CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Zuurstof Medicinaal Vloeibaar AIR LIQUIDE, medicinal gas, cryogenic 100% v/v Air Liquide Santé International, France

oxygen

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.
It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 108572

4 March 2013

Pharmacotherapeutic group:	medical gases
ATC code:	V03AN01
Route of administration:	inhalation
Therapeutic indication:	normobaric oxygen therapy - treatment or prevention of acute or chronic hypoxia, treatment of cluster headache; hyperbaric oxygen therapy - treatment of serious carbon monoxide poisoning, treatment of decompression sickness, or of air/gas embolism of a different origin, as supporting treatment in cases of osteoradionecrosis, as supporting treatment in cases of clostridial myonecrosis (gas gangrene).
Prescription status:	prescription only
Date of authorisation in NL:	15 August 2011
Application type/legal basis:	Directive 2001/83/EC, Article 10a

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Zuurstof Medicinaal Vloeibaar AIR LIQUIDE, medicinal gas, cryogenic 100% v/v from Air Liquide Santé International. The date of authorisation was on 15 August 2011 in the Netherlands.

Normobaric oxygen therapy
- Treatment or prevention of acute or chronic hypoxia.
- Treatment of cluster headache

Hyperbaric oxygen therapy
- Treatment of serious carbon monoxide poisoning. (In the case of carbon monoxide poisoning, hyperbaric oxygen therapy is considered essential for patients who have lost consciousness; neurological symptoms, cardiovascular failure or serious acidosis; or pregnant patients (all of these indications irrespective of COHb content)).
- Treatment of decompression sickness, or of air/gas embolism of a different origin.
- As supporting treatment in cases of osteoradionecrosis.
- As supporting treatment in cases of clostridial myonecrosis (gas gangrene).

A comprehensive description of the indications and posology is given in the SPC.

Oxygen is vital to living organisms, and all tissues must be oxygenated continuously in order to fuel the energy production of the cells. Oxygen in inhaled air enters the lungs, where it diffuses along the walls of the alveoli and surrounding blood capillaries and then enters the bloodstream (mainly bound to haemoglobin), which transports it to the rest of the body. This is a normal physiological process that is essential to the body's survival.
The administration of additional oxygen in hypoxia patients will improve the supply of oxygen to the bodily tissues.
Pressurised oxygen (hyperbaric oxygen therapy) helps to significantly increase the amount of oxygen that can be absorbed into the blood (including the part not bound to haemoglobin), and, as a result, also improves the supply of oxygen to the bodily tissues.
In the treatment of gas/air embolisms, high-pressure hyperbaric oxygenation will reduce the volume of the gas bubbles. As a result, the gas can be absorbed from the bubble into the blood more effectively, and will then leave the lungs in the exhaled air.

Since the "Note for Guidance on medicinal gases: Pharmaceutical documentation" (CPMP/QWP/1719/00) was adopted in 2002, it is mandatory in the European Union to register medicinal gases as medicine replacing the status of medical device. Hence, a number of medicinal gases have now received a marketing authorisation.

This national application is a line extension (a change or addition of a new pharmaceutical form) to Zuurstof medicinaal gasvormig AIR LIQUIDE, inhalatiegas 100% v/v (NL license RVG 30360). The marketing authorisation for this product was granted on 31 January 2006.

The marketing authorisation is granted based on article 10a (well-established medicinal use) of Directive 2001/83/EC.

This application concerns a bibliographical application based on well-established medicinal use of oxygen. This type of application does not require submission of the results of pre-clinical tests or clinical trials if the applicant can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. ''Medicinal use'' does not exclusively mean ''use as an authorised medicinal product'', so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of

the references in the application has to be provided. The documentation submitted by the applicant should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

No scientific advice has been given to the MAH with respect to these products.

No paediatric development programme has been submitted.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is liquid oxygen medicinal, an established active substance described in the European Pharmacopoeia (Ph.Eur.*).

Reference is made to the active substance documentation and assessment of Zuurstof medicinaal gasvormig AIR LIQUIDE, as the only difference between the line extension and the existing product is the dosage form of the drug product, *i.e.* compressed versus cryogenic. This is acceptable.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Zuurstof Medicinaal Vloeibaar AIR LIQUIDE contains as active substance 100% v/v oxygen (O_2) and is a colourless, odourless and tasteless gas. Liquefied oxygen is light blue in colour.

The drug product is packed in mobile cryogenic recipients (up to 450 L) or in stationary cryogenic storage tanks (up to 20.000 L). Mobile cryogenic recipients comprise patient tanks and transport tanks. Patient tanks are medical devices. The container closure systems are usual and suitable for the drug product.

No excipients are present.

Pharmaceutical development
The development of the product was briefly described. The main reason for developing liquid oxygen products is the fact that much higher quantities can be packed in the same volume compared to gaseous oxygen. Compatibility of container, valve and accessory materials with gas contents is according to EN-ISO 11114-1: 1997 for metallic materials and in EN-ISO 11114-2:2000 for non metallic materials. Compatibility between containers, valves and accessories and refrigerated liquefied oxygen is conform EN 1797:1998 or ISO 21010:2004. These requirements are common among manufacturers of cryogenic oxygen.

Manufacturing process
The manufacturing process consists of filling the drug substance in mobile cryogenic recipients or filling of transport tanks and subsequent filling of customer retained storage tanks. The processes were sufficiently described. The MAH confirmed that all container closure systems are dedicated to oxygen. The process of filling of mobile cryogenic recipients was validated with five batches showing that the oxygen quality

remains unaffected during the process. The process of filling of transport tanks was validated with five batches and the trans-filling process to storage tanks at the hospital with four batches. All batches complied with the Ph.Eur. The processes were sufficiently validated.

Quality control of drug product
The drug product specification is in accordance with the Ph.Eur. monograph on oxygen. Ph.Eur. methods are used. Batch analysis results were provided for five drug product batches in transport tanks intended for delivery to stationary tanks at hospitals, one drug product batch in the cryogenic tank intended for filling of mobile cryogenic recipients, two drug product batches in the cryogenic tank intended for the mobile cryogenic recipients on the BE market, and ten batches of drug product packed in mobile cryogenic recipients in BE (the filling process is identical in BE and NL). All batches complied with the drug product specification. The drug product specification is acceptable.

Stability of drug product
No stability studies were performed. The shelf life of six months is based on boil-off losses. This is in line with the *Guideline on Medicinal Gases: Pharmaceutical Documentation*. The proposed storage conditions among which a temperature storage condition of -20° to +50°C are acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

Medical gases containing 100% v/v oxygen have been available on the European market for many years. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the Board agreed that no further non-clinical studies are required.

Environmental risk assessment
No environmental risk assessment has been performed, which is acceptable for this application.

II.3 Clinical aspects

Oxygen is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. As the use of medicinal oxygen is well established and supported by many publications over the years concerning both its safety and efficacy, the Board agreed that no further clinical studies are required.

Oxygen is usually used to supplement the available O_2 in patients with hypoxia of various origins to restore, or at least improve, tissue oxygen levels. The use of oxygen at pressure greater than atmospheric pressure increases the amount of oxygen in the blood above that of normal levels, and thus increases tissue oxygen levels. Hyperbaric oxygen therapy is the primary therapy in patients with severe CO intoxication, decompression sickness and arterial gas embolism and as adjuvant therapy for osteoradionecrosis and clostridial myonecrosis.

Short term use of oxygen carries a high safety profile, as long as oxygen concentration is below 60% and the pressure is at most equal to ambient pressure. Longer exposure and use at higher concentrations may lead to pulmonary and/or CNS toxicity. Patients, in whom the respiratory centre is depressed and therefore rely on hypoxic drive of respiration as well as neonates are particularly at risk if they are exposed to high concentrations of oxygen. The problem may be prevented by careful titration of oxygen concentrations.

In conclusion, oxygen has a well established efficacy and safety profile based on decades of use. The benefit/risk ratio is favourable if the substance is used correctly and well-controlled.

Pharmacovigilance plan
The Pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk management plan
The application concerns a product for which no safety concerns requiring additional risk minimisation activities have been identified. Routine pharmacovigilance activities will be sufficient to ensure safe use of the product. This is considered acceptable.

Product information

SPC
The content of the SPC approved during the national procedure is in accordance with those accepted for other liquid oxygen products approved in the Netherlands.

Readability test
The package leaflet has not been evaluated via a user consultation study. The PIL has been adequately adapted in line with the SPC information and the MEB's comments.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Zuurstof Medicinaal Vloeibaar AIR LIQUIDE, medicinal gas, cryogenic 100% v/v can be considered effective in the approved indications as normobaric oxygen therapy and hyperbaric oxygen therapy. These are consistent with the spectrum of activity reported in standard references and published literature.

Medicinal liquid oxygen is a well-known active substance with established efficacy and tolerability. For this application, no original clinical study data nor clinical trials were conducted nor presented.

The risk of oxygen is low when oxygen is used short term and with concentrations lower than 60%. Longer exposure and use at higher concentrations may lead to pulmonary and/or CNS toxicity, as well as retina toxicity. Patients whose respiratory center is depressed, patients who are dependent on hypoxic drive for their respiration and neonates are at particular high risk from exposure to high concentrations of oxygen. The problem may be prevented by careful titration of oxygen concentrations to prevent over-exposure. In conclusion, as oxygen has been on the market for many years, the efficacy and safety of oxygen is well established. The benefit/risk ratio can be regarded as positive if the substance is used correctly and under well-controlled circumstances.

The medicinal product is manufactured in a standard, well-established process and its quality is sufficiently guaranteed.

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

The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that well-established use has been demonstrated, and has therefore granted a marketing authorisation. Zuurstof Medicinaal Vloeibaar AIR LIQUIDE, medicinal gas, cryogenic 100% v/v was authorised in the Netherlands on 15 August 2011.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached