

MEDICAL LIQUID OXYGEN

PL 15929/0009

UKPAR

TABLE OF CONTENTS

| | |
|------------------------------------|---------|
| Lay summary | Page 2 |
| Scientific discussion | Page 3 |
| Steps taken for assessment | Page 19 |
| Summary of product characteristics | Page 20 |
| Product information leaflet | Page 30 |
| Labelling | Page 32 |

MEDICAL LIQUID OXYGEN

PL 15929/0009

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency granted Linde Gas UK Ltd a Marketing Authorisation (licence) for the medicinal product Medical Liquid Oxygen (Product Licence number: 15929/0009). This product has been granted a general sales licence, which means that it can be bought without prescription from both pharmacies and other vendors.

Oxygen-based treatments similar to this product have been available in the European Union, including the UK, for much more than ten years. Their use is well established with recognised efficacy and acceptable safety.

Medical Liquid Oxygen raised no clinically significant safety concerns and it was therefore judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.

MEDICAL LIQUID OXYGEN

PL 15929/0009

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

| | |
|--|---------|
| Introduction | Page 4 |
| Pharmaceutical assessment | Page 5 |
| Preclinical assessment | Page 15 |
| Clinical assessment (including statistical assessment) | Page 16 |
| Overall conclusions and risk benefit assessment | Page 18 |

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a Marketing Authorisation for the medicinal product Medical Liquid Oxygen (PL 15929/0009) to Linde Gas UK LTD on 1 November 2006. This product is on the general sales list (GSL).

This is a national application submitted under EC Article 10a of Directive 2001/83/EC with a complete bibliography in support of well-established use.

Medical Liquid Oxygen is used in a variety of instances, for example, when a patient may not be receiving enough oxygen through their lungs; when localised blood supply is poor; for use with anaesthetics and for artificial ventilation; in nebuliser treatment; and to reduce damage caused by gas.

PHARMACEUTICAL ASSESSMENT REPORT

1 REQUESTS FOR INSPECTION ACTION PRIOR TO AUTHORISATION

A satisfactory manufacturer's licence has been provided. A flow diagram indicating the sequence of the different sites involved in the manufacture of the finished product is also provided.

Three sources of active substance are proposed. It is confirmed that the sites are compliant with the principles of GMP.

2 INTRODUCTION

2.1 LEGAL BASIS

The applicant is making a stand alone, bibliographical application under Article 10a of EEC Directive 2001/83/EC, as amended. The applicant does not intend to take the licence through the Mutual Recognition procedure.

The application in question is for a new cryogenic liquid oxygen product (LOX).

2.2 USE

This product can be used in the treatment or prevention of acute or chronic hypoxia; as part of the fresh gas supply in anaesthesia or intensive care; as the propellant gas in nebuliser therapy; and in the treatment of acute attack in patients with an established diagnosis of cluster headache. This product is also indicated for the treatment of decompression sickness and air/gas embolisms of other genesis; in carbon monoxide poisoning in patients that are or have been unconscious, that have shown neurological signs, cardiovascular dysfunction or severe acidosis; in pregnant females; and as an adjunctive treatment for osteoradionecrosis and clostridial myonecrosis (gas gangrene).

2.3 SCIENTIFIC ADVICE

None.

2.4 LEGAL STATUS

GSL

2.5 USE IN CHILDREN

The product may be used in children.

2.6 TSE

Section 2.6.2 of the MAA form states that none of the ingredients are of animal origin.

3 DRUG SUBSTANCE

A single complete section of the dossier is provided for the sources of drug substance, which is acceptable for an inorganic drug substance manufactured by a physical process. General information, manufacture, characterization and the drug substance specification are the same for the three sources. All air separation units (ASU; the plants that produce liquid oxygen) utilise the same operating principles. Therefore, the manufacturing process and in process controls that are pertinent to liquid oxygen production are the same for all three sources of the active substance.

The starting material is atmospheric air, no controls are performed on the starting material. This is in line with industry acceptable practices.

The applicant has provided separate process validation and batch analysis data, plus Certificates of Analysis (for at least three batches) for the three sites. Reference standards, containers and stability are the same for the three sites.

3.1 General Information for Active Substance

Liquid oxygen is produced by cryogenic fractional distillation of liquefied atmospheric air.

3.1.1 Nomenclature

Chemical name: Oxygen CAS number: 7782447 INN & Ph Eur: Oxygen

3.1.2 General Properties

Oxygen is a colourless, odourless and tasteless gas, in its liquid form it is a pale blue liquid.

| | |
|--|------------------------|
| Boiling point at 1 bar (750 mmHg): | -183 °C |
| Density at 15 °C and 1 bar: | 1,34 kg/m ³ |
| Compressibility factor at 15 °C and 1 bar: | 0,9994 |
| Molecular mass: | 31.9988 |

Oxygen supports combustion.

3.2 Manufacture of Active Substance

3.2.1 Manufacturer(s)

See section 1.

A CEP or a DMF has not been provided. The applicant has provided a complete dossier section relating to the active substance.

3.2.2 Description of Manufacturing Process and Process Controls

Liquid oxygen is separated from liquid atmospheric air by cryogenic fractional distillation, which is a physical process. The main steps of the process are: compression, purification, cooling, distillation, storage of bulk liquid oxygen and transfer to the filling plant.

3.2.3 Control of Materials

No specification has been provided and no controls are performed. Since the starting material is atmospheric air and the manufacturing process is physical separation, this is acceptable.

3.2.4 Controls of Critical Steps and Intermediates

The oxygen production process is continuous, with no intermediates formed. The product is monitored for purity at specific points throughout the process. The bulk liquid oxygen is tested against its specification; identity and purity is tested on the residual product in the tanker and on the filled tanker.

Summary details of the in process controls, test methods and specifications, as well as processing parameters, target values and tolerances for the drug substance manufacturing process are provided. The process is a physical separation process as opposed to a chemical manufacturing process and, therefore, the only potential impurities in the liquid oxygen in the storage tank at the air separation unit are those that are naturally found in air. The applicant describes the impurities in some detail.

The controls employed during the filling operation are satisfactorily described.

3.2.5 Process Validation and/or Evaluation

GMP criticality analysis indicated that the critical process stages are downstream of the point at which the product can be routed to the ejector system or the bulk storage. After this point, the composition cannot be altered by in-process feed streams. Data and CoAs for the bulk product from one site have been provided to show compliance with the DSS and the Ph Eur monograph. Further batches were tested, with additional tests to the DSS. Data showing compliance to the DSS and the Ph Eur monograph are provided.

Batch data for product produced at the other two plants are also provided. Although processing data, etc are not provided, the batches comply with the DSS and ICH guidance on impurities, therefore production at these two sites is considered validated.

3.2.6 Manufacturing Process Development

The production of liquid oxygen by physical separation is an old and established process, therefore omission of process development is acceptable.

3.3 Characterisation of Active Substance

3.3.1 Elucidation of Structure and other Characteristics

The identity of oxygen is confirmed by the Ph Eur paramagnetic test for determination of assay, which is in line with the monograph requirements.

3.3.2 Impurities

Oxygen is stable, with no potential degradation products. No chemical processing is conducted, therefore potential impurities are limited to the natural constituents of the air: nitrogen, argon, water, carbon dioxide, carbon monoxide, oxides of nitrogen and hydrocarbons. These are monitored during production. In practice, argon and methane are the main contaminants. Ph Eur specified impurities are moisture, carbon dioxide and carbon monoxide. Information on the impurities is provided.

3.4 Control of Drug substance

3.4.1 Specification

A satisfactory drug substance specification has been provided.

It should be noted that the Ph Eur monograph for oxygen relates to the gaseous phase rather than the liquid phase – reference to the monograph will be in principle. The range of tests does not comply with the monograph for oxygen or ICH guidance. The identification test is compliance with assay limits. The limits of the tests specified in the proposed DSS comply with the Ph Eur monograph for oxygen. All other impurities are below the reporting threshold.

3.4.2 Analytical Procedures

The analytical procedures used for testing the drug substance are those specified in the Ph Eur monograph for oxygen.

3.4.3 Validation of Analytical Procedures

Analytical test methods are Ph Eur, therefore no validation is required.

3.4.4 Batch Analyses

Production of liquid oxygen is continuous – each road tanker is analysed after filling and prior to dispatch. The method of manufacture described by the applicant confirms that a filled tanker is regarded as a discrete batch for the purposes of product release.

Satisfactory batch data and corresponding CoAs for five filled tankers from one site together with ‘on receipt’ test data from the finished product manufacturer are provided.

Satisfactory batch data and corresponding CoAs from the other two plants have been provided.

3.4.5 Justification of Specification

The proposed specification is in line with the Ph Eur monograph for oxygen. Although not controlled as a critical quality parameter, the safety of methane has been satisfactorily discussed. The level of methane in batch data is well below the reporting threshold for impurities required under ICH guidance.

3.5 Reference Standards or Materials of Active Substance

The drug substance and product are identical – see corresponding section in product details.

3.6 Container Closure System of Active Substance

The containers are gas industry standard for the storage of cryogenic gases and are fully described in line with the CPMP NfG on medicinal gases. The schematic diagram of the container closure system provided is acceptable. LOX is stored in dedicated vessels or in non-medicinal gas vessels, where the non-medical gas is of equally high quality as a medicinal gas, which is acceptable.

3.7 Stability

The ICH guidance on stability is not relevant for this kind of product. No stability studies have been conducted since oxygen is a highly stable diatomic product with no degradation pathway. However, the shelf life is limited by the boil off losses and the different distribution of impurities between liquid and gaseous phase as a function of their boiling points.

The applicant has proposed a shelf life of 6 months for the finished product, this is acceptable.

3.7.1 Post-approval Stability Protocol and Stability Commitment

The post-approval stability protocol and stability commitment is not provided, but this is acceptable for this well established and stable drug substance.

4 DRUG PRODUCT, (CTD 3.2P)

4.1 Description and Composition of the Drug product/medicinal product

The finished product is medical liquefied oxygen – inhalation gas – complying with the Ph Eur monograph for oxygen. Note: the Ph Eur monograph relates to the gaseous phase rather than the liquid phase, but principles are accepted.

Finished product composition

| Name of component | Concentration | Function | Reference to standards |
|-------------------|---------------|-------------------|------------------------|
| Oxygen | 100%v/v | Active ingredient | European Pharmacopoeia |

Container: transportable vacuum insulated containers made of stainless steel specifically designed to store cryogenic gases at low temperatures (about -180 C).

These are used to fill the medical liquid oxygen storage tank at the customer's location, which are then used to supply medical oxygen piping systems or can be used to fill portable medical liquid oxygen systems.

4.2 Pharmaceutical Development

4.2.1 Formulation Development

Medical liquid oxygen is a well established, well known product, therefore a brief overview of the historic development of liquid oxygen is provided in line with the NfG. The applicant has justified the use of liquid oxygen over the gaseous phase (1 litre LOX \equiv 840 oxygen). This is acceptable.

4.2.2 Overages

None.

4.2.3 Physicochemical and Biological Properties

The properties of oxygen have been described in the drug substance section. Oxygen from vapourised medical liquid oxygen is very dry, therefore the gas should be humidified to prevent dehydration of the mucous membranes, especially if high concentration is administered.

4.2.4 Manufacturing Process Development

Manufacturing and assembly of the medicinal product utilises a well-established method that has been used by Linde Gas for a number of years elsewhere in Europe for the production of medical liquid oxygen. Transportable medical liquid oxygen supply vessels are filled from the bulk liquid oxygen storage tank at the filling plant. The filling plant is supplied by tankers from the drug substance manufacturer. Bulk liquid oxygen (drug substance) has the same specification as the medical liquid oxygen (drug product); both conform to the Ph Eur monograph for oxygen.

4.2.5 Container Closure System

The design of medical LOX containers is determined by pressure vessel codes, which specify the inclusion of double safety valves, reduction of heat influx by insulation and boil off safety pressure valves.

4.2.6 Compatibility

The product containers are composed of stainless steel, which can withstand the rigours and requirements of storing medical LOX.

4.3 Manufacture

4.3.1 Manufacturer(s)

See section 1

4.3.2 Batch Formula

The manufacture of the finished product is essentially a filling/assembly process - Medical LOX is the only ingredient.

Each transportable medical LOX container constitutes a batch.

4.3.3 Description of Manufacturing Process and Process Controls

A satisfactory method of manufacture is provided. Tests performed on receipt of active substance are provided and are satisfactory.

4.3.4 Controls of Critical Steps and Intermediates

The transportable medical LOX container is checked for fitness for use: the vessel is within its test period; connections are undamaged and in a clean state; the vessel contains residual gas, external vessel is in good condition.

Each transportable medical liquid oxygen supply vessel filled constitutes a batch of medical liquid oxygen. Before each transportable medical liquid oxygen supply vessel is filled the residual oxygen within the vessel will be tested for identity and assay. If the purity of the product is at an acceptable level then the vessel will be filled with liquid oxygen. The product is tested for identification (the Ph Eur purity test is also the identification test) and purity before filling and regularly during the filling process. Once the vessel has been filled the oxygen in the vessel will be tested for identity and purity of the liquid oxygen.

4.3.5 Process Validation and/or Evaluation

The filling process uses a well established method that has been used by Linde Gas for a number of years. A satisfactory validation report for this site is provided.

Validation data has been provided to show the bulk LOX complies with the DSS, which is the same as the FPS, which are both in line with the Ph Eur monograph

The finished product manufacturing site has been approved for the manufacture and assembly of other oxygen products.

The medical liquid oxygen filling system is under construction at this time. The applicant has declared that the system will be validated and a copy of the validation report will be supplied as soon as the work has been completed. This is satisfactory.

4.4 Control of Excipients

No excipients are used.

4.5 Control of Drug product

4.5.1 Specification

The specification for the finished product of Medical Liquid Oxygen is the same as the DSS.

The analytical methods are those specified in the Ph Eur, therefore method validation is not provided, which is acceptable.

4.5.4 Batch Analyses

Batch data that will demonstrate compliance of the product filled into the transportable medical liquid oxygen supply vessels with the finished product specification will be supplied as soon as it is available. At this time the filling system is under construction, this is acceptable.

4.5.5 Characterisation of Impurities

Information on the characterisation of impurities is provided.

4.5.6 Justification of Specification(s)

The specification is the same as the DSS, which has been justified.

4.6 Reference Standards or Materials

Calibration gases for the analysis of medical liquid oxygen are traceable to national standards. Satisfactory CoAs are provided for oxygen, carbon monoxide and carbon dioxide. A satisfactory calibration certificate for the moisture meter is provided.

4.7 Container Closure System

Vacuum insulated containers made of stainless steel specifically designed to store cryogenic gases at low temperatures (about -180 °C); coming in 10 litre, 20 litre, 21 litre, 30 litre, 31 litre, 32 litre, 36 litre, 37 litre, 41 litre, 42 litre, 45 litre, 46 litre, 60 litre, 100 litre, 180 litre, 230 litre, 450 litre, 600 litre, 1000 litre and 23500 litre capacity vessels. The design of the container is basically the same and is determined by the pressure vessel codes. Schematics and specifications are provided.

The vessel is determined as full when the medical LOX escapes through the vent valve.

For refrigerated gases ADR specifies that the degree of filling at the filling temperature and at 0.1 MPa (1 bar) shall not exceed 98% of the capacity of a closed cryogenic receptacle. In general, the vessel is full when liquid escapes through the vent valve, this occurs at 95% of the nominal water capacity of the vessel, therefore with the “180” container the nominal water capacity of the vessel is 195 litres and, therefore, the container will be filled with 185 litres of liquid oxygen.

The vessel is fitted with a dual pressure safety relief device set at 4 and 1.5 bar. All containers meet pressure system regulations. That is they have been constructed to meet the requirements of the transportable pressure equipment directive.

4.8 Stability

The ICH guidance on stability is not relevant for this kind of product. No stability studies have been conducted since oxygen is a highly stable diatomic product with no degradation pathway. Also, the rate of any chemical reactions at cryogenic temperatures is low. This is accepted. However, the shelf life is limited by the boil off losses and the different distribution of impurities between liquid and gaseous phase as a function of their boiling points.

The applicant has proposed a shelf life of 6 months, which is much less than other oxygen products (PL 04280/0001; 60 months) and Oxygen gas (PL 015929/0005; 60 months). Therefore, this is acceptable.

5 ASSESSOR'S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET

5.1 Product Name and Appearance

The product name is satisfactory.

5.2 Summary of Product Characteristics

The Summary of Product Characteristics is pharmaceutically satisfactory.

5.3 Patient Information leaflet

The Patient Information leaflet is satisfactory.

5.4 Labelling

Satisfactory mock ups have been provided.

5.5 Comment on QOS

The quality expert has provided a satisfactory article 12.2 declaration and CV. A satisfactory QOS is provided.

5.6 MAA Form

The Marketing Authorisation Application (MAA) form submitted with this application is satisfactory.

5.7 Part I C: Additional Data Requirements

All additional data requirements have been met.

6 ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

A product license may be granted for this product.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

INTRODUCTION

LEGAL BASIS

The applicant is making a stand alone, bibliographical application, under article 10a of EEC Directive 2001/83/EC, as amended, for marketing authorisation in the UK of Medical Liquid Oxygen. The applicant does not intend to take the licence through the MR procedure.

The application in question is a new cryogenic liquid oxygen product (LOX). The product is similar to Medical Oxygen (PL 15929/0005) except that the test product is cryogenic liquid oxygen, not gaseous, and the storage vessels are cryogenic vessels, not gas cylinders

USE

This product can be used in the treatment or prevention of acute or chronic hypoxia; as part of the fresh gas supply in anaesthesia or intensive care; as the propellant gas in nebuliser therapy; and in the treatment of acute attack in patients with an established diagnosis of cluster headache. This product is also indicated for the treatment of decompression sickness and air/gas embolisms of other genesis; in carbon monoxide poisoning in patients that are or have been unconscious, that have shown neurological signs, cardiovascular dysfunction or severe acidosis; in pregnant females; and as an adjunctive treatment for osteoradionecrosis and clostridial myonecrosis (gas gangrene).

SCIENTIFIC ADVICE

None.

LEGAL STATUS

GSL

USE IN CHILDREN

The product may be used in children.

Clinical Particulars (CTD Module 5)

The applicant has provided extensive references in support of the clinical particulars, which has been discussed in the clinical overall summary.

ASSESSOR'S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET

Product Name and Appearance

See pharmaceutical assessment report.

Summary of Product Characteristics

Sections 1-3 and 6-12, see pharmaceutical report.

Sections 4 and 5 of the Summary of Product Characteristics are satisfactory.

Patient Information leaflet

The PIL is in line with the SPC and is satisfactory.

Labelling

Satisfactory mock ups have been provided.

2.5 Comment on PCOS & COS

The preclinical expert has provided a satisfactory article 12.2 declaration and CV. A satisfactory PCOS is provided

The clinical expert is medically qualified. A satisfactory article 12.2 declaration and CV are provided. A satisfactory COS is provided, which supports the indications sought.

2.6 MAA Form

The Marketing Authorisation Application (MAA) form submitted with this application is satisfactory.

ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

A product license may be granted for this product.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Medical Liquid Oxygen (PL 15929/0009) are well defined and controlled. The specification and batch analysis results confirm consistencey from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY AND SAFETY

The efficacy of medical liquid oxygen has been well documented in the past. No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The risk benefit ratio is considered to be positive.

MEDICAL LIQUID OXYGEN

PL 15929/0009

STEPS TAKEN FOR ASSESSMENT

| | |
|----|---|
| 1 | The MHRA received the marketing authorisation application on 17 August 2005. |
| 2 | Following assessment of the application the MHRA requested further information relating to the quality dossier on 29 November 2005. |
| 3 | The applicant responded to the MHRA's requests, providing further information relating to the quality dossier on 4 May 2006. |
| 4 | Following assessment of the response the MHRA requested further information relating to the quality dossier on 4 May 2006. |
| 5 | Following assessment of the application the MHRA requested further information relating to the clinical dossier on 6 June 2006. |
| 6 | The applicant responded, providing further information on the clinical dossier on 3 July 2006. |
| 7 | Following assessment of the response the MHRA requested further information relating to the clinical dossier on 3 July 2006. |
| 8 | The applicant responded, providing further information relating to the clinical dossier on 3 July 2006 and the quality dossier on 11 September 2006. |
| 9 | Following assessment of the response the MHRA requested further information relating to the quality dossier on 11 September 2006 and the clinical dossier on 4 October 2006 |
| 10 | The applicant responded to the MHRA's requests, providing further information relating to the dossier on 31 October 2006 |
| 11 | The application was determined on 1 November 2006. |

SUMMARY OF PRODUCT CHARACTERISTICS

1 Name of the Medicinal Product

Medical Liquid Oxygen

2 Qualitative and quantitative composition

Oxygen Ph. Eur. 100 %

There are no other ingredients

3 Pharmaceutical form

Inhalation gas

Light blue cryogenic liquid of about -180 deg C contained within a closed container/vessel (see section 6.5). The liquid rapidly evaporates to form oxygen gas.

4 Clinical particulars

4.1 Therapeutic indications

Normobaric oxygen therapy:

- Treatment or prevention of acute or chronic hypoxia, irrespective of genesis.
- As part of the fresh gas supply in anaesthesia or intensive care.
- As the propellant gas in nebuliser therapy.
- Treatment of acute attack in patients with an established diagnosis of cluster headache

Hyperbaric oxygen therapy:

For treatment of decompression sickness, air/gas embolisms of other genesis and carbon monoxide poisoning.

- In carbon monoxide poisoning hyperbaric oxygen therapy is indicated in patients that are or have been unconscious, that have shown neurological signs, cardiovascular dysfunction or severe acidosis and in pregnant females all irrespective of COHb.
- As adjunctive treatment for osteoradionecrosis and clostridial myonecrosis (gas gangrene).

4.2 Posology and method of administration

Method of administration

Oxygen is administered via the inspiratory air.

Oxygen can also be administered through a so-called oxygenator directly to the blood in, among other things, heart surgery with a cardio-pulmonary bypass system, and in other conditions that require extracorporeal circulation. Oxygen is (preferably) administered via special equipment. With this equipment, oxygen is administered with the inspiratory air, and on exhalation the exhaled gas with any oxygen excess leaves the patient and is mixed with the surrounding air (non-rebreathing system).

For anaesthesia, special equipment is often used, when the exhaled gas is recirculated and can be rebreathed (circular system with rebreathing).

There are a large number of devices intended for administration of oxygen.

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 oxygen concentration that is not influenced – diluted by the surrounding air, e.g. Venturi mask with fixed oxygen flow in order to give a fixed oxygen concentration in the inspiratory air.

Hyperbaric oxygen therapy (HBO) is given in a specially constructed pressure chamber designed for hyperbaric oxygen treatment, in which pressures up to 3 times atmospheric pressure can be maintained. HBO can also be administered within the chamber via a very closely fitting facemask, a hood that closes around the head, or through a tracheal tube.

Posology

The purpose of oxygen therapy is to ensure that the partial arterial oxygen pressure (PaO₂) is not less than 8.0 kPa (60 mmHg) or the oxygen saturation of haemoglobin in arterial blood is not less than 90 %, by adjusting the fraction of oxygen in inspired gas (FiO₂).

The dosage must be regulated according to the patient's need. The oxygen fraction must be adjusted according to each individual patient's unique requirement, taking account of the risk of oxygen intoxication. (See 4.9.)

The general recommendation is that the lowest dose – FiO₂ – to achieve the desired result of therapy, a safe PaO₂, must be the aim. In severe hypoxia, oxygen fractions that may involve a risk of oxygen intoxication may be indicated.

The therapy must be evaluated continuously and the effect of treatment measured with PaO₂ or alternatively arterial oxygen saturation (SpO₂).

For short term oxygen therapy, the fraction of oxygen in inspired gas (FIO₂) (avoid FiO₂ > 0.6 = 60 % O₂ in the inhaled gas mixture) must be kept so that with or without positive end-expiratory airway pressure (PEEP) or continuous positive airway pressure (CPAP), a partial arterial oxygen pressure (PaO₂) > 8 kPa is maintained.

Short term oxygen therapy must be monitored by repeated measurements of arterial blood gases (PaO₂) or by pulse oximetry which provides a numerical value for the haemoglobin oxygen saturation (SpO₂). However, these indices are only indirect measures of tissue oxygenation. Clinical assessment of the treatment is of the utmost importance.

For long term treatment, the need for supplemental oxygen should be determined by obtaining arterial blood gas values. To avoid excessive retention of carbon dioxide, blood gases should be monitored so to adjust oxygen therapy in patients with hypercapnia.

If the oxygen is mixed with other gases, its concentration in the gas mixture inhaled (FiO₂) must be maintained at least at 21 % in the inhaled gas. Oxygen inhaled fraction can be increased up to 100 %.

Neonates may be given up to 100% of Oxygen if required. However, careful monitoring should be performed during the treatment. As a common recommendation, oxygen concentrations exceeding 40 % should be avoided on account of the risk of damaging the crystalline lens or lung collapse. The oxygen pressure in arterial blood (PaO₂) should be monitored, and if PaO₂ is kept below 13.3 kPa (100 mmHg) and no major variations in oxygenation is avoided, the risk of damage to the eyes is reduced.

For the indication acute attack of cluster headache, Oxygen is to be delivered by facemask, in a non re-breathing system, with an oxygen flow of about 7 – 10 l/min.

Oxygen therapy should be instituted as early as possible after onset of the attack and should last for about 15 minutes or until pain has disappeared/vanished.

Hyperbaric Oxygen therapy:

Hyperbaric oxygenation (HBO) means delivering 100% oxygen at pressure above 1.4 times the atmospheric pressure at sea level (1 atmosphere = 101.3 kPa = 760 mmHg). For safety reasons the pressure for HBO should not exceed 3 atmospheres.

The duration of a single treatment with HBO at a pressure of 2 to 3 atmospheres is normally between 60 minutes and 4 - 6 hours depending on the indication. Sessions may, if necessary, be repeated 2 to 3 times a day, depending on the indication and the patient's clinical condition. Multiple sessions are often necessary for treatment of soft-tissue infections and hypoxic wounds that do not respond to the usual conventional treatment.

HBO should be given by staff qualified to give this treatment.

Compression and decompression should be slow in accordance with common routines in order to avoid the risk of pressure damage (barotrauma).

Instructions for handling and use of Medical Liquid Oxygen Equipment

Only use equipment designated for use with Medical Liquid Oxygen

Hospital pipelines for medical gases should be installed in accordance with the guidance given in HTM 02.

Equipment for use with oxygen must be clean and dry. If necessary, clean only with plain water. Do not use solvents. Use clean, lint free cloths for cleaning and drying off. Use no oil or grease on equipment for use with oxygen.

Do not allow naked flames near the container. Do not smoke when using oxygen.

Should leaks occur this will usually be evident by a hissing noise.

There are no user serviceable parts associated with Medical Liquid Oxygen containers, do not attempt to correct any problems with leakage.

Sealing or jointing compounds must never be used to cure a leak.

Contact Linde Gas to arrange repair of the faulty container.

Use of Medical Liquid Oxygen Containers

Containers should be handled with care.

Containers must only be moved with an appropriate size and type of trolley.

Smoking and naked flames must not be allowed near containers or pipeline outlets.

Equipment for use with Medical Liquid Oxygen must never be lubricated and must be kept free from oil and grease.

Contact with medical liquid oxygen can cause burns.

Always follow the instructions for use for the equipment.

4.3 Contra-indications

Patients should not smoke while on oxygen therapy due to increased risk from fire.

4.4 Special warnings and precautions for use

As a general rule, high concentrations of Oxygen should only be administered for the minimum time required to achieve the desired result, and should be

monitored by repeated analyses of the arterial oxygen pressure (PaO₂) or oxygen saturation of the haemoglobin (SpO₂) and the inhaled oxygen concentration (FiO₂).

There is literature supporting the safety of oxygen fraction:

Oxygen is safely administered in the following concentration during the indicated times:

- Oxygen in concentration up to 100 % (FiO₂ 1,0) for less than 6 h
- Oxygen in concentration of 60 – 70 % (FiO₂ 0,6 – 0,7) during 24h
- Oxygen in concentration of 40-50 % (FiO₂ 0,4 – 0,5) during the second 24 h
- Any Oxygen concentration > 40 % (FiO₂ > 0.4) is potentially toxic after 2 days.

Premature infants are excluded from these guidelines because retrolental fibroplasia occurs with a much lower FiO₂.

Special precautions for use

Special caution should be observed when treating newborn and premature infants. The absolute lowest concentration which gives the desired result should be used in order to minimise the risk of ocular damage, retrolental fibroplasia, or other potential undesirable effects. The arterial oxygen pressure should be monitored and kept below 13,3 kPa (100 mmHg).

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

The formation of atelectasic lung areas may impair oxygenation of arterial blood because there will be no gas exchange in the atelectasic area despite perfusion, there will be ventilation/ perfusion mismatching – an increased shunt.

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

In hyperbaric oxygen therapy compression and decompression should be slow in order to avoid the risk of pressure damage - barotrauma.

Rebound attacks may be experienced by patients suffering from cluster headaches treated with oxygen.

4.5 Interaction with other medicinal products and other forms of interactions

- a. Interactions with amiodarone have been reported.
- b. Relapse of bleomycin-induced lung disease may be associated with a fatal outcome.

- c. Patients with pre-existing oxygen radical damage to the lung may have damage exacerbated by oxygen therapy, e.g. in the treatment of paraquat poisoning.
- d. Respiratory depression due to alcohol may potentiate that caused by oxygen.

4.6 Use during pregnancy and lactation

Oxygen can be used during pregnancy or lactation.

4.7 Effects on ability to drive and use machines

Oxygen therapy at ambient pressure has no adverse effect on the ability of the patient to drive or operate machinery.

4.8 Undesirable effects

Oxygen therapy causes only minor effects on pulmonary and cardiovascular function.

In treatment with high oxygen concentrations and consequently reduced nitrogen pressure in the inspiratory air/gas, the nitrogen concentration in tissue and lung is reduced. This can lead to resorption atelectases caused by a reduced volume in the alveoli in combination with an oxygen-induced effect on the surfactant. This can lead to a poorer ventilation/perfusion ratio and this to poorer oxygenation. (see 4.4).

Heart rate and cardiac output are reduced when 100 % Oxygen is administered for short periods (< 6 hours) and under normobaric conditions.

Early symptoms of oxygen toxicity are pleuritic pain and dry cough.

Vital capacity is seen to decrease slightly after treatment with 100 % Oxygen for prolonged periods (approx. 18 hours). On continued treatment with 100 % oxygen for more than 24 – 48 hours a condition with acute pulmonary failure may develop Acute Respiratory Distress Syndrome (ARDS). Long-term treatment with 100 % Oxygen may also result in toxic effects on other organs. Toxic effects of high Oxygen concentrations are due both to the oxygen concentration and to the length of exposure. Clinical symptoms are not usually seen until after 6 – 12 hours.

The adverse effects of hyperbaric oxygenation (HBO) are usually mild and reversible. HBO may cause middle ear barotrauma, sinus squeeze, myalgia and central nervous system toxicity varying from nausea, vertigo, anxiety – confusion, muscle twitching to loss of consciousness and epileptic seizures. Those CNS symptoms may occur during HBO treatment at more than two atmospheres lasting more than a few hours. At higher pressures more rapid onset of those symptoms will occur.

Patients should be carefully monitored by competent personnel.

In patients with chronic severe airway disease, who rely on hypoxic drive of respiration, the administration of high levels of oxygen will result in further under-ventilation, and further accumulation of carbon dioxide and acidosis.

Paediatric Patients

Retrolental fibroplasia with fibroblastic infiltration of the retina, which can lead to blindness, has been claimed to be associated to oxygen treatment in concentrations greater than 40 % in neonates. Other negative effects of Oxygen therapy in high concentration (FiO₂ 1.0) in neonates are haemolytic anaemia, pulmonary fibrosis, cardiac, renal and hepatic toxicity.

All ages may be at risk for toxic side effects of high inspired oxygen fractions. In order to reduce the risk of parenchymal damage, including an effect on the lungs (broncho-pulmonary dysplasia), it is of the utmost importance to continually monitor arterial oxygen pressure (see 4.4.).

4.9 Overdose symptoms, emergency procedures, antidotes

Oxygen overdose does not occur outside the intensive care setting and the risks of this are greater during hyperbaric treatment.

In case of oxygen toxicity, apart from decreasing the Oxygen concentration, therapy should be instituted in order to maintain critical physiology (e.g. in case of respiratory depression, institute respiratory support).

Prolonged hyperoxygenation can result in lung injury. Cases must be assessed individually, but experience from healthy volunteers would suggest that prolonged exposure, over a period of months, to concentrations up to 30% whilst producing sub-clinical pathologic changes has not been proven to cause specific lung injury. The same applies for exposure up to 60% oxygen, for up to one week. However, administration of 100% oxygen for more than 24 to 30 hours will result in substernal chest pain and mild dyspnoea. Symptoms may progress, become systemic and include malaise, nausea and transient paraesthesia.

5 Pharmacological Properties

5.1 Pharmacodynamic properties

All other therapeutic products, Medical Gases.
ATC class: VO3A

Oxygen constitutes approx. 21% of air. Oxygen is vital to life and must be continuously supplied to all tissues in order to maintain the cells' energy production. 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, mainly bound to haemoglobin, further with the systemic circulation to the capillary bed in tissue where it is transported by the pressure gradient to the different cells. 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 inspired air, the inspired gas mixture, the partial pressure gradient transporting oxygen to the cells is increased.

When oxygen is given to a patient at pressure higher than atmospheric (HBO), it greatly increases the amount of oxygen that is transported to the peripheral tissues by the blood. Intermittent hyperbaric therapies generate oxygen transport even within oedematous tissue and tissue with poor perfusion and in this way can maintain cellular energy production and function.

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.

Hyperbaric oxygen treatment (HBO) inhibits the growth of anaerobic organisms.

5.2 Pharmacokinetic properties

Inhaled oxygen is absorbed – taken up – by a pressure-dependent gas exchange between alveolar gas and the capillary blood that passes the alveoli. The oxygen is transported, mainly bound to haemoglobin, with the systemic circulation to all tissues in the body. Only a very small proportion is free, dissolved in plasma. During passage through the tissues, a partial pressure-dependent transport of the oxygen to the individual cells takes place. Oxygen is a vital component in the cell's intermediate metabolism for creation of energy – the aerobic ATP production in the mitochondria.

5.3 Preclinical safety data

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.

Hyperbaric oxygen therapy also causes the release of carbon monoxide at a rate greater than that achievable by breathing 100% oxygen at normal pressure.

Oxygen taken up in the body is excreted almost entirely as carbon dioxide formed in the intermediary metabolism.

6 Pharmaceutical particulars

6.1 List of Excipients

None

6.2 Major incompatibilities

Not applicable

6.3 Shelf life

6 months

6.4 Special precautions for storage

Liquid oxygen containers should be kept out of the reach and sight of children.

Oxygen is non flammable but strongly supports combustion. It is highly dangerous when in contact with oils and greases due to the risk of fire.

The normal precautions required in the storage of medical gas containers as described below are applicable:

Containers should be stored separately from containers containing non-medical gases.

Medical containers containing different medical gases should be segregated and identified within the store.

Full and empty containers should be stored separately.

Containers should be stored under cover, kept dry and clean and not subjected to extremes of temperature.

Containers should not be stored near stocks of combustible materials or sources of heat.

Warning notices prohibiting smoking and naked lights should be clearly posted.

Emergency services should be advised of the location of the Medical Liquid Oxygen store.

Precautions should be taken to protect containers from theft

6.5 Nature and contents of container

The medical liquid oxygen is packaged in vacuum insulated containers made of stainless steel specifically designed to store cryogenic gases at low temperatures (about -180 C). The transportable medical liquid oxygen supply vessel – 10 litre, 20 litre, 21 litre, 30 litre, 31 litre, 32 litre, 36 litre, 37 litre, 41 litre, 42 litre, 45 litre, 46 litre, 60 litre, 100 litre, 180 litre, 230 litre, 450 litre, 600 litre, 1000 litre and 23500 litre – is used to fill the medical liquid oxygen storage tank at the customer's location or is supplied for use at the customer's location.

6.6 Special Precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Contact Linde Gas to arrange refill of the container.

Containers that are no longer required should be returned to Linde Gas.

7 Marketing authorisation holder

Linde Gas UK Ltd,
Johnson's Bridge Road,
Church Lane,
West Bromwich,
West Midlands,
B71 1LG

8 Marketing authorisation number

PL15929/0009

9 Date of first authorisation/renewal of the authorisation

01/11/2006

10 Date of revision of the text

01/11/2006

PATIENT INFORMATION LEAFLET

Medical Liquid Oxygen

Read all of this leaflet carefully before you start to use this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What Medical Liquid Oxygen is and what it is used for.
2. Before you use Medical Liquid Oxygen.
3. How to use Medical Liquid Oxygen.
4. Possible side effects.
5. Storing Medical Liquid Oxygen.

The name of your medicine is Medical Liquid Oxygen. Medical Liquid Oxygen is supplied as a pure gas containing only oxygen. It does not contain any other ingredients.

1. What is Medical Liquid Oxygen and what it is used for.

Medical Liquid Oxygen is an inhalation gas (a gas that is breathed in). It is colourless, odourless and tasteless. It is supplied as a liquid gas (at very low temperatures) in a cryogenic vessel.

Oxygen is essential for life. Oxygen breathed in with air goes into your lungs where it is taken into your blood. The blood carries the oxygen to all your body tissues. The tissues take the oxygen from the blood so that they can work properly.

If, for any reason, you are not getting enough oxygen into your blood from your lungs you may be given Medical Liquid Oxygen to breathe to increase the level of oxygen in your body tissues. You will be able to breathe more easily.

Medical Liquid Oxygen is used when you are not getting enough oxygen into your body through the lungs due to lung disease or damage or when you have breathing difficulties.

It is used in the treatment of cluster headaches and other conditions where localised blood supply is poor.

It is used with anaesthetics during surgery and for artificial ventilation in intensive care after surgery or following an accident.

It is used as a propellant for inhaling other medicines in nebuliser treatment.

It may be used in pressure chambers to reduce the risk of damage as a result of gas bubbles in the blood vessels or if there is gas trapped in body spaces. When the oxygen carrying ability of the blood is reduced such as in the case of severe carbon monoxide poisoning. It may also be used as part of the treatment of gas gangrene (damage to soft tissue caused by bacterial infection)

2. Before you use Medical Liquid Oxygen

Do not smoke or allow those near you to smoke during treatment with Medical Liquid Oxygen.

Oxygen helps things burn. Oxygen can cling to fabrics. Smoking during oxygen treatment has proved fatal (due to fire and burns) to more than one patient.

Do not allow naked flames near you when you are using your Medical Liquid Oxygen.

Unless specially advised to by your doctor to do so, do not use Medical Liquid Oxygen:

- If you are taking or have recently taken amiodarone
- If you are taking or have recently taken bleomycin (a drug for cancer)
- If you have chronic severe airways disease.

Take special care with Medical Liquid Oxygen

If you suffer from a chronic lung disease you should only receive a carefully monitored dose of Medical Liquid Oxygen – Carefully follow your doctor’s instructions.

If Medical Liquid Oxygen is being used for a premature infant, the infant should only receive a carefully monitored dose of oxygen. – Carefully follow the doctor’s instructions

Although Medical Liquid Oxygen may be necessary for the treatment of patients with lung damage due to poisons such as paraquat, it may worsen the lung injury.

A slowing down in your breathing caused by drinking alcohol may be made worse by the use of Medical Liquid Oxygen

Pregnancy

Ask your doctor or pharmacist for advice before taking any medicine.

Medical Liquid Oxygen can be used if you are pregnant.

Breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Medical Liquid Oxygen can be used if you are breast- feeding.

LABELLING

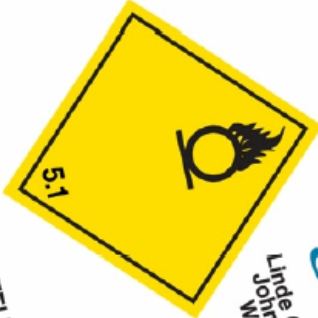
REVISION 1 - 05/06
MEDICAL - NO 900

MEDICAL LIQUID OXYGEN

For Inhalation Ph. Eur 100%, Inhalation Gas
Keep out of reach and sight of children
Use no oil or grease
Contact with combustible materials may cause fires
No smoking or naked flames in the vicinity of the container
Keep clean and away from extremes of temperature
Full and empty containers should be stored separately
NOMINAL FILL VOLUME XXXX LITRES
UN No. 1073, OXYGEN, REFRIGERATED LIQUID



PL No. 15929/0009



Linde
Linde Gas's Bridge
Johnson's Bromwich
West Midlands
B71 1 LG

EMERGENCY TELEPHONE No. 0800 581614

MEDICAL LIQUID OXYGEN

OXYGEN Ph. Eur 100%, Inhalation Gas

For Inhalation Use Only.

Keep out of reach and sight of children

Use no oil or grease

Contact with combustible materials may cause fires

No smoking or naked flames in the vicinity of the container

Keep clean and away from extremes of temperature

Containers should be stored separately from containers

containing non-medical gases.

Full and empty containers should be stored separately

NOMINAL FILL VOLUME XXXX LITRES

UN No. 1073, OXYGEN, REFRIGERATED LIQUID



PL No. 15929/0009



EMERGENCY TELEPHONE No. 0800 581614

Linde

Linde Gas UK Ltd.
Johnsons Bridge Road
West Bromwich
West Midlands
B71 1LG