LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Medicinsk oxygen Yara Praxair oxygen

SE/H/658/01-02/DC

This module reflects the scientific discussion for the approval of Medicinsk oxygen Yara Praxair. The procedure was finalised at 2007-10-16. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

I. INTRODUCTION

Yara Industrial AS has applied for a marketing authorisation for Medicinsk oxygen Yara Industrial, 100% medicinal gas, compressed, and 100% medicinal gas, cryogenic. The active substance is oxygen, for treatment of prevention of acute and chronic hypoxia, used in anaesthesia, in nebuliser treatment, for treatment of cluster headache, for hyperbaric oxygen therapy, and as adjunct treatment in gas gangrene. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Finished product is presented in the form of medicinal gas, compressed containing 100 % of oxygen (medicinal oxygen). Medicinal oxygen is packaged in compressed form at a pressure of 200 bar at 15 ºC in dedicated gas cylinders.

Finished product is also presented in the form of medicinal gas, cryogenic containing 100 % of oxygen (medicinal oxygen). Medicinal oxygen is packaged in cryogenic cylinders.

II.2 Drug Substance

Drug substance" has a monograph in the Ph Eur. Information on "drug substance" has been supplied in the Module 3 of the dossier.

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 obtained by the fractional distillation of liquid air. The manufacturing process of the medicinal oxygen has been adequately described. The starting material is atmospheric air.

The specification for the medicinal oxygen complies with Ph. Eur. requirements. The analytical methods used are those specified in the European Pharmacopoeia.

II.3 Medicinal Product

Medicinal oxygen 100% medicinal gas, compressed
The drug product consists of oxygen without any excipients. The production is performed by standard process and equipment, from distillation of liquid air, to the filling of compressed gas in gas cylinders.
The manufacturing consists of filling gaseous oxygen into gas cylinders to a pressure corresponding to 200 bar at 15 ºC.

All filling activities are performed in areas dedicated to filling of medicinal products only.

The filling process has been sufficiently described and critical steps identified.
Batch analysis data provided confirms the capability of the filling process to produce filled cylinders complying with the designed specification for the drug product.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Medicinal oxygen 100% medicinal gas, cryogenic
Finished product is also presented in the form of medicinal gas, cryogenic containing 100 % of oxygen (medicinal oxygen). Medicinal oxygen is packaged in cryogenic cylinders.

Independent of the size, the containers for medicinal oxygen, cryogenic are designed in basically the same way, the main design problem being insulating a liquid with a boiling point of -183 °C from ambient temperatures in a way that permits storage of the product with low boil-off losses.
The filling of bulk drug product in cryogenic cylinders is performed in dedicated areas for filling of medicinal products. The manufacturing consists of filling bulk liquid oxygen medicinal into cryogenic cylinders. Batch analysis data provided confirm the capability of filling process to fill cryogenic cylinders complying with the designed specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

III. NON-CLINICAL ASPECTS

III.1 Introduction
The active ingredient of Medicinsk oxygen Yara Industrial is oxygen (O_2). The potential hazards of oxygen have been known for many years. On the basis of animal data the use of an FIO_2 of > 0.6 should be avoided if possible because of cellular damage. However, caution must be exercised in extrapolating animal pathological changes to oxygen induced pulmonary oxygen toxicity in humans since data indicates that the human lung is much more resistant to oxygen exposure than the rat lung. Hence, the safety assessment of Medicinal Oxygen should be made from human clinical experience.

The RMS will not circulate a separate non-clinical assessment report.

IV. CLINICAL ASPECTS

IV.1 Clinical efficacy
The efficacy of oxygen in treatment or prevention of acute and chronic hypoxia, as fresh gas flow in anaesthesia or intensive care and for hyperbaric treatment of decompression sickness, air/gas emboli from other causes and carbon monoxide poisoning and as adjunct treatment in severe osteoradionecrosis and clostridium myonecrosis must be regarded as well established. The scientific basis for its effectiveness is mostly firm.

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 CO_2 drive or respiratory centre narcotization by an only slight elevation of $PaCO_2$. The final treatment strategy will probably be the same irrespective of explanations. Guidelines on the use of oxygen for these patients are published.

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 SPC is with one exception (cluster headache) scientifically well established.
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.

User testing of the package leaflet has not been performed, but an acceptable bridging to a test for a similar product (SE/H/607/01-02 Medicinsk Oxygen AGA) has been made.

The risk/benefit ratio is considered positive and Medicinsk oxygen Yara Industrial, 100% medicinal gas, is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Medicinsk oxygen Yara Industrial, 100% medicinal gas, was successfully finalised on 2007-10-16.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

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)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se