SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Niontix 100%, medicinal gas, liquefied.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Nitrous oxide (N_2O, medicinal laughing gas) 100%.

There are no excipients.

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

Nitrous oxide is indicated in patients of all age groups.

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.

Posology

General anaesthesia
When used in general anaesthesia, Nitrous oxide is commonly used in concentrations between 35 and 75 % 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 interactions with other medicinal products and other forms of interaction, Section 4.5).
Nitrous oxide in combination with oxygen in a composition such as one part of oxygen and two parts of nitrous oxide, creating a mixture of about 33% oxygen and 66% nitrous oxide is commonly used.

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. A more pronounced effect can be seen in older age groups with the relative MAC reducing-effect increasing after the age of about 40-45 years.

Analgesia, conscious sedation

Nitrous oxide exhibits analgesic and sedative properties.

When used as a sole agent, concentrations of 30-60 % nitrous oxide possess dose dependent analgesia and sedative effects.
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.

Nitrous oxide should be used during the entire duration of the procedure or for as long as the analgesic effect is desired.

Breathing, circulation and protective reflexes are normally preserved at these concentrations (also see overdose, Section 4.9).

Nitrous oxide should not be administered in concentrations greater than 70-75 % so that a safe oxygen fraction can be guaranteed.
In patients with compromised oxygenation, oxygen fraction greater than 30% might be required.

Nitrous oxide can be administered for up to 6 hours without haematological monitoring in patients with no risk factors (see special warnings and precautions for use, Section 4.4.).

Paediatric population

There is no difference in the dosage recommendations for the paediatric population.

Nitrous oxide can be used for procedural pain management and as part of general anaesthesia. The effects increase with the dose administered and children may lose consciousness and also protective reflexes at higher doses. The so called vomiting reflex may thus become compromised at higher concentrations. The doctor should ascertain that adequate dose is provided and surveillance is secured. The combination with other sedative and/or analgesic drugs enhances the sedative effect and increases the risk for reflex depression.

Method of administration

Precautions to be taken before handling or administering the medicinal product, see special precautions for disposal and other handling (section 6.6).

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

Nitrous oxide should be administered 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 ($FiO_2 < 21$ %) is not administered.

When used in anaesthesia, nitrous oxide is administered through special equipment where the exhaled gas is recirculated and can be rebreathed (i.e a circular system with rebreathing).

Nitrous oxide should be administered 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 (see special warnings, Section 4.4).

4.3 Contraindications

During inhalation of nitrous oxide, gas bubbles (gas emboli) and enclosed gas filled spaces may expand due to the enhanced diffusivity of nitrous oxide. Consequently, the use of nitrous oxide is contraindicated:

- In patients presenting with symptoms of pneumothorax, pneumoperocardium, severe bullous emphysema, gas embolus, or severe head trauma
- After a recent dive (with the attendant risk of decompression sickness),
- After recent cardiopulmonary bypass with heart-lung machine.
- In patients with a recent intra ocular injection of gas (e.g. SF_6, C_3F_8) until said gas has been completely reabsorbed, due to the risk of further expansion of the gas bubble possibly leading to blindness.
- In patients with gross abdominal gaseous distension.

Nitrous oxide is also contraindicated:

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

- In patients presenting signs of confusion, altered consciousness or in some other way showing signs of increased intracranial pressure, since nitrous oxide may increase this further.

- In patients with a decreased level of consciousness or impaired ability to cooperate and follow instructions when nitrous oxide is used to alleviate pain, due to the risk that further sedation may affect natural protective reflexes.

- In patients with diagnosed but untreated vitamin B_{12} or folic acid deficiency or diagnosed genetic disorder of the enzyme system involved in the metabolism of these vitamins.

4.4 Special warnings and precautions for use

The effects of nitrous oxide on the cardiovascular system are negligible in healthy patients with good cardiovascular function. Nitrous oxide has been shown to have a slight depressant effect on the contractility of heart muscle, but this is offset by a slight increase in the sympathetic stimulation of the heart, such that there is normally no significant net effect on the circulation. However, due to the potential for myocardial depression, nitrous oxide should be used with caution in patients with mild to moderate cardiac dysfunction and is contraindicated in patients with severe cardiac dysfunction or pronounced cardiac failure.

Nitrous oxide should only be used where supplemental oxygen can be given and in the presence of personnel trained in emergency procedures.

Nitrous oxide may diffuse into air filled spaces. Nitrous oxide may thus increase middle ear pressure as well as the pressure in other gas filled areas. Nitrous oxide administration may also increase the pressure in catheter balloons e.g. in tracheal intubation.

Nitrous oxide should not be used during laser surgery in the airways due to the relative risk for explosive fire.

After general anaesthesia consisting of a high percentage of nitrous oxide the risk for hypoxaemia (diffusion hypoxaemia) is a well-recognised clinical problem dependent on not only the alveolar gas composition but also the compromised responses to hypoxia, hypercapnia and hypoventilation. After general anaesthesia supplementary oxygen and monitoring of oxygen saturation with pulse oximetry is recommended.

Occupational exposure, pollution of surrounding ambient air.
Effort should be made to keep working environment with nitrous oxide concentrations as low as possible in accordance with local regulations.

At present, it is not possible to document a clear causal relationship between exposure to trace concentrations of nitrous oxide and any negative health effects. The risk for impaired fertility that has been reported in medical or paramedical personnel during chronic exposure and in rooms not properly ventilated cannot be entirely ruled out.

Rooms where nitrous oxide is frequently used should have appropriate ventilation or scavenging system allowing the maintenance of nitrous oxide concentration in the ambient air below national set guidelines, occupational exposure limit (OEL), commonly assessed by time weighted average (TWA). See also the environmental risk assessment in section 5.3. 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 potential for abuse should be acknowledged. 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 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 B12, 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.

Nitrous oxide should be used with caution in patients at risk of vitamin B_{12} or folic acid deficiency, i.e. those with deficient intake or absorption of vitamin B_{12}/folic acid, or genetic perturbations in this system, and in immunocompromised patients, for example in patients with concomitant treatment with methotrexate (see section 4.5).Nitrous oxide should therefore not be used for prolonged periods of time, e.g. for sedation in the ICU.
The possibility of vitamin B_{12}/folic acid replacement or substitution therapy should be considered after a prolonged use exceeding 6 hours or recurrent use and haematological monitoring should be instituted to minimise risk of potential side effects.

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

Paediatric population
The special warnings and precautions for use in the paediatric population are the same as in the adult populations.

4.5 Interaction with other medicinal products and other forms of interaction

Combination with other medicinal products
Nitrous oxide interacts in an additive manner with inhaled and/or intravenous anaesthetics and/or active substances with effects on the central nervous system (e.g. opiates, benzodiazepines and other psychomimetics).
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.
The use of nitrous oxide potentiates the effect of methotrexate on folate metabolism, yielding increased toxicity such as severe, unpredictable myelosuppression, and stomatitis. Whilst this effect can be reduced by administering calcium folinate, the concomitant use of nitrous oxide and methotrexate should be avoided.
Other interactions
Nitrous oxide causes inactivation of vitamin B_{12} (a co-factor in methionine synthetase) which interferes with folic acid metabolism. Thus, DNA synthesis is impaired following prolonged nitrous oxide administration. These disturbances can result in megaloblastical bone marrow changes and possibly polyneuropathy and/or a subacute combined degeneration of the spinal cord (see undesirable effects Section 4.8).

Paediatric population
No other interactions are known, than those in the adult population.

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.

In rare cases, nitrous oxide may induce respiratory depression in the neonate. When nitrous oxide is used close to delivery, newborns should be monitored for respiratory depression as well as other possible adverse effects (see sections 4.4 and 4.8)

No risk for adverse foetal effects has been observed for women occupationally exposed to chronic inhalation of nitrous oxide during pregnancy when an appropriate scavenging or ventilation system is in place. 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).

Breastfeeding
Although no excretion data of nitrous oxide in human milk are available, based on its rapid elimination from circulation via pulmonary exchange, and poor solubility in blood and tissue, significant oral ingestion by the infant with the milk is unlikely. Interruption of breastfeeding is not needed after short-lasting use. Thus, nitrous oxide may be used during lactation, but should not be given during breastfeeding itself.

Fertility
No relevant data are available in humans. The potential effect of clinical doses of nitrous oxide on fertility is unknown. (see also section 5.3).
The potential risk associated to chronic work place exposure cannot be ruled out (see special warnings and precautions for use, Section 4.4).

4.7 Effects on ability to drive and use machines

Nitrous oxide affects both cognitive and psychomotor functions. Nitrous oxide is rapidly eliminated from the body after brief inhalation as the sole agent 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 sole agent, driving, and use of complex machinery in not recommended for at least 30 minutes after cessation of administration of Nitrous oxide and until the patients have returned to their initial mental status as judged by attending healthcare professional.

4.8 Undesirable effects

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

Tabulated summary of adverse reactions

System organ class	**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)**
Blood and lymphatic system disorders	-	-	-	-	-	Leukopenia, megaloblastic anaemia

Psychiatric disorders	-	Euphoria,		-	-	Psychosis, confusion, anxiety, addiction
Nervous system disorders	-	Dizziness, light-headedness	Severe fatigue	-	Paraparesis	Headache, Myelopathy, neuropathy, subacute degeneration of the spinal cord Generalised seizures
Ear and labyrinth disorders	-	-	Feeling of pressure in the middle ear	-	-	-
Gastrointestinal disorders	-	Nausea, vomiting	Bloating, increased gas volume in the intestines	-	-	-
General disorders and administration site conditions	-	Sense of intoxi-cation	-	-	-	-
Respiratory, thoracic and mediastinal disorders	-	-	-	-	-	Respiratory depression

*only when nitrous oxide is used as a sole agent
In suspected or confirmed vitamin B_{12} deficiency, or where symptoms compatible with affected methionine synthetase occur, vitamin B substitution therapy should be given in order to minimize the risk for adverse signs/symptoms associated to methionine synthetase inhibition such as leukopenia, megaloblastic anaemia, myelopathy and polyneuropathy.

Paediatric population
There are no known additional undesirable effects in the paediatric population than in adults.

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

Niontix should always be used in combination with sufficient oxygen in order to guarantee adequate oxygenation/oxygen saturation. Administration equipment should not allow concentration of oxygen below 21%.

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.

If during the administration of nitrous oxide in analgesic concentrations the patient shows signs of decreased alertness, does not respond adequately to command, or in some other ways shows signs of pronounced sedation, 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.
The patient should not receive any further nitrous oxide until full consciousness has been restored.

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

Paediatric population
The risk for overdose in the paediatric populations is the same as in the adult population.

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

Absorption
Nitrous oxide is administered by inhalation and its uptake is dependent on the pressure gradient between inhaled gas and the blood passing through the ventilated alveolar sections.

Distribution
Distribution in the body tissues is dependent on blood perfusion and the nitrous oxide saturation of the blood. The equilibration in other tissues is dependent on the solubility, which is governed by the partition (distribution) coefficient for individual tissues. Nitrous oxide has low solubility in blood as well as other compartments leading to a fast equilibration between inspired and end-tidal gas concentration.

Elimination
Nitrous oxide is inert and is not metabolised; it is excreted through alveolar ventilation and exhaled. Elimination is solely dependent on alveolar excretion and ventilation. The required

time for elimination of nitrous oxide after discontinuation of administration is similar to that of saturation with the gas.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.
Prolonged continual exposure to 15-50% nitrous oxide has been shown to induce neuropathy in fruit bats, pigs and monkeys.
Teratogenic effects of nitrous oxide have been observed in rats after chronic exposure to levels higher than 500 ppm.
Pregnant rats exposed to 50 – 75% nitrous oxide for 24 hours on each of days 6 to12 of gestation show higher incidence of foetal wastage and malformations of the ribs and vertebrae.
Studies in rodents showed adverse effects on reproductive organs. Chronic exposure to trace concentrations of nitrous oxide (≤1%) adversely affected fertility in male and female rats (small dose-related trend to low increase of resorptions and decrease of live births).
No effect has been described in the rabbit and mouse.
The above described adverse effects were seen at high continuous doses which are not representative for the short-lasting clinical use of nitrous oxide in humans.

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 for cylinders ≤ 5 litres
5 years for bundle and cylinders >5 litres

6.4 Special precautions for storage

This medicinal product does not require any special storage instructions with regard to temperature other than those that apply for gas containers and gas under pressure (see below).

- Do not smoke or use a naked flame in areas where medicinal gases are stored.
- Cylinders should be stored in a locked and well-ventilated area reserved for the storage of medicinal gases.
- Keep this medicine out of the sight and reach of children.
- Cylinders should be stored under cover, kept dry and clean, kept free from oil and grease, free from combustible material
- Must not be exposed to strong heat.
- If at risk of fire – move to a safe place.
- Precautions should be taken to prevent blows or falls.
- Cylinders containing different types of gases should be stored separately.
- Full and empty cylinders should be stored separately.

- 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, 4 litres, 5 litres, 10 litres, 20 litres, 40 litres, 50 litres.
Bundle 12 x 27 litres, 9 x 50 litres, 12 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 15°C (a variant of the 10-litre cylinder is filled with 0.74 kg per litre of cylinder).

One 2.5 litre cylinder filled with 1.9 kg produces ca. 1000 litres of gas.
One 4 litre cylinder filled with 3.0 kg produces ca. 1600 litres of gas.
One 5 litre cylinder filled with 3.8 kg produces ca. 2000 litres of gas.
One 10 litre cylinder filled with 7.5 kg produces ca. 4100 litres of gas.
One 10 litre cylinder filled with 7.4 kg produces ca. 4000 litres of gas.
One 20 litre cylinder filled with 15 kg produces ca. 8100 litres of gas.
One 40 litre cylinder filled with 30 kg produces ca. 16,200 litres of gas.
One 50 litre cylinder filled with 37.5 kg produces ca. 20,300 litres of gas.
One 12 x 27 litre bundle filled with 240 kg produces ca. 130,000 litres of gas.
One 9 x 50 litre bundle filled with 337.5 kg produces ca. 183,000 litres of gas.
One 12 x 40 litre bundle filled with 360 kg produces ca. 195,000 litres of gas.
One 12 x 50 litre bundle filled with 450 kg produces ca. 244,000 litres of gas.

6.6 Special precautions for disposal and other handling

The cylinder package must not be disposed, but returned to the supplier.

General precautions
Medicinal gases must only be used for medicinal purposes.
Do not smoke or use a naked flame in areas where medicinal gases are administered
Never use grease, oil or similar substances, even if the cylinder valve sticks or if the regulator is difficult to connect.
Handle valves and devices belonging to them with clean and grease-free hands (i.e. no use of hand cream, etc.).

In case of cleaning of cylinders or attached equipment, do not use combustible products and especially not oil-based material. In case of doubt, verify compatibility.
Prior to any use, ensure sufficient quantity of product remains to allow completion of the planned administration.
Only use standard devices designed for administration of nitrous oxide.
When delivered from the manufacturer, the cylinders should have an intact tamper evident seal.

Preparation for to use
Remove the seal from the valve before use.
Open the cylinder valve gently, at least half a turn.

Use only regulators intended for nitrous oxide.
Check that the connection on the coupling or regulator is clean and that the connections including 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.
Check that the regulator is properly attached before opening the valve.

Check for leakage in accordance with the instruction that accompany the regulator.
In the event of leakage, close the valve and disconnect the regulator. Mark the defective cylinder, keep it separate and return it to the supplier.

Using the cylinder

Close the cylinder in the event of fire or when not in use.
Carry to safety in the event of fire.
Ensure cylinders are secured to a suitable cylinder support in vertical position when in use, to prevent them from falling. For cylinders that are not equipped with residual pressure valves, the cylinder valve should be closed when a small amount of gas remains in the cylinder (approx. 2 bars). It is important to leave a slight residual pressure in the cylinder in order to protect it from contamination.
After use, the cylinder valve should be closed by hand and the regulator or connection depressurised.

Transportation of cylinders
When being transported, the cylinders must be secured to prevent them from falling.
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.

7 MARKETING AUTHORISATION HOLDER

Linde Sverige AB
Rättarvägen 3
16968 Solna
Sweden

8 MARKETING AUTHORISATION NUMBER(S)

19004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 January 2006
Date of latest renewal: 20 January 2011

10 DATE OF REVISION OF THE TEXT

17 January 2025