SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Livopan 50%/50% medicinal gas, compressed.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nitrous oxide (N_2O, medicinal laughing gas)	50% v/v
and	
Oxygen (O_2, medicinal oxygen)	50 % v/v
at a pressure of 170 bar (15°C)	

For the full list of excipients, see section 6.1.

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.
It may be used in patients of all ages except children below one month.

4.2 Posology and method of administration

Livopan should only be administered by competent personnel with access to adequate resuscitation equipment.
Special precautions should be taken when working with nitrous oxide. Nitrous oxide should be administered according to local guidelines.

Posology
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.

Paediatric population
There is no differences in dose recommendations in the paediatric population.

Method of administration
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.

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.
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).

Paediatric population
In children 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.

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. SF_6, C_3F_8) 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 persistent signs of confusion, changed cognitive function or other signs that could be related to increased intracranial pressure as nitrous oxide may further increase the 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 presenting with a vitamin B_{12}- or folic acid deficiency or genetic perturbation in this system.
- In patients with facial injury where use of a facemask may present difficulties or risks.

4.4 Special warnings and precautions for use

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.

Nitrous oxide may diffuse into air filled spaces. Livopan can, thus induce increase in middle ear pressure as well as pressure in other gas filled areas.

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)

Livopan should be used with caution in patients with compromised chemoreceptor sensitivity/function (e.g. Chronic Obstructive Pulmonary Disease - COPD) due to the relative high content (50 vol.%) of oxygen. Inhalation of high doses of oxygen may in such patients cause respiratory depression and increase in PaCO2.

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.

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.

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.

<u>Occupational exposure, pollution of surrounding ambient air</u>

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 potential of drug 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.

Nitrous oxide can affect vitamin B_{12} and folate metabolism; consequently, Livopan should therefore be used with caution in risk patients, i.e. patients with reduced intake or uptake of vitamin B_{12} 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 B_{12}/folic acid should be considered. The concomitant use of nitrous oxide and methotrexate should be avoided (see section 4.5).

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.

Paediatric population
Livopan can be used in children that are able to follow instructions on how to use the equipment. In the treatment of younger children 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.).

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.

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 (See 4.4).

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 nitrous oxide and methotrexate should be avoided.

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 B_{12} (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 4.8). Therefore the administration of Livopan should be limited in time (see also 4.4).

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 foetal 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
The potential effect of clinical doses of Livopan on fertility in patients, are unknown. No data are available. (see also section 5.3).
The potential risk associated to chronic work place exposure cannot be ruled out (see section 4.4).

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 as a 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 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

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

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. 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

Other analgesic therapies should be considered in patients showing signs of vitamin B_{12}/folate deficiency.

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 (can not be estimated from the available data)**
Blood and lymphatic system disorders	-	-	-	-	-	Megaloblastic anaemia, leukopenia
Psychiatric disorders	-	Euphoria	-	-	-	Psychosis, confusion anxiety, addiction
Nervous system disorders	-	Dizziness Light-headedness	Severe fatigue	-	Paraparesis	Headache, Myeloneuropathy, Neuropathy, Subacute degeneration of the spinal cord Generalised seizures
Ear and labyrinth disorders	-	-	Feeling pressure in the middle ear	-	-	-
Gastrointestinal disorders	-	Nausea, vomiting	Bloating, increased volume of gas in the intestines	-	-	-
Respiratory, thoracic and mediastinal disorders	-	-	-	-	-	Respiratory depression

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

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.
Reversible neurological toxicity and megaloblastic bone marrow change have also been observed following exceptionally prolonged inhalation.
Overdose of nitrous oxide and or hypoxic gas mixture can occur if the equipment is exposed to cold, 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 physio-chemical 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 armacology, repeated dose toxicity, genotoxicity and carcinogenic potential.
Prolonged continual exposure to 15 to 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 to 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.

Oxygen
Non-clinical data reveal no special hazards for humans. Effects in non-clinical studies were observed only 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).

Aluminium gas cylinder, filling pressure 170 bar:

2-litre aluminium gas cylinder with shut-off valve with integrated in pressure regulator, flow selector 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 selector 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 selector 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 170 bar delivers approximately X litre gas at atmospheric pressure and 15°C according to the table below:

Cylinder size in litre	2 (170 bar)	5 (170 bar)	10 (170 bar)
Litre of gas	560	1400	2800

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for use and handling

General
Medicinal gases must be used for medicinal purposes only.

Different gas types must be separated from each other. Full and empty gas cylinders must be stored separately.
Never use oil or grease, even if the cylinder valve is 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.
Check that the quick connector is clean and that the connections are in good condition.
Open the cylinder valve slowly – at least half a turn.
In the event of leakage, close the valve. 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

Linde Sverige AB
Rättarvägen 3
169 68 Solna
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

23301

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

16/04/2008 / 07/12/2012

10. DATE OF REVISION OF THE TEXT

2025-01-16