SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Kalinox 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

3. PHARMACEUTICAL FORM

Medicinal gas, compressed
Colourless, odourless gas

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kalinox 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.

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

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

Method of administration
Kalinox is administered via inhalation in spontaneously breathing patients via a face mask. Administration of Kalinox 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 Kalinox 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 Kalinox 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.

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

Ideally, the patient should hold the mask through which Kalinox 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 Kalinox than is necessary, and wakefulness becomes affected, the patient will drop the mask and administration will cease. By breathing ambient air, the effect of Kalinox rapidly wears off and the patient will regain consciousness.

Kalinox 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 not capable to understand and follow the instructions, Kalinox 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, Kalinox 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 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 should be available whenever constant flow is used.

When administration is ended the patient should be allowed to recover under calm and controlled conditions for about 5 minutes or until the patient’s degree of alertness/consciousness has satisfactorily recovered.

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

4.3 Contraindications

When 100% O2 ventilation is required.

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

- Hypersensitivity to the active substance.
- In patients with signs or symptoms of pneumothorax, pneumopericardium, severe emphysema, gas emboli or head injury.
- Maxillofacial injuries.
- Following deep sea diving with risk of decompression sickness (bubbles of nitrogen).
- Following treatment 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, or within 3 months after the last injection of an intraocular gas, because the gas volume may increase in pressure/volume and consequently result in blindness (see sections 4.5 and 4.8).
- In patients with a severely dilated gastrointestinal tract.
- Following air encephalography
- During middle ear, inner ear and sinus surgery

- If air has been injected into the epidural space to determine the placement of the needle for epidural anaesthesia

Kalinox 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 showing signs of confusion or in some other way showing signs of increased intracranial pressure.
- In patients with untreated vitamin B12- or folic acid deficiency or diagnosed genetic disorder of the enzyme system involved in metabolism of these vitamins. (see 4.4)
- 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 facial injury where use of a face mask may present difficulties or risks.

4.4 Special warnings and precautions for use

Self-administration should be preferred to allow the assessment of the level of consciousness.

Kalinox 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.

Attentive monitoring is required in patients taking central nervous system depressant drugs and in particular opiates and benzodiazepines, because of the increased risk of deep sedation (see section 4.5).

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.

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

Warnings

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 one of the probable reasons for the influence of nitrous oxide on blood formation and the foetal damage seen in animal studies (see section 5.3).

Due to the risk during pregnancy for women occupationally exposed, 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 (see section 4.6).

Areas in which Kalinox 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 (see section 4.9).

Kalinox 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 of following 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 cause inactivation of vitamin B12 (a co-factor of methionine synthase) which interferes with folate metabolism. Assessment of vitamin B12 levels should be considered in people with risk factors for vitamin B12 deficiency prior to using Kalinox. Consequently, Kalinox 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, alcoholic patients, patients suffering from anaemia, or atrophic gastritis, those with vegetarian diet, or recent use of medications that interfere with vitamin B12 and/or folate metabolism (see Section 4.5 and 4.8). If necessary, substitution treatment with vitamin B12/folic acid should be considered, in case of repeated or prolonged administration.

Continuous administration for periods of more than 6 hours should be applied with caution because of the potential risk for clinical manifistations from the inhibitory effects on the methionine synthase. Prolonged continuous use or recurrent use should be accompanied by haematological monitoring to minimize the risk of potential side effects.

Due to its nitrous oxide content, Kalinox can increase pressure in the tympanic cavity and other air-filled cavities(see also 4.3). In the event of obstruction of the Eustachian tube, an earache and/or middle ear disorders and/or tympanic rupture may be observed (see section 4.8).

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

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

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

Paediatric population:

Nitrous oxide may in rare case causes respiratory depression in the neonate (see section 4.8). The neonate should be checked for possible respiratory depression when KALINOX is used around childbirth

4.5 Interaction with other medicinal products and other forms of interaction

Combinations which are contraindicated

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

Combination with other medicinal products requiring precautions for use

The nitrous oxide component of Kalinox interacts in an additive manner with inhaled anaesthetics. It can potentiate the hypnotic effects of other active substances with effects on the central nervous system (e.g. opiates, benzodiazepines and other psychomimetics). If concomitant central acting agents are used, the risk for pronounced sedation and depression of protecting reflexes should be acknowledged.

Kalinox 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 is exacerbated by inhalation of increased concentrations of oxygen.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data on pregnant women exposed to a single administration of nitrous oxide during the 1st trimester (more than 1000 exposed outcomes) indicate no malformative toxicity. Moreover no fetal nor neonatal toxicity has been specifically associated with nitrous oxide exposure during pregnancy. Therefore, nitrous oxide can be used during pregnancy if clinically needed. When used close to delivery, newborns should be supervised for possible adverse effects (see sections 4.4 and 4.8).

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

Fertility

No relevant data are available in humans.

Lactation

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

Kalinox can be used during the breast-feeding period.

4.7 Effects on ability to drive and use machines

The nitrous oxide component of Kalinox has effects on the cognitive and psychomotor functions. Kalinox is rapidly eliminated after ending inhalation. However, after stopping administration of nitrous oxide and in particular after prolonged administration, outpatients who must drive or use machines should be monitored until they have recovered the same state of alertness as before administration.

4.8 Undesirable effects

Megaloblastic anaemia and leukopenia have been reported following prolonged or repeated exposure to Kalinox. 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.

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

	Common *(≥1/100 to <1/10*	*Uncommon: (≥1/1000 to <1/100)*	*Not known (cannot be estimated from the available data)*
Blood and lymphatic system disorders			Megaloblastic anaemia, Leucopenia/ Pancytopenia(1), Agranulocytosis (2)
Metabolism and nutrition disorders			Vitamin B12 deficiency (see sections 4.4 and 4.5)
Psychiatric disorders		Euphoria Agitation* Anxiety* Dreams* Hallucination*	Disorientation, Addiction
Nervous system disorders		Paraesthesia Excessive sedation*	Dizziness, Myelopathy, Myeloneuropathy, Neuropathy, Subacute degeneration of the spinal cord, Headache*, Intracranial pressure increased Generalised seizures
Eye disorders			Severe visual impairment (caused by expansion of an intraocular gas, see Sections 4.3 and 4.5).
Ear and labyrinth disorders			Ear pain, Middle ear disorders,

			Tympanic rupture (in the event of non permeability of the Eustachian tube - see Section 4.4).
Respiratory, thoracic and mediastinal disorders			Respiratory depression(in the neonate, when nitrous oxide was used during delivery around childbirth - see Section 4.4).
Gastrointestinal disorders	Nausea Vomiting		

*specific to analgesia

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V

4.9 Overdose

Since participation of the patient is required to administer the gas mixture, the risk of overdose is minimised (see section 4.2).
If during use of Kalinox 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 Kalinox until full consciousness has been restored.
If the patient becomes cyanotic during use of Kalinox, the treatment must immediately be discontinued and appropriate measures may be required.

Overdose of nitrous oxide and or hypoxic gas mixture can occur if the equipment is exposed to cold conditions, below -5°C. This can result in separation of the gas mixture. Consequently an excessively high nitrous oxide concentration can be supplied from the equipment with a risk of a hypoxic gas mixture being supplied (see section 6.4).

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 optimum 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/Kalinox.

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 continuous exposure to 5-15% nitrous oxide has been shown to induce neuropathy in 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.

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 Kalinox has been stored under too cold conditions, the cylinders should be stored in a 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 excessive 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

Packaging: Gas cylinders are combined as listed below with various kinds of valves and sometimes also with additional built in pressure regulator and flow regulator. The body of the gas cylinder is white (medicinal gas).The shoulder of the gas cylinder is marked in white and blue (oxygen/nitrous oxide). The indicated volume is expressed as water volume.

Steel cylinder with shut-off valve
2.5-litre filled at 131 bar gives 0.519 m^3 gas at atmospheric pressure and 15°C
5-litre filled at 131 bar gives 1.038 m^3 gas at atmospheric pressure and 15°C
11-litre filled at 131 bar gives 2.284 m^3 gas at atmospheric pressure and 15°C

Aluminium cylinder with shut-off valve
3-litre filled at 131 bar gives 0.623 m^3 gas at atmospheric pressure and 15°C
5-litre filled at 131 bar gives 1.038 m^3 gas at atmospheric pressure and 15°C
11-litre filled at 131 bar gives 2.284 m^3 gas at atmospheric pressure and 15°C

Steel cylinder with integrated shut-off valve
2-litre filled at 170 bar gives 0.59 m^3 gas at atmospheric pressure and 15°C
3-litre filled at 170 bar gives 0.89 m^3 gas at atmospheric pressure and 15°C
5-litre filled at 170 bar gives 1.47 m^3 gas at atmospheric pressure and 15°C
10-litre filled at 170 bar gives 2.95 m^3 gas at atmospheric pressure and 15°C

Aluminium cylinder with integrated shut-off valve
2-litre filled at 170 bar gives 0.59 m^3 gas at atmospheric pressure and 15°C
3-litre filled at 170 bar gives 0.89 m^3 gas at atmospheric pressure and 15°C
5-litre filled at 170 bar gives 1.47 m^3 gas at atmospheric pressure and 15°C
10-litre filled at 170 bar gives 2.95 m^3 gas at atmospheric pressure and 15°C

Aluminium gas cylinder with shut-off valve with integrated pressure and flow regulators
2-litre aluminium gas cylinder filled at 170 bar gives 0.59 m^3 gas at atmospheric pressure and 15°C
5-litre aluminium gas cylinder filled at 170 bar gives 1.47 m^3 gas at atmospheric pressure and 15°C
15-litre aluminium gas cylinder filled at 170 bar gives 4.4 m^3 gas at atmospheric pressure and 15°C

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

General
Medicinal gases must be used for medicinal purposes only.

Different medicinal 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 gas cylinder 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 outdoors. Label defective cylinders, place them in an area intended for claims and return them to the supplier.
Cylinders with a Compact-valve have an built-in pressure regulator in the valve. Consequently, a separate pressure regulator is unnecessary. The Compact-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 Kalinox 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

<To be completed nationally>

8. MARKETING AUTHORISATION NUMBER(S)

<To be completed nationally>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

<To be completed nationally>

10. DATE OF REVISION OF THE TEXT

2022-11-02