LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Medicinsk Oxygen AGA 100%
Oxygen

SE/H/607/01-02/MR

This module reflects the scientific discussion for the approval of Medicinsk Oxygen. The procedure was finalised at August 1st, 2006. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

AGA AB has applied for a marketing authorisation for Medicinsk Oxygen AGA 100%, Medicinal gas, compressed and cryogenic. The active substance is Oxygen. The application follows Directive 2001/83/EC article 10a, implying that the constituent of the medical product have a well established medical use with recognized efficacy and an acceptable level of safety, and therefore the application can be, and in this case is, purely bibliographical. The product is indicated for

Oxygen therapy
- For treatment or prevention of acute and chronic hypoxia irrespective of cause.
- As part of the fresh gas flow in anaesthesia or intensive care.
- As the propellant in nebuliser treatment.
- For treatment of an acute attack of cluster headache

Hyperbaric oxygen therapy
- For treatment of decompression sickness, air/gas emboli from other causes and carbon monoxide poisoning. Treatment of patients who have been exposed to carbon monoxide is especially indicated in pregnant patients or patients who are or have been unconscious, or who have displayed neurological symptoms and/or cardiovascular effects or severe acidosis, irrespective of the measured COHb value

as adjunct treatment in:
severe osteoradionecrosis and clostridium myonecrosis (gas gangrene).

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.

No stability data has been performed for the medicinal oxygen. (The drug product is the pure drug substance packaged in gas cylinders). For this reason the drug product stability data also applies to the oxygen drug substance.

II.3 Medicinal Product

Medicinal oxygen 100% medicinal gas, compressed
The drug product consists of oxygen without any excipients. The development work has centered 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 filling process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product 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.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions as specified in the SPC.

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 boil-off loss for a liquid cylinder is less 3 % per day.

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. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product 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

The active ingredient of Medicinal Oxygen AGA is oxygen (O2). The potential hazards of oxygen have been known for many years. On the basis of animal data the use of an FIO2 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.

IV. CLINICAL ASPECTS

IV.1 Clinical efficacy

Normobaric oxygen therapy
The *short term normobaric use of oxygen therapy* is non-controversial. The toxicity of oxygen is not of clinical significant concern until 8 to 12 hours treatment at high concentrations. As the consequences of tissue hypoxia can be very severe and may occur rapidly the therapeutic use of supplemental oxygen can and should be liberal.
The scientific basis for *long term normobaric oxygen therapy* is firm. The oxygen concentration in this setting has not shown toxic effects.
The indications *"As part of fresh gas flow in anaesthesia or intensive care"* and *"As propellant in nebulisation therapy"* are non-controversial.
The scientific basis for an approval of the *cluster headache* indication is sparse; the effect mechanism is not fully known, there are no dose-finding studies and there are only two smaller systematic outcome studies. However, these outcome studies support the established use of 100% oxygen for the treatment of acute attacks in cluster headache. The lack of side effects of the treatment increases the favourable benefit/risk ratio.

Hyperbaric oxygen therapy
Available data indicate that controlled application of elevated pressure in conjunction with 100% oxygen is the most effective way for rapid complete removal of air/gas emboli.
In severe CO poisoning with short delay to hyperbaric oxygen treatment the efficacy of this method is obviously very good. In reviews and editorials there is a lack of consensus which patients that should have this treatment and which patients that could be treated with the more accessible 100% normobaric O_2. So, firm inclusion criteria for hyperbaric oxygen therapy in CO poisoning seem not possible to establish with current knowledge. However, in light of the literature published, a recommendation that seems sensible is to treat patient who are unconsciousness, have neurologic signs, cardiovascular dysfunction or severe acidosis all irrespective of COHb levels **or** have experienced loss of consciousness **or** are pregnant.
The indication "Hyperbaric oxygen therapy; as additional therapy in severe osteonecrosis" is based on several studies.
The use of *hyperbaric oxygen therapy* with the simultaneous use of antibiotics and surgical debridement in *Clostridial myonecrosis* has been established as the treatments of choice.

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

User testing of the package leaflet has not been performed. The applicant has made a commitment to perform user testing and to have the results ready not later than one year after the end of the mutual recognition procedure.

The body's vital need for continuous oxygen delivery makes liberal administration of this "drug" highly recommendable in any clinical situation where tissue hypoxia is suspected. Special patient groups that are in risk for adverse events are few and are identified.

The risk/benefit ratio is considered positive and Medicinsk Oxygen AGA 100%, Medicinal gas, compressed and cryogenic, is recommended for approval.

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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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