				Respiratory depression

Paediatric population

The safety and efficacy of Protoxan in children younger than 1 month has not been established.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9. Overdose

Since participation of the patient is required to administer the gas mixture, the risk of overdose is very small.

If while using Protoxan the patient shows signs of reduced consciousness, becomes unresponsive, or does not respond properly to commands, or shows other signs of sedation, administration should be stopped immediately. The patient should not receive further Protoxan until full consciousness has been restored.

If the patient becomes cyanotic ***or measured oxygen saturation drops*** during the use of Protoxan, treatment should be stopped immediately, pure oxygen should be supplied and the patient may require assisted breathing.

Reversible neurological toxicity and megaloblastic bone marrow change have also been observed following exceptionally prolonged inhalation.

Overdose of nitrous oxide and / or hypoxic gas mixture can occur if the equipment is exposed to cold conditions, below -5 ºC. This can lead to separation of the gas mixture. Consequently an excessively high nitrous oxide concentration can be supplied from the equipment with a risk of a hypoxic gas mixture being supplied.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Other general anaesthetics, ATC code N01AX63.

Nitrous oxide in concentrations of 50% has analgesic effects, raising the threshold of pain to various painful stimulus. The intensity of analgesic effect depends mainly on the patient's psychological state. At this concentration (50%), nitrous oxide has limited anaesthetic effects.

At these concentrations, nitrous oxide provides a sedative and calming effect but the patient remains conscious, easily arousable but with a certain detachment from his/her surroundings.

The concentration of 50% oxygen (more than twice the concentration of ambient air) ensures good oxygenation and optimal oxygen saturation of haemoglobin.

5.2. Pharmacokinetic properties

The absorption and elimination of nitrous oxide occur exclusively through lungs. As a result of the low solubility of nitrous oxide in the blood and other tissues, the saturation of the blood and target organ is quickly reached. These physicochemical characteristics explain the rapid onset of analgesia and the fact that the effects of nitrous oxide rapidly disappear after cessation of application. The gas is eliminated exclusively by respiration, nitrous oxide is not metabolized in the human body.

The rapid diffusion of nitrous oxide in blood and gas explains some of the contraindications and special precautions to be taken into account when using nitrous oxide / Protoxan.

5.3. Preclinical safety data

Preclinical data indicate that there is no special hazard for humans based on conventional studies of safety pharmacology, repeated dosed toxicity, mutagenicity and carcinogenicity potential.

It was observed that prolonged continuous exposure to 15 - 50% nitrous oxide cause neuropathy in bats, pigs and monkeys.

Teratogenic effects have been observed with nitrous oxide in rats after chronic exposure to levels above 500 ppm.

Pregnant rats exposed to nitrous oxide of 50 - 75% for 24 hours in each of the 6 to 12 days of gestation, showed higher incidence of miscarriage and malformations of ribs and vertebrae. No effects on rabbits and mice were described.

Non-clinical data have shown that chronic exposure at trace concentrations of nitrous oxide (≤1%) is not embryotoxic or teratogenic in rats but suggest that nitrous oxide may induce slight changes in

fertility in female and male rats (trend low, dose related, to a slight increase in reabsortion and decrease in live births).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

None

6.2. Incompatibilities

The degree of incompatibility of materials with the mixture of oxygen and nitrous oxide 50%, depends on the conditions of gas pressure. However, the risk of fire is higher when the mixture is in contact with fuel compounds, especially grease (lubricant, oils) and organic materials (plastics, wood, paper, textiles). Fire can start spontaneously or by spark ignition, at the flame or ignition points, or by adiabatic compression. Therefore:

- Never use oil or grease, even if the cylinder valve is difficult to open or if the regulator is difficult to connect.
- Never put this gas mixture in contact with devices that are suspected to contain combustible material or grease.
- Use only standard equipment that is intended for the gas mixture 50% N_2O/50% O_2.
- Handle valves and accompanying equipment with clean and grease-free (hand cream etc.) hands.
- Do not use aerosols (hairspray, deodorant, etc.) or solvents (alcohol, perfume, etc.) on/or near the equipment.
- Do not use any oily product (petroleum jelly, ointment, etc.) in the face of patients when they are using the mixture.
- Do not smoke while handling the product or in its proximities.

6.3. Shelf life

3 years

6.4. Special precautions for storage

Do not store below -5 ºC.

The mixture is unstable below -5 ºC. Lower temperatures can cause a temporary liquefaction of the nitrous oxide, which would lead to a uneven mix, with too much oxygen at the beginning of the administration (mixture with little analgesic effect) and too much nitrous oxide at the end (hypoxic mixture) of the inhalation.

On suspicion that Protoxan has been stored at temperatures below -5ºC the cylinders should be stored in a horizontal position at a temperature above 10 ºC for at least 48 hours before use. It is recommended that the cylinder is shaken by inverting it completely at least three times to ensure homogenization before use.

When it is used in emergency service vehicles, the cylinders must be protected from the cold and firmly secured, inside and outside of the vehicles.

Storage precautions related to gas cylinders and pressurized gases
- Vapour may cause drowsiness and dizziness.
- Different gas types must be separated from each other. Full and empty gas cylinders must be stored separately.
- No smoking. Must not be exposed to strong heat.
- Keep away from combustible material.

- If at risk of fire – move to a safe place.
- Keep the cylinder clean, dry and free from oil and grease.
- Keep in upright position.
- Make sure the cylinder is not knocked over or dropped.
- Store and transport with valves closed.

6.5. Nature and contents of container

Cylinders

The cylinders are of seamless steel or aluminium of various sizes. The cylinders are identified through specific colours for the product defined according to EN 1089-3 (white body with blue and white shoulder, with two horizontal bands and the blue is the lower).

Pack sizes

Aluminium cylinder with integrated valve or normal PRV valve:
2-litres filled at 170 bar gives 0.56 m3 gas at atmospheric pressure and 15 °C.
5-litres filled at 170 bar gives 1.4 m^3 gas at atmospheric pressure and 15 ˚C.
10-litres filled at 170 bar gives 2.8 m^3 gas at atmospheric pressure and 15 ˚C.

Seamless steel gas cylinder with integrated valve or normal PRV valve:
5-litres filled at 170 bar gives 1.4 m^3 gas at atmospheric pressure and 15 ˚C.
10-litres filled at 170 bar gives 2.8 m^3 gas at atmospheric pressure and 15 ˚C.

Seamless steel gas cylinder with normal PRV valve:
50-litres filled at 170 bar gives 14 m^3 gas at atmospheric pressure and 15 ˚C.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

General
Medicinal gases must be used for medicinal purposes only.

Different gas types must be separated from each other. Full and empty gas cylinders must be stored separately.

Never use oil or grease, even if the cylinder valve is difficult to open or if the regulator is difficult to connect. Handle valves and accompanying equipment with clean and grease-free (hand cream etc.) hands.

Shut off the equipment in the event of fire, or if not in use. If at risk of fire, move to a safe place.

Use only standard equipment that is intended for the gas mixture 50% N_2O / 50% O_2.

Check that the cylinders are sealed before they are taken into use.

Preparation prior to use
Remove the seal from the valve and the protective cap before use.

Use only regulators intended for the gas mixture 50% N_2O / 50% O_2.

Check that the quick connector and regulator are clean and that the connections are in good condition.

Never use a tool to connect a pressure/flow regulator that is intended to be connected manually, as this can damage the coupling.

Open the cylinder valve slowly at least half a turn.

Always follow the instructions accompanying the regulator. Check for leakage in accordance with the instructions accompanying the regulator. Do not try to deal with leakage from the valve or equipment yourself, other than by changing the gasket or O-ring.

In the event of leakage, close the valve and uncouple the regulator. If the cylinder continues to leak, empty the cylinder out of doors. Label defective cylinders, place them in an area intended for claims and return them to the supplier.

Cylinders with a compact-valve have an inbuilt pressure regulator in the valve. Consequently, a separate pressure regulator is unnecessary. The compact-valve has a quick connector for connecting “on demand” masks, but also a separate outlet for constant flow of gas, where the flow can be regulated from 0-15 litres/min.

Using the gas cylinder
Larger gas cylinders must be transported by means of a suitable type of cylinder trolley. Take special care that connected devices are not inadvertently loosened.

Smoking and open flames are strictly forbidden in rooms where treatment with Protoxan is taking place.

When the cylinder is in use it must be fixed in a suitable support.

The gas cylinder should be replaced when the pressure in the cylinder has dropped to a point where the indicator on the valve is within the yellow field.

When a small quantity of gas is left in the gas cylinder, the cylinder valve must be closed. It is important that a small amount of pressure is left in the cylinder to avoid the entrance of contaminants.

After use the cylinder valve must be closed hand-tight. Depressurise the regulator or connection.

7. MARKETING AUTHORISATION HOLDER

To be completed nationally

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21-02-2013

To be completed nationally

10. DATE OF REVISION OF THE TEXT

8 November 2019