HOT-ICU

December 7th 2015

Translated from Danish: 'PRODUKTRESUMÉ' by Danish Medicines Agency

SUMMARY OF PRODUCT CHARACTERISTICS

for

Medicinal Oxygen "Air Liquide" 100 %, medicinal gas, cryogenic

0. D.SP.NR.
25715

1. NAME OF THE MEDICINAL PRODUCT
Medicinal Oxygen "Air Liquide" 100 %

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Oxygen 100 %.

3. PHARMACEUTICAL FORM
Medicinal gas, cryogenic.
Colourless, odourless and tasteless

4. CLINICAL PARTICULARS

4.0 Therapeutic indications

Oxygen therapy
- Treatment or prevention of acute and chronic hypoxia irrespective of cause.
- Part of the fresh gas flow in anaesthesia or intensive care treatment.
- Propellant gas in the treatment with a nebulizer
- Treatment of an acute attack of cluster headache

Hyperbaric oxygen therapy
Treatment of decompression sickness, air and gas embolism from other causes and carbon monoxide poisoning.
Treatment of patients who have been exposed to carbon monoxide are indicated especially in pregnant women or patients who are or have been unconscious or who have shown neurological symptoms and/or cardiovascular effects or severe acidosis regardless of the measured COHb value.

Additionally, it can be used in the treatment of severe osteoradionecrosis and clostridial myonecrosis (gas gangrene).

4.1 Posology and method of administration

Dosage

Oxygen therapy
The purpose of the therapy is to ensure that the oxygen partial pressure in arterial blood (PaO_2) does not fall below 8.0 kPa (60 mmHg) or the oxygen saturation of haemoglobin in arterial blood does not fall below 90% by adjusting the oxygen fraction in the inhaled air (FiO_2)

The dose (FiO_2) should be adapted to the individual needs of the patient, taking the risk of oxygen toxicity into account. In order to obtain the expected results of the treatment, it is generally recommended to use the lowest dose (FiO2) as possible. In case of pronounced hypoxia, fractions of oxygen that may induce a risk of oxygen toxicity can be indicated (see section. 4.9).

The treatment must be continuously evaluated and the effect measured by means of PaO_2 or arterial oxygen saturation (SpO_2).

In short-term oxygen therapy, the oxygen concentration – the fraction in the inhaled gas mixture (FiO_2) (avoid> 0.6 = 60% O_2 in the inhaled gas mixture) - must be kept so that with or without a positive end-expiratory pressure (PEEP) or a continuous positive airway pressure (CPAP) can reach an arterial oxygen pressure (PaO_2)> 8 kPa.

Short-term oxygen therapy must be monitored/observed by repeated measures of the arterial oxygen pressure (PaO_2) or pulse oximetry, which gives a numerical value for haemoglobin oxygen saturation (SpO_2). They are, however, only indirect measurements of the oxygen saturation in tissues. The effect of the therapy must also be clinical evaluated.

In an acute situation, the usual dose for adults in treatment or prevention of *acute oxygen deficiency* is 3-4 liters per minute when using nasal cannula and 5-15 liters per minute when using a mask.

In long-term therapy the need for extra oxygen is controlled by the result of the measurements of arterial blood gas. For adjusting oxygen therapy in patients with hypercapnia, blood gases should be monitored in order to avoid a significant increased carbon dioxide tension in arterial blood.

If oxygen is mixed with other gases, the oxygen fraction in the inhaled gas mixture (FiO_2) must not be lower than 21% and may be up to 100%.

For treatment of cluster headache, oxygen is delivered by a facemask, in a non-rebreathing system. Oxygen therapy should be instituted early after onset of the attack and should last for about 15 minutes or until the pain has disappeared. Usually, a flow of 7-10 litres/min is sufficient but a flow rate up to 15 litres/min. may be required in some patients to achieve an effect. Oxygen should be discontinued if no effect occurs within 15-20 minutes.

Hyperbaric oxygen therapy
Hyperbaric oxygen therapy (HBO) is to administer 100% oxygen at pressures over 1.4 times the atmospheric pressure at sea level (1 atmosphere = 101.3 kPa = 760 mmHg). For safety reasons the pressure in HBO should not exceed 3.0 atmosphere. Each treatment session at 2-3 atm usually lasts between 60 minutes and 4-6 hours depending on the indication. If necessary, the sessions can be repeated 2-3 times a day depending on the indication and the clinical condition. Repeated treatments are often necessary when it comes to treatment of soft tissue infections and ischemic ulcers that do not respond to conventional therapy. HBO should be given by personnel

who are competent to do so. Increasing and reducing the pressure must be conducted slowly in order to avoid the risk of pressure damage (barotrauma).

Pediatric population
Neonates must be closely monitored during treatment. The lowest effective concentrations should be kept to ensure adequate oxygenation.

Administration

Oxygen therapy
Oxygen is administered via the inspired air.

Oxygen can also be supplied through a so-called 'oxygenator' directly into the blood e.g. in the case of cardiac surgery with a heart–lung machine and in other conditions that require extracorporeal circulation.

Oxygen is administered by means of equipment intended for this purpose. With this equipment, the oxygen is supplied to the inspired air and upon expiration the exhaled gas with any excess of oxygen passes from the patient and is mixed with the surrounding air (non-rebreathing system). For treatment of cluster headache, oxygen is delivered by a facemask in a non re-breathing system. For anaesthesia, special equipment is often used in which the exhaled gas recirculates and can in part be re-inhaled (circular system with rebreathing). There are a large number of devices intended for oxygen administration.

Low-flow system:
The simplest system, which mixes oxygen with the inhaled air, e.g. a system in which the oxygen is dosed via a simple rotameter and a nasal cannula or facemask.

High-flow system:
A system intended to supply a gas mixture corresponding to the patient's breath. This system is intended to produce a fixed oxygen concentration that is not affected or diluted by the surrounding air, e.g. a Venturi mask with a constant oxygen flow in order to deliver a fixed oxygen concentration in the inhaled air.

Hyperbaric oxygen therapy
Hyperbaric oxygen therapy (HBO) is administered in a specially constructed pressure chamber intended for hyperbaric oxygen therapy in which pressures up to 3 atmospheres (atm) can be maintained. HBO can also be given using a close-fitting facial mask, a hood covering the head or through a tracheal tube.

4.2 Contraindications
There are no absolute contraindications for oxygen therapy.

4.3 Special warnings and precautions for use
High oxygen concentrations should be given for the shortest possible time required to achieve the desired result and must be monitored with repeated checks of arterial gas pressure (PaO_2) or haemoglobin oxygen saturation (SpO_2) and the inhaled oxygen concentration (FiO_2).

In the literature evidence is found that the risk of oxygen toxicity can be considered minimal if the following recommendations are followed:

- Oxygen concentrations up to 100 % (FiO_2 1.0) should not be given for more than 6 hours
- Oxygen concentrations above 60-70 % (FiO_2 0.6-0.7) should not be given for more than 24 hours
- Oxygen concentrations > 40 % (FiO_2 > 0.4) can possibly cause damage after 2 days

These recommendations do not apply in neonates because retrolental fibroplasia occurs at a much lower FiO_2 level. Therefore, the aim must be to keep the concentration at the absolute lowest to ensure appropriate oxygenation.

In any use of oxygen caution should be taken in regards to the high-risk of spontanteous combustion. This risk increases at procedures involving diathermy, defibrillation and electro conversion.

With high concentrations of oxygen in the inspired air/gas, the concentration/pressure of nitrogen is reduced. As a result, the concentration of nitrogen in tissues and lungs (the alveoli) falls. If oxygen is taken up from the alveoli into the blood more rapidly than it is supplied through ventilation alveolar collapse may occur (development of atelectasis). The development of atelectatic sections of the lungs lead to a risk of poorer arterial blood oxygen saturation, due to lack of gas exchange in the atelectatic sections of the lungs in spite of good perfusion. The ventilation/perfusion ratio worsens, leading to intrapulmonary shunt.

High concentrations of oxygen in vulnerable patients, with reduced sensitivity to the carbon dioxide tension in arterial blood can cause carbon dioxide retention, which in extreme cases can lead to carbon dioxide narcosis.

In hyperbaric oxygen therapy, the pressure should be increased and reduced slowly in order to avoid the risk of pressure damage (barotrauma).
Hyperbaric oxygen therapy should be used with caution during pregnancy and in fertile women (see section. 4.6).

HBO should be used with caution in patients with pneumothorax.

4.4 Interaction with other drugs and other sorts of interaction

The pulmonary toxicity associated with the use of drugs such as bleomycin, amiodarone and nitrofurantoin and similar antibiotics, can be aggravated by inhalation of high oxygen concentrations.

4.5 Pregnancy and lactation

Oxygen may be used during pregnancy and lactation.
Hyperbaric oxygen therapy should be used with caution during pregnancy and in fertile women due to the potential risk of oxidative stress induced damage to the fetus. In severe carbon monoxide poisoning the advantage of using hyperbaric oxygen therapy seems to outweigh the risk. However, the use should be evaluated individually for each patient.

4.6 Effects on ability to drive or operate machines

No labelling.
Not relevant.

4.7 Adverse reactions

	Uncommon (≥ 1/1.000 to < 1/100)	**Rare (≥ 1/10.000 to < 1/1.000)**	**Very rare (< 1/10.000)**
The nervous system			Hyperbaric oxygen therapy Anxiety; confusion; loss of consciousness; unspecified epilepsy
Eyes		Retrolental fibroplasia in neonates who have been exposed to high concentrations of oxygen	
Ears and labyrinth	Hyperbaric oxygen Sensation of pressure in the middle ear; rupture of eardrum		
Airways, thorax and mediastinum	Atelectasis; pleuritis		Acute Respiratory Distress syndrome

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. Physicians and healthcare professionals are asked to report any suspected adverse reactions to:

Lægemiddelstyrelsen
Axel Heides Gade 1
DK-2300 København S
Web: www.meldenbivirkning.dk
E-mail: dkma@dkma.dk

4.8 Overdose
Overdose of oxygen does not occur outside the intensive care unit and the risk is higher with hyperbaric oxygen therapy.

In case of oxygen intoxication (symptoms of oxygen toxicity), the oxygen treatment must be reduced or if possible stopped and symptomatic treatment should be initiated in order to maintain vital functions (e.g. artificial ventilation/assisted ventilation should be started if the patient shows signs of respiratory depression).

4.9 Delivery
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5. PHARMACOLOGICAL PROPERTIES

5.0 Therapeutic classification: ATC code: V03AN01. All other therapeutic products - medicinal gases, oxygen.

5.1 Pharmacodynamic properties

Oxygen constitutes approx. 21 % of the air we breathe. Oxygen is vital for humans and must be supplied continually to all tissues in order to maintain the cellular energy production. Oxygen in inhaled air is transported through the airways into the lungs. As a result of the difference in partial pressures a gas exchange in the alveoli of the lungs from the inhaled air/gas mixture to the blood in the capillaries occurs. Oxygen is transported further into the systemic circulation, mainly bound to haemoglobin, to the capillaries in the bodily tissues. Oxygen is transported through the pressure gradient out into the various cells. Its goal being the mitochondria in the individual cells, in which the oxygen takes part in an enzymatic chain reaction creating energy. By increasing the oxygen fraction in the inhaled air/gas mixture, the partial pressure gradient that controls the transport of oxygen to the cells increases.

When oxygen is supplied at a pressures higher than the atmospheric pressure (HBO), the amount of oxygen carried in the blood to the peripheral tissues increases significantly. Intermittent hyperbaric oxygen therapy even generate oxygen transport to oedematous tissue and tissue with inadequate perfusion and may in this way maintain cellular energy production and function. In accordance with Boyle's law, HBO reduces the volume of air bubbles in tissue in relation to the pressure at which it is given.

HBO counteracts the growth of anaerobic bacteria.

5.2 Pharmacokinetic properties

Inhaled oxygen is absorbed by a pressure-dependent gas exchange between alveolar gas and the capillary blood that passes the alveoli.

Oxygen is transported by the systemic circulation to all tissues in the body, mostly bound to haemoglobin (21 ml/100 mg blood). Only a very small proportion of oxygen is freely dissolved in the plasma (0.3 ml/100 ml blood). On passage through tissue, partial pressure-dependent transport of the oxygen to the individual cells takes place. Oxygen is a vital component in the intermediate metabolism of the cell. Oxygen is important to the cell’s metabolism primarily in order to create energy through the aerobic ATP production in the mitochondria.

Oxygen accelerates the release of carbon monoxide that is bound to haemoglobin, myoglobin and other iron-containing proteins, and thus counteracts the negative obstructing effects caused by the binding of carbon monoxide to iron.

Hyperbaric oxygen therapy further accelerates the release of carbon monoxide, as compared with 100 % oxygen under normal pressure.

Virtually all oxygen that is absorbed in the body is exhaled as carbon dioxide formed in the intermediate metabolism.

5.3 Preclinical safety data

Animal studies have shown that long-term continuous inhalation of pure oxygen may elicit harmful effects. Tissue damage can be induced in the lungs, the eyes and the central nervous system. A profound variability of the time to occurrence of pathological changes in different species and in animals of the same species exists.
Hyperbaric oxygen therapy during gestation in mice, rats, hamsters and rabbits led to increased resorption and foetal abnormalities and reduced birth weight.

6. PHARMACEUTICAL PARTICULARS

6.0 List of excipients

None.

6.1 Incompatibilities

Not relevant.

6.2 Shelf life

Cryogenic vessels < 30 litres: 1 month
Cyrogenic vessels ≥ 30 litres: 45 days

6.3 Special precautions for storage

Storage instructions relating to the medicinal product

This medicinal product does not require any special storage instructions in regards to temperature other than those that apply for gas containers and gas under pressure (see below). Store cryogenic vessels in a locked room reserved medicinal gases (does not apply in private homes).

Storage instructions relating to gas containers and gases under pressure

Contact with combustible material may cause fire.
Keep away from combustible material.
No smoking.
Risk of explosion upon contact with oil and grease.
Must not be exposed to strong heat. Move to a safe place in the event of fire.
Handle carefully. Do not drop or bump.
Keep clean and dry. Store in a ventilated place reserved medicinal gases.
Store and transport upright with valves closed.

6.4 Nature and contents of container

All container closure systems are vacuum-insulated containers made of stainless steel and aluminium intended for storing low temperature condensed gases at approximately -180ºC. The following sizes are used:

Containers:
Storage tank for cryogenic gas, portable and equipped with a dosing device for regulating the gas flow to the patient: 10 liters - 36 litres.
Storage tank for cryogenic gas, portable: 228 litres – 627 litres.

All pack sizes may not necessarily be marketed.
The table below gives the approximately volume of gas in kg.

Vessel size in litre	10	12	15	20	21	30	31	36	37	40
kg gas	11.4	13.7	17.1	22.8	24.0	34.2	35.4	41.1	42.2	45.6

Vessel size in litre	228	450	600	627
kg gas	260	513	685	715

6.5 Special precautions for disposal and other handling

Instructions for use and handling

Storage tank for cryogenic gas, portable

In general

Medicinal gases must only be used for medicinal purposes.

Different gas types and gas qualities must be separated from each other.

Full and empty containers should be stored separately.

Never use oil or grease as lubricant in screw threads, even if the vessel valve is stiff or if the regulator is difficult to connect.

Handle valves and matching devices with clean and grease-free (hand cream, etc.) hands.

Use only standard equipment that is intended for medicinal oxygen.

Preparation for use

Use only regulators intended for medicinal oxygen.

Check that the automatic coupling or regulator is clean and that the gaskets are in good condition. Never use a tool on a stuck pressure/flow regulator which is intended to be connected manually, as this may damage the coupling.

Open the vessel valve slowly – at least half a turn.

Check for leakage in accordance with the instruction that accompanies the regulator.

In the event of leakage, close the valve and uncouple the regulator. Label defective vessels, put them aside and return them to the supplier.

Using the gas vessel

Smoking and open flames are absolutely prohibited in rooms where oxygen therapy is being carried out.

Close down the equipment in the event of fire or if it is not being used.

Carry to safety in the event of fire.

Larger gas cylinders must be transported by means of a suitable type of trolley.

Take special care that connected devices are not inadvertently loosened.

When the vessel is empty, the gas flow will fall. Close the vessel outlet valve and disconnect after depressurising.

7. MARKETING AUTHORISATION HOLDER

AIR LIQUIDE Santé INTERNATIONAL

75 quai d'Orsay

75007 Paris

France

Representative

AIR LIQUIDE GAS AB

Lundevägen 151

S-212 24 Malmø

Sweden

8. MARKETING AUTHORISATION NUMBER(S)

42860

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

November 18th 2010

10. DATE OF REVISION OF THE TEXT

December 7th 2015