**IPAR**

**Public Assessment Report for a**
**Medicinal Product for Human Use**

Scientific Discussion

Medical Liquid Oxygen 100% Medicinal gas, cryogenic
Oxygen
PA22852/001/002

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

**CONTENTS**

## I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Medical Liquid Oxygen 100% Medicinal gas, cryogenic, from Air Liquide Healthcare Ireland Limited on 31st May 2024 for the following indications:

- At high concentrations in the treatment of acute severe asthma, pulmonary thrombo-embolism, pneumonia and fibrosing alveolitis.
- At low concentrations in the treatment of ventilatory failure due to chronic obstructive airways disease and other causes.
- For the treatment of carbon monoxide poisoning.
- To reduce the volume of air trapped in body cavities, as for example, in patients with pneumothorax, air embolism and decompression sickness. Inhalation of air containing a high concentration of oxygen (and hence low concentration of nitrogen) enhances removal of trapped oxygen.
- Pulmonary oedema.
- As a diluent or carrier gas in anaesthesia.
- Other indications include cystic fibrosis, shock, severe anaemia, sleep apnoea, cluster headaches and anaerobic infections.,

This application is submitted in accordance with Article 10(a) of Directive 2001/83/EC.

This application is an extension application to register a new pharmaceutical form (Medicinal gas, cryogenic) to the existing medicinal product Medical Liquid Oxygen (PA22852/001/001) (Medicinal gas, compressed).

This medicinal product is subject to prescription.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website.

## II. QUALITY ASPECTS

### II.1. Introduction

This application is for Medical Liquid Oxygen 100% Medicinal gas, cryogenic.

### II.2 Drug substance

The active substance is oxygen, an active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

### II.3 Medicinal product

P.1 Composition

The composition is 100% oxygen.
This product has no excipients.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines where required and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

There are no other substances in this medicinal product.

P.5 Control of Finished Product

The Finished Product Specification is based on the Ph. Eur. monograph for oxygen for medical use, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data where required.

Batch analytical data for a number of batches from the proposed production site(s) have been provided and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur. / EU legislation requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

**II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects**

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of the aforementioned product Medical Liquid Oxygen 100% Medicinal gas, cryogenic.

## III. NON-CLINICAL ASPECTS

**III.1 Introduction**

This active substance has been available on the European/Irish market for more than 40 years. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

**III.2 Ecotoxicity/environmental risk assessment**

Since oxygen is a naturally occurring substance in the environment, the absence of an environmental risk assessment is appropriate. Introduction of medical liquid oxygen is not expected to increase environmental exposure.

## IV. CLINICAL ASPECTS

**IV.1 Introduction**

This active substance has been available on the European/Irish market for more than 40 years. As such the clinical characteristics of the product are well established and described in the Summary of Product characteristics.

No new clinical evidence has been submitted as part of this application, which is appropriate.

**IV.2 Pharmacokinetics**

The uptake of oxygen by the blood in the lungs and discharge to the tissues is determined by the oxygen dissociation curve. The characteristic sigmoid shape ensures that, at tensions between 5kpa (40mm Hg) and 2kpa (15mm Hg) the oxygen carried in the blood from the lungs can readily be given up to the tissues.

The uptake from the lungs is rapid because blood flow through the capillaries, where the exchange takes place, occurs in about 0.5 seconds. The uptake of oxygen is favoured by the simultaneous loss of carbon dioxide which is then excreted in the expired air. Conversely, the entry of carbon dioxide into the blood from the tissues facilitates oxygen transfer to the cells.
At rest, mixed venous blood returning to the lungs contains 13-14ml of oxygen per 100ml, but with severe exercise, the oxygen content may fall to 3-4ml. In very active tissue, almost complete extraction occurs.

**IV.3 Pharmacodynamics**

All other therapeutic products, Medical Gases, ATC class: VO3AN01

The characteristics of oxygen are:
Odourless, colourless gas.
Molecular weight 32.00
Boiling point -183.1 degrees Celsius (at 1 bar)
Density 1.355kg/m3 (at 15° Celsius)

Oxygen is present in the atmosphere at 21% and is an absolute necessity for life.

The basal oxygen consumption in man is about 250ml/min for a body surface of 1.8sq metres. It is reduced by about 10% during anaesthesia and natural sleep and by about 50% for a 10 degree Celsius fall in body temperature.

Alveolar air contains about 15% oxygen at 14 kpa (105mm Hg) and arterial blood has an oxygen tension of 13 kpa (97mm Hg).

The difference, known as the alveolar-arterial oxygen tension gradient, increases with age. The difference may be as great as 4kpa (30mm Hg) in a healthy, elderly individual.

Oxygen in the blood is mostly combined with haemoglobin. Normally, haemoglobin in arterial blood is 97% saturated and the oxygen content of the blood is 19.8 vol%, 0.3ml of this being carried in solution. The remainder is held in chemical combination with haemoglobin.

The concept of oxygen availability can be expressed as the product of the cardiac output and the oxygen content of the blood.

The average healthy individual with a basal oxygen consumption has no more than 4 minutes supply of oxygen in the blood.

**IV.4 Clinical Efficacy**

No new efficacy information has been provided as part of this application.

**IV.5 Clinical Safety**

No new safety information has been provided as part of this application.

**Risk Management Plan**

A risk management plan was submitted, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Medical Liquid Oxygen.

Summary of safety concerns:

| | |
|---|---|
| Important identified risks | Fire due to oxygen<br>Pulmonary toxicity<br>Risk related to HBOT - Central nervous toxicity<br>Risk related to HBOT – Barotrauma<br>Risk related to HBOT – Myopia<br>Risks related to damages to VIPRs (Valves with an Integrated Pressure Reducer)<br>Respiratory acidosis and worsening hypercapnia in patients with baseline hypercapnia<br>Retinopathy of Prematurity |
| Important potential risks | Vascular effects of hyperoxia |
| Missing information | None |

Routine pharmacovigilance activities and routine risk minimisation measures are considered sufficient to identify, characterise, prevent or minimise risks relating to Medical Liquid Oxygen.

Periodic safety update reports (PSURs) shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

**IV.6 Discussion on the clinical aspects**

The clinical aspects of this medicinal product are well established and acceptable.

**V. OVERALL CONCLUSIONS**

The HPRA, on the basis of the data submitted, considered that Medical Liquid Oxygen 100% Medicinal gas, cryogenic demonstrated adequate evidence of efficacy for the approved indications as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

**VI. REVISION DATE**