LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Medicinsk Oxygen Air Liquide, 100% v/v, medicinal gas, compressed (oxygen)

SE/H/1054/01/MR

This module reflects the scientific discussion for the approval of Medicinsk Oxygen Air Liquide, 100% v/v, medicinal gas, compressed. The procedure was finalised at 2011-09-16. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Air Liquide Santé International has applied for a marketing authorisation for Medicinsk Oxygen Air Liquide, 100% v/v, medicinal gas, compressed. The active substance is oxygen. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Medicinsk Oxygen Air Liquide is presented in the form of medicinal gas, compressed, v/v containing 100% v/v of medicinal oxygen. There is no excipient in Medicinal Oxygen Air Liquide. The medicinal oxygen (the finished product) is produced by filling gas cylinders with gaseous oxygen.

II.2 Drug Substance

The drug substance oxygen has a monograph in the Ph Eur.
Molecular Oxygen, with the chemical formula O_2 is a colourless, odourless and tasteless gas at normal temperature and pressure. In liquid form it is a pale blue liquid.
Boiling point at 1 bar (760 mmHg) is -183 ºC
Molecular mass is 31.9988

Oxygen is manufactured by distillation of liquefied air in a distillation column, a physical separation process. The products are separated according to their boiling points. The main products are nitrogen (78%) and oxygen (21%). The starting material is ambient atmospheric air. The oxygen production process is a continuous distillation process. There are no intermediates during the production process.

The specification for the oxygen complies with Ph. Eur. requirements. The analytical methods used are those specified in the European Pharmacopoeia. As the methods are according to Ph. Eur. no validation has been performed.

The liquid medicinal oxygen, is delivered to storage tanks. The storage tank for the liquid medicinal oxygen is vertical and has a capacity of one million litres. The liquid medicinal oxygen is stored in the storage tank at -183°C at a pressure of 66 mbar. The storage tank is equipped with a non-return valve at the exit of the pumps (transfer and filling). The filling of the mobile tank takes place at the top of the tank and thus the risk of backflow is eliminated.

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II.3 Medicinal Product

The drug product consists of oxygen without any excipients. The development work has centred on making handling of the product more convenient through use of lighter gas cylinders and cylinder valves/pressure reducers, which are safer and more easy to use.

All filling activities are performed in areas dedicated to filling of medicinal products only. The manufacturing consists of filling gaseous oxygen into gas cylinders to a pressure corresponding to 200 bar at 15 ºC.

The medicinal oxygen (the finished product) is produced by filling gas cylinders with gaseous oxygen (oxygen medicinal) from a storage tank of liquid oxygen medicinal. The cylinders are connected to the filling manifold and gaseous oxygen is then filled into the cylinders. The filling process, connection and disconnection of cylinders are performed manually.

The specification for the finished product is the same as for the drug substance which complies with the Ph. Eur. requirements. In addition, to the tests and limits proposed in the Ph. Eur. the specification for the finished product includes a test and limits for the pressure at 15 ºC.

The stability data provided support the support the shelf life claimed in the SPC.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of oxygen are well known. As oxygen is a widely used, well-known active substance, no further studies are required. Overview based on literature review is, thus, appropriate.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate and is considered sufficient to support the application. The proposed SPC describes the pharmaco/toxicological properties of oxygen and appropriate warning and contraindication statements are made.

There are no objections for approval of Medicinsk Oxygen Air Liquide, 100% v/v from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Clinical efficacy

The efficacy of oxygen for the applied indications, are regarded as well established. The scientific basis for its effectiveness is mostly firm. The use of oxygen in areas outside those discussed here cannot be considered as regulatory “well established” and any extension of the indication list should primarily be based on new trial data.

IV.2 Clinical safety

The spectrum of adverse effects of normobaric oxygen therapy is established after almost 100 years of its use. Guidelines on the maximum duration of oxygen therapy for different concentrations to avoid oxygen toxicity or other adverse effects have been published. Neonates is a population where the detailed use of oxygen therapy still is controversial. Intensive monitoring and avoiding high concentrations of oxygen are mandatory.
The adverse spectrum associated with hyperbaric oxygen therapy will possibly expand as the treatable diseases still are not clearly defined and thereby patients with other severe concomitant diseases might be treated in the future.
The ventilatory depression seen from normobaric oxygen therapy in patients with severe respiratory failure has been attributed to either loss of hypoxic ventilatory drive in the absence

of a CO2 drive or respiratory centre narcotization by an only slight elevation of PaCO2. The final treatment strategy will probably be the same irrespective of explanations. Guidelines on the use of oxygen for these patients are published.
The supplied references on safety are also judged as relevant and non-biased. Additional published information, besides the bibliographic data submitted by the MAH, support the statements made.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The absolute necessity of continuous oxygen delivery to the brain and the heart and the almost absence of storage in these organs makes normobaric oxygen, if viewed as a drug, the most valuable drug ever used.
The efficacy of oxygen therapy for indications included in the proposed SmPC is with one exception (cluster headache) scientifically established. However, due to a favourable benefit/risk, treatment of cluster headache must be considered approvable.
The adverse effects of normobaric oxygen therapy for the overwhelming number of treated patients are well known.
Recommendations for duration of treatment as well as concentrations of oxygen to avoid oxygen toxicity are published.
The danger of high concentrations of oxygen administered to patients with severe chronic respiratory insufficiency is recognised.
The adverse effects of hyperbaric oxygen are usually mild and/or reversible.
The optimal oxygen delivery for premature infants is still an unsettled issue.

The use of supplemental normobaric oxygen therapy is well established. For the vast majority of patients treated, the risks are small and well known. The risk/benefit for normobaric oxygen therapy is in most cases very favourable.

User consultation
A user consultation with target patient groups on the package information leaflet (PIL) has not been performed. The applicant has committed to submit the results of a user test in a variation within three months after finalisation of the procedure.

The risk/benefit ratio is considered positive and Medicinsk Oxygen Air Liquide, 100% v/v, medicinal gas, compressed is recommended for approval.

VI. APPROVAL

The Mutual recognition for Medicinsk Oxygen Air Liquide, 100% v/v, medicinal gas, compressed was successfully finalised on 2011-09-16.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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