THE LINDE GROUP

Linde

LIVOPAN®

Pain relief. Just a few breaths away.

Linde: Living healthcare

Release the unease.

The reduction and elimination of pain and anxiety is extremely important to patients and healthcare professionals alike. When inhaled, LIVOPAN® produces a pain-relieving and sedative effect without loss of consciousness. Moreover, it also has properties that help to reduce anxiety. The onset of relief is almost immediate.

Non-invasive, inhaled analgesic.

LIVOPAN is a ready-to-use gas mixture consisting of 50% nitrous oxide and 50% oxygen. The balanced nitrous oxide/oxygen ratio assures good oxygenation and minimises the risk of over sedation [1]. It is administered through an inhalation facemask or mouthpiece with patients' intake of the gas mixture controlled by an on-demand valve or, where appropriate, with a continuous flow valve [2].

Rapid onset/offset of action.

The analgesic and sedative effects of pre-mixed nitrous oxide/oxygen are well documented. Because of its rapid onset and offset of action in combination with a high degree of safety, LIVOPAN is an attractive alternative where rapid and controlled pain relief is required. It has been used successfully in situations such as, but not limited to, acute trauma [3], repositioning of fractures [4,5], joint manipulation [6], painful diagnostic procedures [7–14], venipuncture [15,16], wound care and abscess drainage [6], and childbirth [17]. Its analgesic and anxiolytic properties play an important role in helping patients overcome the apprehension associated with pain.

Nitrous oxide exhibits classical dose dependent analgesic effects, raising the pain threshold and reducing the level of pain experienced [18]. Once the nitrous oxide/oxygen mixture has been administered it starts working within minutes. Residual cognitive and/or psychometric effects disappear rapidly following cessation of administration and are negligible 5–10 minutes after exposure.

Complement to other analgesics.

With its high levels of safety and efficacy, LIVOPAN can also be used as an adjunct to other analgesic therapies to potentiate beneficial effects.

Easy on the patient.

Fast-acting, self-administered and rapidly eliminated from the body once inhalation stops, with predictable and reliable responses. Extensive experience in the use of LIVOPAN has shown it to be a very safe analgesic with minimal side effects.

Non-cumulative, negligible side effects.
Nitrous oxide/oxygen mixture is associated with only minor effects on the heart, circulation and breathing. Even if the patient is suffering from cardiac disease or has respiratory problems, the effects of nitrous oxide on circulation or breathing are in most cases small and without clinical relevance [19,20].

Nitrous oxide/oxygen mixture has also been shown to have minor effects in patients with coronary artery disease. Studies in connection with acute heart attack have noted the analgesic effect of nitrous oxide without hemodynamic effects or significant side effects [21,22].

Apart from minor side effects such as drowsiness and nausea, no serious adverse effects have been reported in studies examining the use of nitrous oxide/oxygen mixtures in adults as well as children [1,23,24].

LIVOPAN nitrous oxide/oxygen mixture

Fast onset and offset make nitrous oxide/oxygen mixture ideal for acute pain of relatively short duration. The analgesic effect begins within a few minutes and wears off within 5-10 minutes.

Simple

- Non-invasive
- On demand
- Effective use of care resources

On/Off

Safe

- Minimal cardiovascular or respiratory effects
- Minimal side effects

A choice for comfort.

LIVOPAN is indicated for treatment of short term pain, conditions of mild to moderate intensity. Its non-invasiveness, rapid onset and offset of action, predictable effects and ease of administration have established LIVOPAN's analgesic usefulness in a variety of clinical applications.

Paedeatric procedural pain.

The lack of adequate pain relief for children undergoing painful procedures has been noted in a number of studies [5,15,16,23,24,25]. Without adequate relief during a painful procedure, children may experience a pain memory which could worsen the situation for subsequent procedures. This is especially valid for children with chronic diseases[26]. A fast-acting, non-invasive technique is also advantageous in small children who are unable to rationalise their pain or communicate the level of pain they are experiencing.

The analgesic and anxiolytic effects associated with nitrous oxide suggest it increases acceptance of future procedures [27]. Mild side effects and fast offset aid recovery, almost eliminating the need for more extensive post-procedural monitoring. Studies have shown that using the treatment in paedeatric procedures is highly satisfactory to children as well as parents and staff [28].

Obstetrics.

Self-administered nitrous oxide/oxygen mixture is simple, safe and less resource demanding than other analgesic techniques used during labour, for instance epidural analgesia. It does not require extended supervision and is acceptable to mothers [17]. Nitrous oxide/oxygen provides pain relief and is reassuringly safe for both mother and newborn [29]. Nitrous oxide does not affect the duration of labour and has no relaxation effects on the uterus [30].

Emergency medicine.
Examination of the use of nitrous oxide in a pre-hospital setting for self-administration by patients in severe pain found it to be well tolerated and effective in reducing pain and anxiety [25]. Studies have proven the value of a short-duration analgesic with minor complications or negative side effects apart from slight drowsiness. The low incidence of significant adverse events from nitrous oxide/oxygen mixture suggests its safety for use by lay responders [1].

Biopsies and painful diagnostic procedures.
Several studies have shown the effectiveness of nitrous oxide/oxygen mixtures compared with placebo or alternative treatment methods in connection with minor surgical procedures in adults.

In one placebo-controlled trial, nitrous oxide was used to provide safe and effective analgesia for percutaneous liver biopsies [7]. In patients scheduled for transrectal ultrasound-guided prostate biopsy, nitrous oxide was found to provide rapid and effective pain relief compared to placebo and 1% lidocaine [8,9]. Nitrous oxide sedation during colonoscopy has been shown to be safe and effective compared to intravenous sedation techniques, with faster recovery, shorter discharge times and reduced discomfort and nausea [10,11,12].

The analgesic and sedative properties of nitrous oxide/oxygen mixtures have also been investigated for fiberoptic bronchoscopy in adults and children. In adults, inhalation of equimolar nitrous oxide/oxygen mixture has been shown to be efficient in reducing patient discomfort and a possible alternative to general anaesthesia [13]. Among children, improved efficacy of sedation, pain control and safety has been demonstrated [14].

Administered with care.

Healthcare professionals and patients can rely on the quality of Linde Healthcare medical gas solutions to deliver the therapy efficiently, conveniently and safely.

Secure in handling.
LIVOPAN is easy to use and can be administered under the supervision of specially trained paramedics, nurses or midwives.

Linde Healthcare has developed LIVOPAN as a complete nitrous oxide/oxygen analgesia solution to ensure safe handling and delivery. It is distributed in lightweight cylinders, which means less effort in lifting, carrying and operation. An integrated valve ensures patient and user safety, with no change of regulators necessary, no more handling of high filling pressure and no risk of leakage. With the integrated regulator you get low constant outlet pressure and flow gauged to the treatment required.

Effective use of resources.
Hospitals, ambulances, emergency or day surgery units all look for cost effectiveness in the products they choose, as well as safety, efficacy, ease of use and efficiency. Even a small reduction in cost per case is economically significant.

The rapid offset of LIVOPAN minimises post-procedural monitoring, a clear advantage in situations where rapid recovery and ambulation is sought [1].

Attuned to the environment.
According to the American Society of Anesthesiologists' task force on trace anaesthetic gases, there is insufficient evidence to recommend any routine medical surveillance of personnel exposed to trace concentrations of waste anaesthetic gases as long as routines are followed that ensure compliance with existing occupational limits [31].

To minimise the potentially negative effects on health from chronic exposure to trace concentrations in the working environment, most authorities have set clear recommendations on ambient air quality.

Maximum allowable levels of nitrous oxide vary between countries, but are generally in the range of 25ppm–100ppm for each eight-hour work period. These levels should be adhered to wherever nitrous oxide is used.

- As nitrous oxide is not metabolised, exhaled gas should be scavenged to avoid concentrations in the work environment.
- Nitrous oxide should be administered in rooms with proper ventilation and/or scavenging equipment.
- Nitrous oxide should be administered at the lowest effective flow to avoid waste and ecological consequences.
- National air quality guidelines should be followed.

Summary of Product Characteristics.

1. Name of the medicinal product.

LIVOPAN 50%/50% medicinal gas, compressed.

2. Qualitative and quantitative composition.

Each cylinder contains:
Nitrous oxide (N_2O, medicinal laughing gas) 50% v/v and Oxygen (O_2, medicinal oxygen) 50% v/v at a pressure of either 138 or 170 bar (15°C)

3. Pharmaceutical form.

Medicinal gas, compressed
Colourless, odourless gas.

4. Clinical particulars

4.1 Therapeutic indications.

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

4.2 Posology and method of administration.

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

LIVOPAN is administered via inhalation in spontaneously breathing patients via a face mask. Administration of LIVOPAN is governed by the patient's breathing. By holding the mask securely around the mouth and nose and breathing via the mask, a so-called "demand valve" is opened and LIVOPAN flows out of the equipment and is administered to the patient via the airways. Uptake occurs from the lungs.

In dentistry, the use of a double mask is recommended, alternatively, a nasal mask or nasobuccal mask with adequate scavenging/ventilation is used.

Administration via endotracheal tubes is not recommended. If LIVOPAN is to be used in patients breathing through an endotracheal tube, the administration should only be done by health care personnel skilled in the delivery of anaesthesia.

Administration of LIVOPAN should commence shortly before the desired analgesic effect is required. The analgesic effect is seen after 4–5 breaths and reaches its maximum within 2–3 minutes.

Administration of LIVOPAN should continue throughout the painful procedure, or for as long as the analgesic effect is desired. Following discontinuation of the administration/inhalation, the effects wear off quickly within a few minutes.

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

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

Ideally, the patient should hold the mask through which LIVOPAN 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 minimise the risk of overdose. If for any reason the patient receives more LIVOPAN than is necessary, and wakefulness becomes affected, the patient will drop the mask and administration will cease. By breathing ambient air, the effect of LIVOPAN rapidly wears off and the patient will regain consciousness.

LIVOPAN should preferably be used in patients capable of understanding and following instructions about how the equipment and the mask should be used. In children or in other patients that are not capable to understand and follow the instructions, LIVOPAN 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, LIVOPAN 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 only be used 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 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.

LIVOPAN can be administered for up to 6 hours without haematological monitoring in patients with no risk factors (see Section 4.4).

4.3 Contraindications.

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

- In patients with signs or symptoms of pneumothorax, pneumopericardium, severe emphysema, gas emboli 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 recently having undergone intraocular injection of gas (e.g. SF6, C3F8) until the gas in question is fully absorbed, because the gas volume may increase in pressure/volume and consequently result in blindness.
- In patients with a severely dilated gastrointestinal tract.

LIVOPAN is also contraindicated:

- In patients with heart failure or cardiac dysfunction (e.g. after cardiac surgery) in order to avoid the risk of further deterioration in heart function.
- In patients presenting signs of confusion or in some other way showing signs of increased intracranial pressure.
- In patients with a decreased level of consciousness or impaired ability to cooperate and follow instructions due to 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 diagnosed genetic disorder of the enzyme system involved in metabolism of these vitamins.
- In patients with facial injury where use of a facemask may present difficulties or risks.

4.4 Special warnings and precautions for use.

LIVOPAN should only be administered by competent personnel with access to adequate resuscitation equipment. (see 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. It 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. The inhibition of methionine formation by nitrous oxide may lead to defects and reduced myelin formation, and hence to damage to the spinal cord. The effect on DNA synthesis is one of the probable reasons for the influence of nitrous oxide on blood formation and the foetal 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 nitrous oxide exposure. It is important that the nitrous oxide content in the ambient air is kept as low as possible and well below the nationally set limit value.

Areas in which LIVOPAN is used should be adequately ventilated and/or equipped with scavenging equipment in order that the concentration of nitrous oxide in ambient air is 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.

LIVOPAN can be used in children that are able to follow instructions on how to use the equipment.In the treatment of younger children, or in other patients that are not capable to follow instructions, the use of constant gas flow may be required. Constant gas-flow should only be provided by healthcare personnel trained in use of the gas, with equipment available to secure the airway and for provision of assisted ventilation. (see also 4.2.)

Special precautions for use: Nitrous oxide can affect vitamin B12 and folate metabolism; consequently, LIVOPAN should therefore be used with caution in risk patients, i.e. patients with reduced intake or uptake of vitamin B12 and/or folic acid or a genetic disorder in the enzyme system 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 of more than 6 hours should be applied with caution because of the potential risk for clinical manifestations from the inhibitory effects on the methionine synthase. Prolonged continuous use or recurrent use should be accompanied by haematological monitoring to minimise risk of potential side effects.

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

In patients taking other centrally acting medicinal products, e.g. morphine derivatives and/or benzodiazepines, concomitant administration of LIVOPAN may result in increased sedation, and consequently have effects on respiration, circulation and protective reflexes. If LIVOPAN is to be used in such patients, this should take place under the supervision of appropriately trained personnel. (See 4.5)

Following discontinuation of administration of LIVOPAN, the patient should be advised to recover under proper supervision until these potential risks resulting from use of LIVOPAN have subsided and the patient has recovered satisfactorily. Recovery of the patient should be assessed by health care personnel.

After cessation of LIVOPAN administration, nitrous oxide rapidly diffuses from blood to 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.

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

Combination with other medicinal products: The nitrous oxide component of LIVOPAN interacts in an additive manner with inhaled anaesthetics and/or 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.

LIVOPAN enhances the inhibiting effect of methotrexate on methionine synthase and folic acid metabolism. The pulmonary toxicity associated with active substances such as bleomycin, amiodarone, furadantin and similar antibiotics may be exacerbated by inhalation of increased concentrations of oxygen.

Other interactions: The nitrous oxide component of LIVOPAN causes inactivation of Vitamin B12 (a co-factor of methionine synthesis), which interferes with folic acid metabolism. Thus, DNA synthesis is impaired following prolonged nitrous oxide administration. These disturbances can result in megaloblastic bone marrow changes and possibly polyneuropathy and/or subacute combined degeneration of the spinal cord (see also 4.8). Therefore the administration of LIVOPAN should be limited in time. (see also 4.4).

4.6 Pregnancy and lactation.

Pregnancy: The nitrous oxide component of LIVOPAN may interfere with Vitamin B12/folic acid metabolism (see section 4.4).

Inhibition of the methionine synthase may cause adverse effects during early stages of pregnancy.

There are no adequate data from the use of LIVOPAN in pregnant women to assess the potential harmful effects on human embryonic / foetal development. Animal studies have demonstrated that high concentration or prolonged exposure during particular stages of pregnancy can induce teratogenic effects (see section 5.3). The potential risk for humans is unknown.

It is therefore recommended to avoid using LIVOPAN during the first two trimesters of pregnancy.

LIVOPAN can be used during later stages of pregnancy, third trimester and delivery. When used close to delivery, newborns should be supervised for any adverse effects.

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

4.7 Effects on ability to drive and use machines.
The nitrous oxide component of LIVOPAN has effects on the 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 LIVOPAN 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 LIVOPAN. Neurological effects such as polyneuropathy and myelopathy have been reported with 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.

Common (≥1/100 to <1/10): Nervous system disorders: Dizziness, light-headedness, euphoria. Gastrointestinal disorders: Nausea and vomiting.

Uncommon: (≥1/1000 to <1/100): Nervous system disorders: Severe fatigue Ear and labyrinth disorders: Feeling of pressure in the middle ear. Gastrointestinal disorders: Bloating, increased volume of gas in the intestines.

Not known (cannot be estimated from the available data): Blood and lymphatic system disorders: Megaloblastic anaemia, leukopenia. Nervous system disorders: Polyneuropathy, paraparesis and myelopathy, respiratory depression, headache. Psychiatric disorders: psychosis, confusion anxiety.

4.9 Overdose.
Since participation of the patient is required to administer the gas mixture, the risk of overdose is very small. If during use of LIVOPAN the patient shows signs of decreased alertness, does not respond, or does not respond adequately to command, or in some other way shows signs of pronounced sedation, administration should be stopped immediately. The patient should not receive further LIVOPAN until full consciousness has been restored. If the patient becomes cyanotic during use of LIVOPAN, treatment must immediately be discontinued and pure oxygen should be supplied, assisted ventilation may be required.

Overdose of nitrous oxide and or hypoxic gas mixture can occur if the equipment is exposed to cold, below -5°C. This can result in separation of the gas mixture, and 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, raises the pain threshold for various painful stimuli. The intensity of the analgesic effect depends mainly on the psychological state of the patient. 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 50% concentration of oxygen (more than twice the concentration in ambient air) guarantees good oxygenation and optimally oxygen saturation of the haemoglobin.

5.2 Pharmacokinetic properties.
Both uptake and elimination of nitrous oxide occur exclusively via the lungs. Due to the low solubility of nitrous oxide in blood and other tissues, saturation of both blood and the target organ (CNS) is achieved rapidly. These physiochemical properties explain the rapid onset of analgesia and the fact that the effects of nitrous oxide rapidly subside following discontinuation of administration. The gas is eliminated exclusively by respiration; nitrous oxide is not metabolised in the human body.

The rapid diffusion of nitrous oxide from both gas and blood explains some of the contraindications and special precautions which should be taken into consideration when using nitrous oxide/LIVOPAN.

5.3 Preclinical safety data.
Nitrous oxide
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Exposure to 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.

Oxygen
Non-clinical data reveal no special hazards for humans. Effects in non-clinical studies were observedonly at exposures sufficiently in excess of 50% oxygen.

6. Pharmaceutical particulars.

6.1 List of excipients.
None.

6.2 Incompatibilities.
Not applicable.

6.3 Shelf life.
3 years.

6.4 Special precautions for storage.
Medicinal product related storage precautions:
Do not store below -5°C.

On suspicion that LIVOPAN has been stored in too cold conditions, the cylinders should be stored in
horizontal position at a temperature above +10°C for at least 48 hours before use.

Storage precautions related to gas cylinders and pressurized gases:
- Contact with combustible material may cause fire.
- Vapour may cause drowsiness and dizziness.
- Keep away from combustible material.
- Use only in well-ventilated areas.
- No smoking. Must not be exposed to strong heat.
- If at risk of fire – move to a safe place.
- Keep the cylinder clean, dry and free from oil and grease.
- Keep the cylinder in locked storage reserved for medicinal gases.
- Make sure the cylinder is not knocked over or dropped.
- Store and transport with valves closed.

6.5 Nature and contents of container.
The shoulder of the gas cylinder is marked in white and blue (oxygen/nitrous oxide). The body of the gas cylinder is white (medicinal gas).

Steel gas cylinder, filling pressure 138 bar.
2,5-litre steel gas cylinder with shut-off valve and filling pressure of 138 bar.

5-litre steel gas cylinder with shut-off valve and filling pressure of 138 bar.

Aluminium gas cylinder, filling pressure 170 bar:
2-litre aluminium gas cylinder with shut-off valve with integrated in pressure regulator, flow meter and 170 bar filling pressure

2-litre aluminium gas cylinder with shut-off valve with integrated in pressure regulator and 170 bar filling pressure

5-litre aluminium gas cylinder with shut-off valve with integrated in pressure regulator, flow meter and 170 bar filling pressure

5-litre aluminium gas cylinder with shut-off valve with integrated in pressure regulator and 170 bar filling pressure

10-litre aluminium gas cylinder with shut-off valve with integrated in pressure regulator, flow meter and 170 bar filling pressure

10-litre aluminium gas cylinder with shut-off valve with integrated in pressure regulator and 170 bar filling pressure

Cylinders filled to 138/170 bar delivers approximately X litre gas at atmospheric pressure and 15°C according to the table below:

Cylinder size in litre	Litre of gas
2 (170 bar)	560
2.5 (138 bar)	550
5 (138 bar)	1.100
5 (170 bar)	1.400
10 (170 bar)	2.800

Not all pack sizes may be marketed.

6.6 Special precautions for disposal.
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 stiff or if the regulator is difficult to connect.
- Handle valves and accompanying equipment with clean, 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 an LIV-valve have an inbuilt pressure regulator in the valve. Consequently, a separate pressure regulator is unnecessary. The LIV-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 LIVOPAN is taking place.
- When the cylinder is in use it must be fixed in a suitable support.
- One should consider replacing the gas cylinder when the pressure in the bottle 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 be 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.
AGA AB
SE-181 81 Lidingö
Sweden

8. Marketing authorisation numbers(S).
23301.

9. Date of first authorisation/renewal of the authorisation.
16/04/2008.

10. Date of revision of the text.
04/06/2010.

Linde: Living healthcare

Linde Healthcare is committed to working with healthcare providers and regulatory authorities to continuously promote safe use of medical products and improve patient care. We provide medical gas products, therapies, technical solutions and services to hospitals, clinics, nursing facilities, emergency management services and home healthcare providers around the world. With our long experience and understanding of healthcare realities, you can depend on solutions that are delivered and serviced to the highest possible standards of quality, safety and efficacy.

References.

1. Faddy SC and Garlick SR. A systematic review of the safety of analgesia with 50% nitrous oxide: Can lay responders use analgesic gases in the prehospital setting? Emerg Med J 2005; 22:901-908. Review.
2. Luhmann JD, Kennedy RM, Lang Porter F, Miller JP, Jaffe DM. A randomized trial of continuous flow nitrous oxide and midazolam for sedation of young children during laceration repair. Ann Emerg Med 2001; 37(1):20-7.
3. Baskett PJF. Nitrous oxide in prehospital care. Acta Anaesthesiol Scand 1994; 38:775-776.
4. Hennerikus WL, et al. Self-administered nitrous oxide analgesia for pediatric fracture reductions. J Pediatr Orthop 1994; 14:538-42.
5. Migita RT, Klein EJ, Garrison MM. Sedation and analgesia for pediatric fracture reduction in the emergency department. A systematic review. Arch Pediatr Adolesc Med 2006; 160:46-51.
6. O'Sullivan I, Benger J. Nitrous oxide in emergency medicine. Emergency Med Journal 2003; 20:214-7.
7. Castera L, Negre I, Samii K, Buffet C. Patient-administered nitrous oxide/oxygen inhalation provides safe and effective analgesia of percutaneous liver biopsy: a randomized placebo-controlled trial. Am J Gastroenterology 2001; 96(5):1553-7.
8. Masood J, Shah N, Lane T, Andrews H, Simpson P, Barua JM. Nitrous oxide (Entonox) inhalation and tolerance of transrectal ultrasound guided prostate biopsy: a double-blind randomized controlled study. J Urol 2002; 168(1):116-20.
9. Manikandan R, Srirangam SJ, Brown SC, O'Reilly PH, Collins GN. Nitrous oxide vs periprostatic nerve block with 1% lidocaine during transrectal ultrasound guided biopsy of the prostate: a prospective, randomized, controlled trial. J Urol. 2003; 170(5):1881-3
10. Saunders BP; Fukumoto M, Halligan S, Masaki T, Love S, Williams CB. Patient-administered nitrous oxide/oxygen inhalation provides effective sedation and analgesia for colonoscopy. Gastrointest Endosc 1994; 40(4): 418-21.
11. Lindblom A, Jansson O, Jeppsson B, Tornebrandt K, Benoni C, Hedenbro JL. Nitrous oxide for colonoscopy discomfort: a randomized double-blind study. Endoscopy 1994; 26(3):283-6.
12. Notini-Gudmarsson AK, Dolk A, Jakobsson J, Johansson C. Nitrous oxide: a valuable alternative for pain relief and sedation during routine colonoscopy. Endoscopy 1996; 28(3):283-7.
13. Atassi K, Mangiapan G, Fuhrman C, Lasry S, Onody P, Housset B. Prefixed equimolar nitrous oxide and oxygen mixture reduces discomfort during flexible bronchoscopy in adult patients. A randomized, controlled, double-blind trial. CHEST 2005; 128 (2):863 - 868.
14. Fauroux B. The efficiacy of premixed nitrous oxide and oxygen for fiberoptic bronchoscopy in pediatric patients: a randomized, double blind, controlled study. CHEST 2004; 125:315-321.
15. Ekbom K, Jakobsson J, Marcus C. Nitrous oxide inhalation is a safe and effective way to facilitate procedures in paediatric outpatient departments. Arch Dis Child 2005; 90:1073-6.
16. Vetter TR. A comparison of EMLA® cream versus nitrous oxide for pediatric venous cannulation. J Clin Anaesth 1995; 7:486-90.
17. Kronberg JE, Thompson DEA. Is nitrous oxide an effective analgesic for labor? A qualitative systematic review in Evidence Based Obstetric Anaesthesia, ed. by Halpern SH, Douglas MJ; Blackwell 2005, pp. 38-55.
18. Dworkin SF, Chen AC, Schubert MM, Clark DW. Analgesic effects of nitrous oxide with controlled painful stimuli. J Am Dent Assoc 1983; 107(4):581-5.
19. Thornton JA. Cardiovascular effects of 50% nitrous oxide and 50% oxygen mixture. Anaesthesia 1973; 28:484-9.
20. Wynne J et al. Hemodynamic effects of nitrous oxide administered during cardiac catheterization. JAMA 1980; 243:1440-3.
21. Kerr F, Brown MG, Irving JB, Hoskins MR, Ewing DJ, Kirby BJ. A double-blind trial of patient-controlled nitrous oxide/oxygen analgesia in myocardial infarction. Lancet 1975; 1(7922):1397-400.
22. Thompson PL, Lown B. Nitrous oxide as an analgesic in acute myocardial infarction. JAMA 1976; 235:924-7.
23. Annequin D, Carbajal R, Chauvin P, et al. Fixed 50% nitrous oxide mixtures for painful procedures: a French survey. Pediatrics 2000; 105(4):47-58.
24. Gall O, Annequin D, Benoit G, et al. Adverse effects of premixed nitrous oxide and oxygen for procedural sedation in children. Lancet 2001; 358:1514-15.
25. Baskett P, Withnell A. Use of Entonox in the ambulance service. Br J Med 1970; 2:41-43.
26. Young KD. Pediatric Procedural Pain. Ann Emerg Med 2005; 45(2):160-171.
27. Bourgois C, Kuchler H. Gebrauch von MEOPA für schmerzhafte Eingriffe in der Pädiatrie. Paediatrica 2003; 14(2):18-21.
28. Burnweit C et al. Nitrous oxide analgesia for minor pediatric surgical procedures: An effective alternative to conscious sedation? J Pediatr Surg 2004; 39:495-499.
29. Rosen MA. Nitrous oxide for relief of labor pain: A systematic review. Am J Obstet Gynecol 2002; 186(5 Suppl Nature):S110-26. Review.
30. Sidebottam P, Yentis S. N2O in obstetric and gynaecological practice. Best Practice & Research Clinical Anaesthesiology 2001; 15(3):447-457.
31. McGregor DG, Baden JM, Bannister C, et al. Task force on trace anesthetic gases – Information for management in anesthetizing areas and the post-anesthetic care unit (PACU). American Society of Anesthesiologists. 1999, Park Ridge, IL, USA

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