SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Medicinsk Lustgas Air Liquide 100%, medicinal gas, liquefied.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nitrous oxide (N_2O, medicinal laughing gas) 100%.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Medicinal gas, liquefied.
Colourless gas with a slightly sweet taste and smell.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nitrous oxide is used:

- in anaesthesia, in combination with other inhalation anaesthetics or intravenous anaesthetics.
- for analgesia/sedation in all situations where pain relief/sedation of rapid onset and rapid elimination are desirable.

4.2 Posology and method of administration

Posology
Nitrous oxide produces dose-dependent pain-relieving and sedating effects and has dose-dependent effects on cognitive functions.

Nitrous oxide is normally used in concentrations between 35 and 75 vol.% in mixtures with oxygen and if necessary with other anaesthetics.

Nitrous oxide as sole anaesthetic is usually not sufficiently potent for surgical anaesthesia, but should therefore be combined with other anaesthetics when used in general anaesthesia.

Nitrous oxide has an additive effect when combined with most other anaesthetics (see section 4.5).

The effects of nitrous oxide given as a sole agent are not dependent on the patient's age, but when co-administered with other anaesthetics the mixture usually has increased effect on older patients compared to younger ones.

Nitrous oxide should not be administered in concentrations greater than 70-75 vol.% so that a safe oxygen fraction can be guaranteed. In patients with lowered oxygen saturation, an oxygen fraction safe for the patient should be used. Nitrous oxide in concentrations of up to 50-60% alleviates pain, sedates, and reduces agitation, but usually without affecting the degree of consciousness or capacity to react to speech. Breathing, circulation and protective reflexes are normally preserved at these concentrations.

Method of administration

Personnel who administer nitrous oxide must be adequately trained and practised in using this medicinal product. Nitrous oxide should only be administered where there is adequate equipment available to secure an open airway immediately and commence emergency cardiopulmonary resuscitation if necessary.

Nitrous oxide should be given by inhalation (either spontaneous breathing by the patient or controlled ventilation).

Nitrous oxide should be given in combination with oxygen, using special equipment that can deliver a mixture of nitrous oxide and oxygen. This equipment should include oxygen concentration monitoring and alarm facilities so that a hypoxic gas mixture (FiO_2 < 21 vol.%) is not administered.

Nitrous oxide should not be administered for more than 12 hours at a time.

Nitrous oxide should be used only in premises with adequate ventilation and/or exhaust facilities to avoid high nitrous oxide gas concentrations in the ambient air. The air quality should accord with local regulations, and exposure to nitrous oxide at work should be below nationally determined hygienic limits.

4.3 Contraindications

Nitrous oxide must not be administered to patients with the following diseases/symptoms/conditions:

- Hypersensitivity to the active substance
- When 100% O2 ventilation is required.
- Any condition where air is entrapped within the body and where its expansion might be dangerous such as:
    - head injury
    - maxillofacial injuries
    - pneumothorax.
    - gas emboli
    - decompression sickness
    - following a recent underwater dive
    - following air encephalography
    - bubbles of emphysema
    - during middle ear, inner ear and sinus surgery
    - gross abdominal distension (e.g. intestinal obstruction)
    - if air has been injected into the epidural space to determine the placement of the needle for epidural anaesthesia
    - following treatment with heart lung machine or coronary bypass without heart lung machine
- Patients having received recent intraocular injection of gas (such as SF6, C3F8, C2F6) as long as an intraocular gas bubble persists or within 3 months after the last injection of an intraocular gas. The expansion an intraocular gas bubble by nitrous oxide can cause severe visual impairment (see Sections 4.5 and 4.8).

- heart failure or severely impaired cardiac function (e.g. after cardiac surgery), since the mild myocardiodepressive effect may cause further deterioration in heart function.

- pronounced confusion, altered consciousness or other signs that might be related to increased intracranial pressure, since nitrous oxide may increase this further.

- impaired consciousness and/or capacity to cooperate when nitrous oxide is used to alleviate pain, because of the risk of inhibited protective reflexes.

- In patients with untreated vitamin B12- or folic acid deficiency or diagnosed genetic disorder of the enzyme system involved in metabolism of these vitamins. (see 4.4)

4.4 Special warnings and precautions for use

Nitrous oxide should never be given with less than 21% oxygen

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

Nitrous oxide should not be used for long periods of time, e.g. for sedation in intensive care, because of the potential risk of affecting vitamin B_{12} (a co-factor in methionine synthetase). Assessment of vitamin B 12 levels should be considered in people with risk factors for vitamin B12 deficiency prior to using nitrous oxide. Risk factors may include alcoholic patients, patients suffering from anaemia, or atrophic gastritis, those with vegetarian diet, or recent use of medications that interfere with vitamin B12 and/or folate metabolism (see Section 4.5). Vitamin B12 supplements should be given in the case of repeated and prolonged administration.

Nitrous oxide causes inactivation of vitamin B12, which is a co-factor of methionine synthase. Folate metabolism 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 subclinical deficiency of vitamin B 12 neurological toxicity has occurred after single exposures to nitrous oxide during anaesthesia.

The effect on DNA synthesis is the reason for the influence of nitrous oxide on blood formation and the foetal injuries seen in animal studies.

The period of treatment should not exceed 12 hours.

Higher concentrations of nitrous oxide (> 50%) may affect protective reflexes and level of consciousness. Concentrations above 60-70% often cause unconsciousness, and the risk of impaired protective reflexes increases.

Nitrous oxide should not be used during laser surgery of the airways because of the risk of explosive combustion.

After general anaesthesia in which a high concentration of nitrous oxide has been used, there is a well-known risk of hypoxia (diffusion hypoxia) which is provoked not only by the alveolar gas mixture but also by a reflexive response to hypoxia, hypercapnia and hypoventilation. Supplementary oxygen administration and oxygen saturation monitoring by means of pulsoximetry is recommended after general anaesthesia until the patient is awake.

Due to the risk during pregnancy for women occupationally exposed, it is important that nitrous oxide content in the ambient air is kept as low as possible and well below the nationally set limit value (see section 4.6).

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The limit value for a non-dangerous environment in regard to nitrous oxide is currently considered to be a mean value during an eight-hour work cycle that is below 25-100 ppm (TWA value below 25-100 ppm = 0.0025-0.01%).
The objective should be a good working environment with nitrous oxide concentrations as low as possible in accordance with local regulations.

The mechanical ventilation that is normally employed in operating theatres in combination with active extraction of excess gases from anaesthetic equipment is the basis for a good, uncontaminated working environment, ensuring that the concentrations of nitrous oxide and other anaesthetic gases do not exceed the norms imposed (hygienic limit values) for a working day.

In the event of obstruction of the Eustachian tube, an earache and/or middle ear disorders and/or a tympanic rupture may be observed with the increase in pressure in the tympanic cavity (see section 4.8).

Abuse, misuse and diversion: due to euphoric effects of nitrous oxide (see Section 4.8), nitrous oxide may be sought and abused for recreational use.

Intracranial pressure should be monitored closely in patients at risk of intracranial hypertension as an increase of intracranial pressure (see Section 4.8) has been observed during the administration of nitrous oxide in some patients with intracranial disorders

When nitrous oxide is used in analgesia :

- a self-administration should be preferred to allow the assessment of the level of consciousness.
- Attentive monitoring is required in patients taking concomitantly central nervous system depressant drugs and in particular opiates and benzodiazepines, because of the increased risk of deep sedation (see section 4.5).

Paediatric population

Nitrous oxide may in rare cases cause respiratory depression in the neonate (see Section 4.8). The neonate should be checked for possible respiratory depression when nitrous oxide is used around childbirth.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations which are contraindicated

Patients having received recent intraocular injection of gas (such as SF6, C3F8, C2F6) as long as an intraocular gas bubble persists or within 3 months after the last injection of an intraocular gas. The expansion an intraocular gas bubble by nitrous oxide can cause severe visual impairment (see Sections 4.3 and 4.8).

Combination with other medicinal products requiring precautions for use
Nitrous oxide interacts when combined with other inhalation anaesthetics in an additive manner. It also interacts with intravenous anaesthetics.
These interactions have clear clinical effects, reducing the need for other drugs that are combined with nitrous oxide. The combination usually produces less cardiovascular and respiratory depression and improves/hastens emergence. When use during analgesia, Nitrous oxide can potentiate the hypnotic effects of 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.

Other interactions:

Nitrous oxide causes inactivation of Vitamin B_{12} (a co-factor of methionine synthesis), which interferes with folic acid metabolism. Medications that interfere with vitamin B12 and/or folate metabolism can potentiate the inactivation of vitamin B 12 by nitrous oxide (see Section 4.4 and 4.8).

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data on pregnant women exposed to a single administration of nitrous oxide during the 1st trimester (more than 1000 exposed outcomes) indicate no malformative toxicity. Moreover no fetal nor neonatal toxicity has been specifically associated with nitrous oxide exposure during pregnancy. Therefore, nitrous oxide can be used during pregnancy if clinically needed.

When nitrous oxide is used close to delivery, newborns should be supervised for possible adverse effects (see Sections 4.4 and 4.8).

In women occupationally exposed to chronic inhalation of nitrous oxide during pregnancy in the absence of appropriate scavenging or ventilation system, an increase in spontaneous abortions and malformations has been reported. These findings are questionable due to methodological biases and exposure conditions, and no risk was observed in subsequent studies when an appropriate scavenging or ventilation system had been implemented (see section 4.4 regarding need for satisfactory scavenging or ventilation system).

Fertility

No relevant data are available in humans.

Lactation

There are no data on excretion of nitrous oxide in breast milk. However, after a short-term administration of nitrous oxide, taking into account the very short half-life, interruption of lactation is not necessary.

Nitrous oxide can be used during the breast-feeding period.

4.7 Effects on ability to drive and use machines

Nitrous oxide affects both cognitive and psychomotor functions. It is eliminated rapidly after administration ceases. Despite this, as an extra safety measure, patients who must drive or operatemachines should be monitored until they have recovered the same state of alertness as before administration.

4.8 Undesirable effects

Nitrous oxide passes into all gas containing spaces in the body faster than nitrogen passes out. Use of nitrous oxide may result in expansion of non-vented gas containing cavities.

Adverse reactions are listed according to MedDRA frequency convention (very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data)).

System organ class	**Very com-mon (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1 000 to 1/100)**	**Rare (≥1/10 000 to 1/1 000)**	**Very rare (<1/10 000)**	**Not known (cannot be estimated from the available data)**
Blood and lymphatic system disorders	-	-	-	-	-	Leukopenia, Megaloblastic anaemia

						Pancytopenia [(1)] Agranulocytosis[(2)]
Metabolism and nutrition disorders						Vitamin B12 deficiency (see sections 4.4 and 4.5)
Psychiatric disorders	-	-	Euphoria Agitation* Anxiety* Dreams* Hallucination*	-	-	Disorientation Addiction
Nervous system disorders	-	-	Paraesthesia Excessive sedation*	-	-	Dizziness Myelopathy Myeloneuropathy Neuropathy Subacute degeneration of the spinal cord Headache* Intracranial pressure increased Generalised seizures
Eye disorders						Severe visual impairment (caused by expansion of an intraocular gas, see Sections 4.3 and 4.5).
Ear and labyrinth disorders	-	-		-	-	Ear pain Middle ear disorders Tympanic rupture (in the event of non-permeability of the Eustachian tube - see Section 4.4).
Respiratory, thoracic and mediastinal disorders	-	-	-	-	-	Respiratory depression (in the neonate, when nitrous oxide was used during delivery around childbirth - see Section 4.4).
Gastrointestinal disorders	-	Vomiting Nausea		-	-	-

*specific to analgesia

[(1)] observed in predisposing circumstances (cobalamin deficiency, substance abuse).

[(2)] observed observed after very high and prolonged exposure for tetanus treatment in the 50’s.

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

Excessive concentrations of nitrous oxide will cause oxygen deficiency (hypoxia), which may lead to increased light-headedness, unconsciousness , hypoxemia, cyanosis and death from anoxia.

If hypoxemia occurs as a result of excessive nitrous oxide concentration, the nitrous oxide concentration should be reduced or administration suspended. The oxygen content should be increased and adjusted so that the patient recovers adequate oxygen saturation.

Where nitrous oxide is used as an analgesic and the dose has caused unconscious, administration should be suspended and the patient should breathe “fresh air” and/or be given supplementary oxygen if necessary. Monitoring by pulsoximetry is recommended, until the patient has recovered consciousness and is no longer hypoxic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other general anaesthetics, ATC code: N01AX13.

Available data indicate that nitrous oxide has both direct and indirect effects on the transmission of a number of neurotransmitters both in the brain and the spinal cord. Its effect on the endorphin system throughout the CNS is presumably one of the more central mechanisms underlying the analgesic effects. Results have also shown that nitrous oxide affects noradrenaline activity in the posterior horn of the spinal cord and that to some extent it’s analgesic effects depend on spinal inhibition.

Nitrous oxide has dose-dependent effects on sensory and cognitive functions that start at 15 vol.%. Concentrations exceeding 60-70 vol.% cause unconsciousness. Nitrous oxide has dose-dependent analgesic properties that are clinically perceptible at end-tidal concentrations around 20 vol.%.

5.2 Pharmacokinetic properties

Nitrous oxide is administered by inhalation. Its absorption depends on the pressure gradient between inhaled gas and the blood passing through ventilated alveolar sections.

Distribution in different body tissues is dependent on the solubility of nitrous oxide in these tissues. Its low solubility in blood and other tissues generates a rapid equilibrium between the inhaled and exhaled nitrous oxide concentration. Nitrous oxide saturates the blood rapidly and reaches equilibrium faster than other presently available inhalation anaesthetics.

Nitrous oxide is not metabolised, but eliminated unchanged by exhalation. Elimination depends entirely on alveolar ventilation. The elimination time after administration of nitrous oxide ceases corresponds to the saturation time. Because of its low solubility in blood and other tissue, both uptake and elimination are rapid.

5.3 Preclinical safety data
Animal experiments involving long-term exposure to high concentrations of nitrous oxide have shown teratogenic effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

Medicinal nitrous oxide may be mixed with air, medicinal oxygen and halogenated inhalation anaesthetics.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Drug-related storage precautions
This medicinal product does not require any special storage conditions other than those applying to gas containers and gas under pressure (see below).
Store gas cylinders in locked spaces reserved for medicinal gases.

Storage precautions related to gas containers and pressurised gases
Contact with combustible material may cause fire.
Vapours may cause drowsiness and dizziness.
Keep away from combustible material.
Use only in well-ventilated areas.
Keep the cylinder in locked storage reserved for medicinal gases. Should not be exposed to strong heat.
If at risk of fire – move to a safe place. No smoking.
Keep the cylinder clean, dry and free of oil and grease.
Make sure the cylinder is not knocked or dropped.
Store and transport upright with valves closed and, where these are present, with the protective cap and cover in place.

6.5 Nature and contents of container

The shoulder of the gas cylinder is marked in blue (nitrous oxide). The body of the gas cylinder is white (medicinal gas).

Steel cylinder with shut-off valve 2.5 litres, 10 litres, 40 litres, 50 litres.
Steel cylinder with shut-off valve with pin-index 4 litres
Aluminium cylinder with shut-off valve 5 litres, .

Bundle (aluminium) 20 x 20 litres.
Bundle (steel) 8 x 40 litres, 12 x 50 litres.

Not all pack sizes may be marketed.

A pack filled with 0.75 kg of nitrous oxide per litre of cylinder volume produces the following number of litres of gas at atmospheric pressure and 15C (a variant of the 10-litre cylinder, 40-litre cylinder and 50-litre cylinder are filled with 0.70 kg per litre of cylinder volume).

One 2.5 litre cylinder filled with 1.9 kg produces approximately 1,000 litres of gas.
One 4 litre cylinder filled with 3.0 kg produces approximately 1,700 litres of gas.
One 5 litre cylinder filled with 3.8 kg produces approximately 2,100 litres of gas.
One 10 litre cylinder filled with 7.5 kg produces approximately 4,200 litres of gas.
One 10 litre cylinder filled with 7.0 kg produces approximately 3,900 litres of gas.
One 40 litre cylinder filled with 28 kg produces approximately 15,700 litres of gas.

One 40 litre cylinder filled with 30 kg produces approximately 16,800 litres of gas.
One 50 litre cylinder filled with 37.5 kg produces approximately 21,000 litres of gas.
One 50 litre cylinder filled with 35 kg produces approximately 19,600 litres of gas.
One 20 x 20 litre bundle filled with 300 kg produces approximately 168,000 litres of gas.
One 8 x 40 litre bundle filled with 224 kg produces approximately 125,000 litres of gas.
One 12 x 50 litre bundle filled with 450 kg produces approximately 252,000 litres of gas.

6.6 Special precautions for disposal and other handling

General
Medicinal gases must be used for medicinal purposes only.

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

Never use oil or grease even if the cylinder valve is stiff or if the regulator is difficult to connect. Handle valves and devices to match with clean, grease-free (hand cream etc.) hands.
Use only standard equipment that is intended for nitrous oxide (medicinal laughing gas).
Check that the cylinders are sealed before they are taken into use.

Preparation prior to use
Remove the seal from the valve before use.
Use only regulators intended for nitrous oxide. Check that the quick connector and regulator is clean and that the gaskets are in good condition.
Never use a tool on a stuck pressure/flow regulator intended to be connected manually, as this can damage the coupling.
Open the valve of the cylinder slowly – at least half a turn.
Check for leakage in accordance with the instruction that accompanies the regulator. Do not try to deal with leakage from the valve or device yourself other than by changing the gasket or O-ring.
In the event of leakage, close the valve and uncouple the regulator. Label defective cylinders, put them aside and return them to the supplier.

Using the gas cylinder
Smoking and open flame are absolutely forbidden in rooms in which nitrous oxide treatment is being given.
Close down the equipment in the event of fire or if it is not being used.
Carry to safety in the event of fire.
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.
When the cylinder is in use it must be fixed in a suitable support.
When a small amount of gas is left in the gas cylinder, the cylinder valve must be closed. It is important to leave a little pressure in the cylinder to protect it from contamination.
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

<To be completed nationally>

10. DATE OF REVISION OF THE TEXT

2019-09-19