PACKAGE INSERT

CONOXIA® 100% V/V

1. BRAND OR PRODUCT NAME

CONOXIA® Compressed Medicinal Oxygen 100% v/v with LIV®

2. NAME AND STRENGTH OF ACTIVE SUBSTANCE(S)

Oxygen 100%v/v, Medicinal Gas, Compressed

There are no excipients.

3. PRODUCT DESCRIPTION

The drug product for CONOXIA® is medicinal compressed gas oxygen, which is stored in aluminium cylinders equipped with Linde Integrated Valve (LIV®). The physical appearance of the gas cylinder is white colour cylinder shoulder and black colour cylinder body. The CONOXIA cylinders are filled with gaseous oxygen at pressure of 200 bar. Gaseous oxygen is a colourless, odourless gas without taste. LIV is an integrated valve consists of a pressure regulator, a flow outlet, a pressure outlet, and a bed hanger.

4. PHARMACODYNAMICS

Pharmacotherapeutic group: Other therapeutic products, ATC code: V03AN01

Normobaric oxygen

The ambient air consists of approximately 21% oxygen. Oxygen is vital to life and must be supplied continuously to all tissues in order to maintain the cells' energy production. The final target for the oxygen is the mitochondria in the individual cells, where oxygen is consumed in an enzymatic chain reaction forming energy. Oxygen is a vital component in the cell's intermediate metabolism for creation of energy i.e. the aerobic adenosine triphosphate (ATP) production in the mitochondria. By increasing the oxygen fraction in the inspired gas mixture, the partial pressure gradient transporting oxygen to the cells is increased. Oxygen speeds up the release of carbon monoxide (CO) that is bound to haemoglobin and other iron-containing proteins, and therefore counteracts the negative blocking effects caused by the binding of carbon monoxide to iron.

Oxygen is vital to maintain cellular metabolism and for the cellular haemostasis. Lack of oxygen rapidly produces an anaerobic cellular situation with malfunction and subsequent cell death. Oxygen is thus vital for the natural cell function. Hyper-oxygenation may cause production of free radicals. If the capacity for handling of reactive oxygen spices is exceeded, there is a risk for cellular toxicity, inflammatory reaction caused by the oxygen radicals.

Hyperbaric oxygen

HBO therapy increases the oxygen dissolved in plasma and thus the oxygenation of the blood. The oxygenation of tissues is subsequently improved. The increased oxygenation is of importance in critical hypoxic tissue, e.g., the penumbra of severe necrosis. The increased oxygenation subsequently cellular metabolism and thereby improves tissue function, it also facilitates the defence system, and the bacterial killing capacity in tissues, especially in anaerobic infections.

5. PHARMACOKINETICS

Normobaric oxygen

Inhaled oxygen is transported via the airways to the lung with the inspired air. In the alveoli, a gas exchange takes place through the difference in partial pressure from the inspired air/gas mixture to the capillary blood. The oxygen is transported by the systemic circulation mainly bound to haemoglobin to the capillary beds in different tissues of the body. Only a very small portion is dissolved in plasma. During passage through the tissues, a partial pressure-dependent transport of the oxygen to the individual cells takes place. The final target for the oxygen is the mitochondria in the individual cells where oxygen is consumed in an enzymatic chain reaction, forming energy. By increasing the oxygen fraction in the inspired gas mixture, the partial pressure gradient transporting oxygen to the cells is increased. Oxygen taken up in the body is excreted almost entirely as carbon dioxide formed in the intermediary metabolism.

Absorption

Oxygen is administered by inhalation and subsequently transported to the alveoli. The alveolar partial oxygen pressure (PAO_2) is the driving force for the transport of oxygen from the aerated alveoli through the alveolo-capillary membrane. In the capillaries surrounding aerated alveoli, oxygen is dissolved in plasma but also bound to the haemoglobin (content of oxygen: (1.34 x [Hb] x SaO_2) + (PaO_2 x 0.023 mL/dL/kPa).

Distribution

Oxygen is distributed by the systemic circulation. The majority of oxygen is carried by the haemoglobin. Oxygen delivery is dependent on oxygen content and the cardiac output. Tissue perfusion is dependent on cardiac output, systemic circulation, blood pressure and regional perfusion.

Biotransformation

Oxygen diffuses from the blood in the peripheral capillary bed; it reaches the cells where it is part of the internal metabolism, aerobic energy production.

Elimination

The net effect of the aerobic metabolism is energy production [adenosine trisphosphate (ATP)] and carbon dioxide, which is eliminated from the body by the pulmonary ventilation.

5.1 Hyperbaric oxygen

HBO therapy speeds up the release of carbon monoxide at a greater rate than that achievable by breathing 100% oxygen at normal pressure.

HBO therapy constitute the administration of 100% oxygen at a pressure above the atmospheric level, thus facilitating the uptake of oxygen in the blood and thereby increasing the oxygen content of the arterial blood Hyperbaric oxygen therapy (HBO) diminishes in proportion to the pressure that is given with the volume of gas bubbles in the tissues according to Boyle's law.

6. INDICATIONS

Normobaric oxygen

Medicinal Oxygen under normobaric pressure is used for:

- Treatment or prevention of acute or chronic hypoxemia, irrespective of genesis.
- As part of the fresh gas supply in anaesthesia or intensive care.
- As the driving gas in nebulisation therapy.
- As first aid treatment with 100% oxygen in decompression accidents, and suspected carbon monoxide poisoning.

The treatment is indicated in all age groups.

- Treatment of an acute attack in patients with an established diagnosis of cluster headache. This treatment is indicated in adults only.

Hyperbaric oxygen (HBO)

Medicinal oxygen under hyperbaric pressure (HBO)is used for treatment of conditions where it is beneficial to increase the oxygen content of blood and other tissues above which is attainable under normobaric pressure.

- Treatment of decompression sickness, air/gas emboli of other genesis
- In carbon monoxide poisoning. HBO therapy is indicated essentially in patients who are or have been unconscious, that have shown neurological signs, cardiovascular dysfunction or severe acidosis and in pregnant females all irrespective of carbon monoxide haemoglobin (COHb) levels.
- As adjunctive treatment for osteo-radionecrosis and clostridial myonecrosis (gas gangrene).

The treatment can be used in all age groups.

7. RECOMMENDED DOSAGE

Normobaric oxygen

General recommendations

The primary purpose of oxygen therapy, i.e., correction of hypoxia, is to ensure that the partial arterial oxygen pressure (PaO_2) is not less than 8.0 kPa (60 mmHg) or that the oxygen saturation of haemoglobin in arterial blood (SaO_2) is not less than 90%. This is achieved by adjusting the fraction of oxygen in inspired gas. The lowest oxygen fraction of inspired gas needed to achieve the desired result of therapy i.e. a safe PaO_2 should be used. The therapy should be evaluated continuously, and the effect of treatment measured with PaO_2/SaO_2 or an estimate of SaO_2 i.e. SpO_2.The oxygen fraction of inspired gas should be adjusted according to each individual patient's unique requirement, taking the risk of oxygen toxicity into account (See Symptoms and Treatment of Overdose). In severe hypoxia, oxygen fractions that may involve a risk of oxygen toxicity can still be indicated.

Acute or chronic hypoxia - Spontaneous breathing - Short term therapy

In emergency medicine, oxygen is commonly administered by nasal prongs with at flowrate of 2-6 l/min or by face mask with a flow rate of 5-10 l/min. Patients, not at risk of respiratory failure and with an initial SpO_2 <85%, can be treated with 10-15 l/min by mask with a reservoir. Patients with known suspected chronic respiratory disease (e.g. COPD) that may have reduced chemoreceptor sensitivity should be treated with caution as a too liberal use of oxygen may cause respiratory depression. When 100% oxygen is indicated, a face mask with reservoir (oxygen flow should be enough to keep the reservoir partially or completely filled – i.e. not collapsed during - breathing) or a demand valve system should be used.

The fraction of oxygen in inspired gas should be kept so that with or without positive end-expiratory airway pressure (PEEP) or continuous positive airway pressure (CPAP) a PaO_2>8 kPa is maintained. The effect of short-term oxygen therapy should be monitored by repeated measurements of PaO_2 or by pulse-oximetry, which provides a numerical value for the SpO_2. However, these indices are only indirect measures of tissue oxygenation. Clinical assessment of the treatment is of outmost importance.

Acute or chronic hypoxia - Spontaneous breathing - Long-term therapy

In long-term therapy, oxygen can be administered by specially designed masks, e.g. Venturi-masks where the delivered oxygen concentration can be adjusted and dependent on the gas flow and the valve on the mask. Concentrations of 24 to 35% are commonly used.

The need for medicinal oxygen should be determined by obtaining arterial blood gas values and/or by monitoring SpO_2. The inspired oxygen should be titrated when used for long term oxygen therapy in patients with chronic hypoxic respiratory failure. A SaO_2/SpO_2 between 88 and 92% is commonly assessed as adequate in patients with chronic obstructive pulmonary disease (COPD). A too liberal administration can increase the oxygen SaO_2/SpO_2 clearly above the patient's normal range, which may cause respiratory depression because of chemoreceptor insensitivity for CO_2. Blood gases should be monitored to avoid excessive retention of CO_2 in patients with hypercapnia or reduced CO_2- sensitivity, in order to adjust the oxygen therapy.

Fresh gas supply in anaesthesia or intensive care - Assisted or controlled ventilation

Oxygen is commonly used in the intensive care setting. The inhaled oxygen should be titrated to the individual patient's need. The oxygen is commonly administered by assisted or controlled ventilation.

A PEEP is commonly applied to facilitate the ventilation/perfusion matching, recruiting airways and lung volumes, and thereby subsequently decreasing shunt.

During general anaesthesia a fraction of inspired oxygen about 0.3 is usually adequate. Higher fractions can be used in patients when found necessary.

If the oxygen is mixed with other gases, the oxygen fraction should be maintained at least at 0.21 in the inhaled gas mixture. The fraction of inspired oxygen can be increased up to 1.0.

Nebulisation

When oxygen is used for nebulisation, it can be used as a sole driving gas (100% in enough flow rate in order to nebulise the fluid in the nebulisation chamber) or mixed with air. In nebulisation therapy, the flow of oxygen and/or oxygen mixed with air is usually a continuous flow of 6-8 l/min.

First aid treatment

For emergencies if an acute administration of 100% oxygen is indicated, a face mask with reservoir (oxygen flow sufficient to keep the reservoir un-collapsed during breathing) or a demand valve system should be used.

Cluster Headache

Oxygen administration should be instituted as soon as possible after the onset of the attack. Oxygen

should be delivered by facemask in a non-re-breathing system with a continuous flow of 6 to 12 l/min,

for about 15 min.

Paediatric population

The safety and efficacy of oxygen in children of all ages is well established. The dosing instructions for the paediatric population are the same as for adults, except for new-borns (term, near term, and preterm). In new-borns careful monitoring should be performed during the treatment. Oxygen in concentrations up to 100% can be administered in order to ascertain adequate oxygenation but for shortest time possible. Oxygen may be used during resuscitation in new-borns, but guidelines recommend that air is used initially. The lowest effective concentration should be sought in order to achieve an adequate oxygenation. Oxygen in low concentrations up to 40% (FiO_2 0.4) in combination with CPAP is recommended as an initial therapy.

There is no relevant use of oxygen in the paediatric population since oxygen for treatment of an acute attack in patients with an established diagnosis of cluster headache is not indicated in the paediatric. population.

7.1 Hyperbaric oxygen

General recommendations

Qualified healthcare professionals should administer HBO. HBO means that 100% oxygen is delivered at a pressure above the atmospheric pressure at sea level (1 atmosphere=101.3 kPa=760 mmHg). For safety reasons the pressure of HBO should not exceed 3 atmospheres.

The duration of a single treatment with HBO at a pressure of 2-3 atmospheres is normally between 60 min and 4-6 h depending on the indication. Sessions may, if necessary, be repeated 2-3 times a day depending on the indication and the patient's clinical condition. Compression and decompression should be slow in accordance with common routines in order to avoid the risk of pressure damage i.e. baro-trauma. The length and frequency of treatment should be decided by the attending physician taking the patient's physical and medicinal status into account. Recommendations for each indication are provided below.

Decompression sickness and air/gas embolism due to other reasons

HBO therapy with 2.5-3 atmospheres for up to 24 h, repeatedly as needed, is recommended.

Carbon monoxide poisoning

HBO therapy with 2.5-3 atmospheres is recommended. Usually, 45 min of treatment is required.

Osteo-radionecrosis and clostridial myonecrosis (gas gangrene)

For osteo-radionecrosis 2.4 atmospheres for about 90 min is recommended and for clostridial myonecrosis the recommendation is 3 atmospheres for about 90 min. The treatment could be repeated depending on therapy result.

Paediatric population

HBO can be used in children of any age. The length and frequency of treatment should be decided by the attending physician taking the patient's physical and disease status into account.

8. METHOD OF ADMINISTRATION

Precautions to be taken before handling or administering the medicinal product, see special precautions for Disposal and Other Handling.

Oxygen is administered with the inspiratory air. On exhalation the exhaled gas, with any oxygen excess, leaves the patient and is mixed with the surrounding air. Oxygen should be administered via special equipment.

Normobaric oxygen

Spontaneous breathing

There are many devices intended for the administration of oxygen in spontaneous breathing patients for example:

- Low-flow systems

The simplest systems, which deliver a mixture of oxygen to the inspiratory air, e.g., a system in which the oxygen is administered via a simple rotameter connected to a nasal catheter or facemask.

- High-flow systems

Systems designed to provide a gas mixture corresponding to the patient's entire inspiratory atmosphere. These systems are designed to deliver a fixed concentration of oxygen that is not influenced (diluted) by the surrounding air, e.g., Venturi masks with a fixed flow of oxygen in order to give a fixed concentration of oxygen in the inspired air.

- Demand valve

A demand valve system (i.e., a valve triggered by spontaneous ventilation) is system designed to deliver 100% oxygen without entrainment of ambient air, intended for short duration of administration by mask.

- High Flow Nasal Cannula systems is also an option for spontaneously breathing patients.

Assisted and controlled ventilation

When oxygen is administered by assisted or controlled ventilation, an oxygen air mixture is commonly used in order to achieve a desired oxygen fraction. The gas can be administered by mask, tracheal tube or tracheostomy.

Fresh gas flow during general anaesthesia

During anaesthesia, special anaesthesia equipment is used. Anaesthesia equipment commonly consists of a specially designed breathing circle intended for partial re-breathing. A circle system with a carbon dioxide absorber allowing a portion of the expired gas to be re-circled and inhaled again is often used.

Extracorporeal membrane oxygenation

Oxygen is usually administered via inhalation but can also be administered through a so-called oxygenator directly to the blood e.g. in conjunction with heart surgery (when a heart-lung machine is used) or in patients with severe therapy resistant hypoxia requiring extracorporeal membrane oxygenation/extracorporeal lung assist (ECMO/ECLA).

Hyperbaric oxygen

HBO is given in a specially constructed pressure chamber designed for HBO treatment in which pressures up to three times atmospheric pressure can be maintained. HBO can also be given via a very closely fitting facemask i.e. a hood that closes around the head, or through a tracheal tube.

9. ROUTE OF ADMINISTRATION

Inhalation

10. CONTRAINDICATIONS

Normobaric oxygen

There is no absolute contraindication to oxygen therapy under normobaric conditions.

Hyperbaric oxygen

HBO is contraindicated in patients with an untreated pneumothorax, or other accidentally gas filled spaces with no ability to vent.

11. WARNINGS AND PRECAUTIONS

Normobaric oxygen

Whenever oxygen is used, the increased risk for spontaneous ignition should be taken into account. This risk is increased in procedures involving diathermy, and defibrillation/electro conversion therapy.

As a general rule, high concentrations of oxygen should only be administered for the minimum time required to achieve the desired clinical outcome. The inspired oxygen concentration should be reduced as soon as possible to the lowest concentrations needed. The patient should be monitored by repeated analyses of the PaO_2 or SpO_2 and the concentrations of inhaled oxygen should be titrated to maintain these parameters at an acceptable clinical level.

Prolonged exposure to higher concentrations of oxygen than listed below may generate oxygen species/free radicals and subsequently cause inflammation. The lungs as well as the remainder of the respiratory tract are exposed to the highest concentration of oxygen in the human body and are therefore the first organs to show toxicity. Thus, the risk for oxygen induced lung dysfunction (e.g. signs or symptoms of acute lung injury/respiratory distress syndrome) shall be acknowledged.

Studies in animals and humans suggest that inhalation of an oxygen fraction of 1.0 is reasonably safe for periods of less than 24 h. There are data showing that there is a certain degree of tolerance to exposure to high oxygen concentrations, possibly associated with an increased defence against oxygen radicals. There are case reports showing positive effects of up to 2 days exposure to concentrations up to 80%. The benefit versus risk for prolonged exposure to high concentrations shall be assessed on an individual basis. The evidence in the supporting literature suggests that the risk of oxygen toxicity can be minimised if the treatment follows these guidelines [fraction of inhaled oxygen in the inhaled air/gas mixture (FiO_2)]:

- Oxygen in concentrations up to 100% (FiO_2 1.0) should not be given for more than 6 h.
- Oxygen in concentrations of 60-70% (FiO_2 0.6-0.7) should not be given for more than 24 h.
- Any oxygen concentrations >40% (FiO_2>0.4) can potentially cause damage after 2 days.

In cases of high concentrations of oxygen in the inspiratory air/gas, the concentration/pressure of nitrogen is lowered. As a result, the nitrogen concentration in tissues and lung (alveoli) is lowered. If oxygen is taken up from alveoli to the blood faster than additional oxygen is delivered by ventilation, alveoli may collapse, causing atelectasis.

The formation of atelectatic lung areas may impair oxygenation of arterial blood, because there will be no gas exchange in the atelectatic area despite perfusion. As a consequence, there will be a ventilation/perfusion mismatching and subsequently an increased shunt.

In patients with reduced sensitivity for carbon dioxide pressure in arterial blood, high concentrations of oxygen may cause, respiratory depression subsequently causing carbon dioxide retention, which in extreme cases can lead to carbon dioxide narcosis.

Risk associated with adjusting the oxygen flow settings

Prolonged exposure to higher concentrations of oxygen may be associated with several side effects. Special precautions should be taken when adjusting the oxygen flow settings beyond the prescribed level. In case of increase demand of oxygen or persistent symptoms of hypoxia, promptly consult with your prescribing physician or seek immediate medical assistant.

Risk associated to hypoxia

Patients treated with oxygen therapy might be prone of suffering hypoxia due to several factors (e.g., disease progression or unintended underdosage). Tiredness, fatigue or exhaustion are early indicators of hypoxia. In case of unexpected or persistent of these symptoms, measure blood oxygen saturation (SpO_2) to detect hypoxia, verify proper oxygen supply is provided and promptly consult your prescribing physician or seek immediate medical assistance.

Paediatric population

Special caution should be taken when treating new-born since they have lower levels of defence systems and less active scavenging of free radicals than other populations. Thus, the potential negative effects of hyper-oxygenation are increased in the preterm and near term. The absolute lowest concentration, which gives the desired result, should be used in order to minimise the risk of ocular damage, retrolental fibroplasia (ROP), and broncho-pulmonary dysplasia (BPD) or other potential undesirable effects, which occur with a much lower oxygen concentration/fraction than in other populations.

Hyperbaric oxygen

Compression and decompression should be slow in order to avoid the risk of pressure damage i.e. baro-trauma.

For HBO during pregnancy or in females of childbearing potential, see pregnancy and lactation.

HBO should be used with caution in patients presenting with pneumothorax or other accidentally gas filled spaces with no ability to vent (e.g. the pneumo-pericard) and who are treated with a chest-tube and/or patients with a medical history of pneumothorax. The use should be evaluated in each individual patient with regard to the risk of a new (tension) pneumothorax.

Exposure to high oxygen concentrations may result in central nervous system (CNS) effects. The risk of CNS oxygen toxicity is a function of both partial pressure of oxygen and exposure time. The symptoms of CNS toxicity include blurred vision, peripheral vision decreased, tinnitus, respiratory disturbances, localized muscular twitching especially eyes, mouth, forehead. Continuation of exposure can lead to vertigo or dizziness and nausea followed by altered behaviour (anxiety, confusion, irritability), and finally generalized convulsions. CNS toxicity is expedited by factors such as raised partial pressure of carbon dioxide, stress, fatigue and cold.

Paediatric population

The experience in new-borns, children and adolescents is limited. HBO should therefore be used with caution in the paediatric population. The benefit-risk should be evaluated in each individual patient.

12. INTERACTION WITH OTHER MEDICAMENTS

The pulmonary toxicity associated with high concentrations of oxygen (see warnings and precautions) can be exacerbated by concomitant use of anticancer drugs e.g. bleomycin, cisplatin, and doxorubicin, anti-arrhythmic drugs e.g. amiodarone, antibiotics e.g. furadantin (nitrofurantoin), alcohol deterrents e.g. disulfiram, and chemicals e.g. paraquat.

Paediatric population

There are no known other interactions than those in the adult population.

13. PREGNANCY AND LACTATION

Normobaric oxygen

No studies examining the potential toxicity of normobaric hyperoxia on embryo-foetal development or reproduction have been identified in the literature.

Pregnancy

Oxygen supplementation has no known negative effects on the foetus. Women of childbearing potential can use oxygen.

Breastfeeding

Oxygen supplementation has no known negative effects on the breastfeeding child. Oxygen can be used during lactation.

Fertility

Oxygen supplementation has no known negative effects on fertility.

Hyperbaric oxygen

Pregnancy

HBO should be used with caution during pregnancy and in females of childbearing potential due to a potential risk of oxidative stress-induced damage in the foetus. In severe carbon monoxide intoxication, the benefit versus risk for the use of HBO should be evaluated in each individual patient.

Breast-feeding

There are no known adverse effects of HBO on lactation. However, lactation should be avoided during the actual HBO therapy.

Fertility

HBO treatment and effects on fertility has not been studied.

14. SIDE EFFECTS

Summary of the safety profile

The undesirable effects listed are derived from public domain scientific medical literature and post marketing safety surveillance. Frequencies of the undesirable effects cannot be estimated based on these data.

The most serious side effects that may occur are severe difficulty in breathing, so called respiratory distress syndrome. Too liberal oxygen administration may also cause respiratory depression in susceptible patients with reduced chemoreceptor sensitivity as seen in e.g. some patients with chronic obstructive pulmonary disease (COPD). It is not known how common this side effect is.

Paediatric population

In the use of oxygen in new-borns the risk for ROP in pre-terms and the development of BPD should be acknowledged. Except for these two risks, there are no other undesirable effects reported than in adults.

Tabulated summary of adverse reactions

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1 000 to 1/100)	Rare (≥1/ 10 000 to 1/1 000)	Very rare (<1/ 10 000)	Not known (cannot be estimated from the available data)
Psychiatric disorders						HBO: Anxiety, confusion
Nervous System Disorders						NBO and HBO: Respiratory depression (chemo-receptor sensitivity) HBO: Loss of consciousness, epilepsy unspecified
Eye disorders						NBO and HBO: Retrolental fibroplasia in prematures HBO: Myopia
Ear and labyrinth disorders						HBO: Feeling of pressure in the middle ear tympanic membrane rupture
Respiratory, thoracic and mediastinal disorders						NBO and HBO: Atelectasis, pleuritis. Respiratory distress syndrome. Pulmonary fibroses. Bronchopulmonary dysplasia HBO: Sinus squeeze
Injury, poisoning and procedural complications						NBO and HBO: Burns HBO: Baro-trauma

HBO: *Hyperbaric oxygen* ***NBO:*** *Normobaric oxygen*

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 *NPRA's ADR (Adverse Drug Reactions) reporting website: npra.gov.my [Consumers -> Reporting Side Effects to Medicines (ConSERF) or Vaccines (AEFI)].*

15. SYMPTOMS AND TREATMENT OF OVERDOSE

Normobaric

Initial symptoms of oxygen toxicity are cough and signs and symptoms of pleuritis and subsequently symptoms of respiratory distress.

In case of oxygen overdose, the oxygen concentration should be decreased. Symptomatic therapy should be instituted in order to maintain critical physiology (e.g. in case of respiratory depression, respiratory support should be instituted).

The administration of oxygen is associated with potential risk of baro-/volu-trauma if there is no venting in the delivery system, e.g., when there is no safety pressure reduction valve in the delivery equipment.

Additional information on special populations

In COPD patients with decreased chemoreceptor sensitivity, administration of oxygen may cause respiratory depression and can in extreme cases lead to carbon dioxide narcosis.

Paediatric population

The risk for overdose, because of a too liberal administration of oxygen in newborns during resuscitation and early part of life, shall be acknowledged. Common guidelines recommend initial resuscitation with air and institution of oxygen supplementation only if the new-born is insufficiently oxygenated.

High oxygen concentration/fraction and fluctuations in oxygenation is considered to contribute to the development of ROP.

Hyperbaric oxygen

The risk of overdose is greater during HBO treatment.

Short exposure to very high partial pressures of oxygen may cause acute cerebral toxicity and related symptoms.

Paediatric population

There is overall limited information available about HBO in the paediatric population.

16. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Medicinal oxygen has no or negligible influence on the ability to drive and use machines.

17. PRECLINICAL SAFETY DATA

Normobaric oxygen

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Pre-clinical studies have shown that prolonged continuous inhalation of pure oxygen may have harmful effects. Tissue injury can be induced in the lung, eye and central nervous system. Marked variability occurs between the time of onset of pathological changes among different species and among animals of the same species.

Hyperbaric oxygen

Effects in pre-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

HBO treatment during gestation in mice, rats, hamsters and rabbits led to increased resorption, foetal abnormalities, and decreased foetal body weight.

Environmental Risk Assessment (ERA)

Oxygen constitutes a natural part of the atmospheric air. The risk for explosive fire whenever the oxygen concentration is increased should be acknowledged

The risks associated with increased pressure and decompression on personal taking part in the HBO therapy, entering the hyperbaric chamber should be acknowledged.

Normobaric oxygen

Non-clinical studies have shown that prolonged continuous inhalation of pure oxygen may have harmful effects. Tissue injury can be induced in the lung, eye, and CNS.

Hyperbaric oxygen

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

18. INSTRUCTION OF USE

General precautions

- Do not smoke or use a naked flame in areas where medicinal gases are administered. High oxygen fraction facilitates ignition and explosive fire thus, any source that may case an ignition must not be used. Electronic cigarettes shall not be used or charged in the vicinity of a patient undergoing oxygen therapy or the oxygen source itself.
- Medicinal gases must only be used for medicinal purposes.
- Never place a mask or nasal prongs directly on textiles while treatment is being carried out since fabrics that become saturated with oxygen can be highly flammable and cause a risk of fire. If this should occur, thoroughly shake and air the textiles.
- Never use grease, oil or similar substances, even if the cylinder valve sticks or if the regulator is difficult to connect.
- Handle valves and devices belonging to them with clean and grease-free hands (i.e. no use of hand cream, etc.).
- Use of greasy substances e.g. hand-cream should be avoided in order to minimise the risk for spontaneous ignition in conjunction with oxygen under high pressure (e.g. HBO).
- In case of cleaning of cylinders or attached equipment, do not use combustible products and especially not oil-based material. In case of doubt, verify compatibility.
- Prior to any use, ensure sufficient quantity of product remains to allow completion of the planned administration.
- Only use standard devices designed for administration oxygen administration.
- When delivered from the manufacturer, the cylinders should have an intact tamper evident seal.

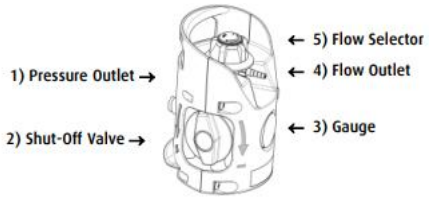
Cylinders equipped with the Linde integrated valve (LIV) have the pressure regulator incorporated in the valve. A separate pressure regulator is therefore not needed. The LIV has a standard quick connector to be used with specific devices. There is also a separate outlet for continuous flow, which may be adjusted to give a flow between 0 and 15 litres/min.

Preparation for use

- . Remove the plastic cover from the valve before use.
- Operating temperature -20 °C to +45 °C.
- Only use with devices intended for the product administration.
- Prepare to change the cylinder when the pointer on the gauge enters the red area.
- To ensure the correct, prescribed flow rate, always make sure that the flow selector is positioned on a numbered flow setting, not between flow settings.

Use of LIV®

- Remove the plastic cover from the valve before use.



Before Use

- Make sure that the pointer on the gauge (3) is not in the red area.
- Make sure that the flow selector (5) is set at zero.
- Slowly turn the shut-off valve (2) anticlockwise to open the LIV® fully.
- Connect the delivery device to outlet (1 or 4)..
- If a delivery device is connected to the flow outlet (4), turn flow selector (5) stepwise up through flow settings to select flow.
- The patient can now be connected to the delivery device.

After Use

- At exchange of an empty cylinder or at conclusion of treatment:
- Remove the delivery device from the patient.
- Turn flow selector (5) stepwise down through flow settings to zero.
- Turn the shut-off valve (2) clockwise to close the LIV®.
- Turn the flow selector (5) fully to vent the equipment.
- Turn the flow selector (5) back to zero.
- Disconnect the delivery device from outlet (1 or 4).

Please refer to "LIV® Instruction for use" for more information.

Use of cylinder

- Close the cylinder in the event of fire or when not in use.
- Ensure cylinders are secured to a suitable cylinder support in vertical position when in use, to prevent them from falling.

- For cylinders equipped with integrated valves, the user should be prepared to change the cylinder when the pressure gauge is in the yellow zone and change it when it enters the red zone.
- For cylinders that are not equipped with residual pressure valves, the cylinder valve should be closed when a small amount of gas remains in the cylinder (approx. 2 bars). It is important to leave a slight residual pressure in the cylinder in order to protect it from contamination.
- After use, the cylinder valve should be closed with normal force and the regulator or connection depressurised.

Transportation of cylinders

- When being transported, the cylinders must be secured to prevent them from falling.
- Larger cylinders should be transported with appropriate type of trolley. Particular attention should be paid to ensuring connected devices are not accidentally loosened.

Special precautions for disposal and other handling

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

Incompatibilities

Oxygen is an oxidiser that facilitates fire and may self-ignite when reduced from high pressure. Handling should secure avoidance of any oil, grease, or other chemicals that may ignite during decompression of high pressure oxygen. Increased oxygen concentrations in the ambient air increase the risk for explosive fires. Oxygen can react with flammable substances.

19. STORAGE CONDITIONS

- Do not smoke or use a naked flame in areas where medicinal gases are stored. Smoking, candlelight, open fire cooking and also electronic cigarettes may cause ignition and explosive fire.
- Cylinders should be stored in a well-ventilated area reserved for the storage of medicinal gases.
- Cylinders should be stored under cover, kept dry and clean, kept free from oil and grease, free from flammable material
- Cylinders should be stored at temperatures below 50°C.
- Precautions should be taken to prevent blows or falls.
- Cylinders containing different types of gases should be stored separately.
- Full and empty cylinders should be stored separately.
- Cylinders should be stored and transported with valves closed.
- After delivery from the manufacturer a cylinder must have an undamaged plastic valve cover.

20. SHELF LIFE

3 years

21. DOSAGE FORM AND PACKAGING AVAILABLE

Dosage form

Medicinal gas, compressed.

Gaseous oxygen is a colourless, odourless gas without taste.

Packaging

The cylinders are made of Aluminium, equipped Linde Integrated Valve

The cylinder body is painted Black and the cylinder shoulder is painted White.

Cylinder size (L water capacity)	Valve type	Cylinder material	Settled Pressure at 27°C (1 bar)	Content (m^3 oxygen at 27°C, 1 bar)
3.5L	LIV® (Linde Integrated Valve)	Aluminium	200	0.7

22. NAME AND ADDRESS OF MANUFACTURER/ PRODUCT REGISTRATION HOLDER

Manufacturer:

Linde Gas Products Malaysia Sdn Bhd (453560-K)

No. 1, Jalan Graphite 3,

Kawasan Perindustrian Bandar Mahkota,

42700 Banting,

Selangor.

Product Registration Holder:

Linde Malaysia Sdn Bhd (100783-W)

Level 13, The Pinnacle Persiaran Lagoon,

Bandar Sunway,

47500 Petaling Jaya,

Selangor Darul Ehsan

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03-56113512

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23. PRODUCT REGISTRATION NUMBER

<MAL24106004X>

24. DATE OF REVISION OF THE TEXT

9 September 2025

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