1. NAME OF THE MEDICINAL PRODUCT

Medicinsk lustgas Nippon Gases Scandinavia 100 % medicinal gas, liquefied

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nitrous oxide (N_2O) 100 %

3. PHARMACEUTICAL FORM

Medicinal gas, liquefied

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

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 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.

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 normally not sufficiently potent for surgical anaesthesia, but should 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.

4.3 Contraindications

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

pneumothorax, gas embolism, after diving (with the attendant risk of decompression sickness), after extracorporeal circulation using a heart-lung machine or in severe cranial injury, since air bubbles (embolisms) / airfilled spaces may expand due to nitrous oxide administration.

- intraocular injection of gas (e.g. SF_6, C_3F_8), because of the risk of the increased pressure in the eye causing blindness.
- signs of intestinal obstruction (ileus) because of the risk of additional intestinal dilation.
- 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.

4.4 Special warnings and precautions for use

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). Nitrous oxide affects vitamin B_{12} and folate metabolism. It also inhibits methionine synthetase, which contributes to the conversion of homocysteine to methionine. The inhibition of this enzyme affects/reduces the formation of thymidine, which is an important part of DNA formation. Nitrous oxide's inhibition of methionine formation may lead to defects and reduced myelin formation, and hence to damage to the spinal cord. 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.

Nitrous oxide should not be used in close connection with injection of gas into the eye, because of the risk of increased intraocular pressure and consequent effect on the sight (see also section 4.3).

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.
Nitrous oxide creates an increase in middle ear pressure.

Chronic exposure to low concentrations of nitrous oxide has been implicated as a possible health risk. At present it is not possible to decide whether there is a causal relationship between chronic exposure to low concentrations of nitrous oxide and any disease, but nor is it possible entirely to discount the possibility of a connection between such chronic exposure and the risk of developing tumors or other chronic diseases, impaired fertility, spontaneous abortion and/or foetal deformities. Hygienic limit values currently exist beneath which (even in chronic exposure) no health hazards are considered to exist. 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.

4.5 Interaction with other medicinal products and other forms of interaction

Combination with anaesthetics/sedatives and analgesics
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 mixture usually produces less cardiovascular and respiratory depression and improves/hastens emergence.

Other interactions
Nitrous oxide causes inactivation of vitamin B_{12} (a co-factor in methionine synthetase). Long-term exposure to the gas affects folate metabolism and DNA synthesis. This may give rise to megaloblastically altered blood profiles and ultimately a form of neuropathy/myelopathy – a subacute combined degeneration of the spinal cord.

4.6 Fertility, pregnancy and lactation

Pregnancy
Nitrous oxide may interfere with folic acid metabolism (see section 4.4).
Epidemiological data from use during pregnancy are insufficient to assess the risks of possibly injurious effects on embryonal-foetal development.
Animal experiments on long-term exposure to high concentrations of nitrous oxide have shown teratogenic effects (see section 5.3).

Nitrous oxide may be used in delivery, but should be administered with caution during the first two trimesters of pregnancy.

Breastfeeding
Nitrous oxide may be given during lactation, but should not be given during breastfeeding itself.

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, driving, operation of machines or other activities that are demanding in terms of psychomotor functions should be avoided for a reasonable period after exposure.

4.8 Undesirable effects

When nitrousoxide is used in analgesia:

Common (>1/100 to <1/10)
General symptoms: dizziness, feeling intoxicated
Gastrointestinal disorders: nausea, vomiting

Uncommon (>1/1,000 to <1/100)
Ear and labyrinth disorders: feeling of pressure in the middle ear
Gastrointestinal disorders: Bloating increased gas volume in the intestines

When nitrousoxide is used as a part of anaesthesia:

Common (>1/100 to <1/10)
Gastrointestinal disorders: nausea

Uncommon (>1/1,000 to <1/100)
Ear and labyrinth disorders: feeling of pressure in the middle ear
Gastrointestinal disorders: Bloating, increase gas volume in the intestines

Very rare (<1/10,000)
Blood and lymphatic system disorders: Megaloblastic anaemia, leukopenia
Nervous system disorders: Polyneuropathy and myelopathy

Undesirable effects reported after marketing authorization with frequency not known:
Nervous system disorders: generalized seizures.

In suspected or confirmed vitamin B_{12} deficiency, or where symptoms compatible with affected methionine synthetase occur, vitamin B substitution therapy should be given.

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 unconsciousness.

If hypoxaemia occurs as a result of excessive nitrous oxide concentration, the 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 unconsciousness, 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 its 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.

It 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

Do not store above 45 °C.

Store gas cylinders in locked spaces reserved for medicinal gases.

Storage precautions related to gas containers and pressurised gases
No smoking.
Gas cylinders should be stored upright in a well-ventilated space.
Gas cylinders should be protected from weather and wind, kept dry and clean, and must not be used/stored near combustible materials and not exposed to strong heat.
Different types and qualities of gas should be kept separate from each other. Full and empty gas cylinders should be kept apart.
Measures should be taken to prevent gas cylinders being knocked or dropped during storage and transport.

Large gas cylinders should be transported on a suitable type of cylinder cart. Take particular care that connected equipment does not come loose inadvertently.

Gas cylinders should be stored and transported with valves closed and, where these are present, with the protective cap and cover in place.

6.5 Nature and contents of container

Steel gas cylinder of 2.5 litre, filled with 1.9 kg, containing ca. 1009 litre gas, shut-off valve with rupture disc 190 bar, threaded connection according to DIN 477.
Steel gas cylinder of 4 litre, filled with 3.0 kg, containing ca. 1 615 litre gas, shut-off valve with rupture disc 190 bar, threaded connection according to DIN 477.
Steel gas cylinder of 4 litre, filled with 3.0 kg, containing ca. 1 615 litre gas, shut-off valve with rupture disc 190 bar, pin index connection.
Steel gas cylinder of 10 litre, filled with 7.5 kg, containing ca. 4 035 litre gas, shut-off valve with rupture disc 190 bar, threaded connection according to DIN 477.
Steel gas cylinder of 40 litre, filled with 30 kg, containing ca. 16 140 litre gas, shut-off valve with rupture disc 190 bar, threaded connection according to DIN 477.
Steel gas cylinder of 50 litre, filled with 37.5 kg, containing ca. 20 175 litre gas, shut-off valve with rupture disc 190 bar, threaded connection according to DIN 477.
Steel gas cylinder bundle of 12x40 litre, filled with 360 kg, containing ca. 193 680 litre gas, shut-off valve with rupture disc 190 bar, threaded connection according to DIN 477.
Steel gas cylinder bundle of 12x50 litre, filled with 450 kg, containing ca. 242 100 litre gas, shut-off valve with rupture disc 190 bar, threaded connection according to DIN 477.

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.

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

Be returned with closed valve and remaining pressure at more than 2 bar (200 kPa)

Preparation prior to use
Remove the seal from the valve before use.
Use only regulators designed for nitrous oxide. Check that the attachment on the connector or regulator is clean and that the attachments are in good condition.
Never use tools to tighten a pressure/flow regulator intended to be tightened by hand, since this

may damage the connection.
Open the cylinder valve gently, by at least half a revolution.
Do a leakage check in accordance with the instructions accompanying the regulator. Do not attempt to remedy leakage from the valve or equipment other than by changing the gasket or 'O' ring.
If leakage occurs, close the valve and disconnect the regulator. Mark faulty cylinders, put them in the space reserved for rejections and return them to the supplier.

Using the gas cylinder
Smoking and naked flame are absolutely forbidden in rooms in which nitrous oxide treatment is being given.
Turn off the equipment in the event of fire or when not in use.
Remove to a safe place if there is a danger of fire.
During use, the cylinder should be fixed in a suitable supporting device.
The cylinder valve should be closed when a small quantity of gas remains in the cylinder. It is important to leave a small amount of pressure in the cylinder to avoid the entrance of contaminants.
After use, the cylinder valve should be closed by ordinary hand pressure. Depressurise the regulator or connector.

7. MARKETING AUTHORISATION HOLDER

Nippon Sanso Norge AS
P.O. Box 23 Haugenstua
0915 Oslo
Norway

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 16 October 2007
Date of latest renewal: 10 February 2012

10. DATE OF REVISION OF THE TEXT

04/2026