CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Zuurstof YES 100% v/v, medicinal gas, compressed
Yes Pharmaceutical Development Services GmbH, Germany

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 and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states 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.

EU-procedure number: NL/H/2625/001/DC
Registration number in the Netherlands: RVG 111774

8 August 2013

Pharmacotherapeutic group:	medical gases
ATC code:	V03AN01
Route of administration:	inhalation
Therapeutic indication:	normobaric oxygen therapy - treatment or prevention of hypoxia and hypoxaemic conditions, 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:	31 July 2013
Concerned Member States:	Decentralised procedure with BE, BG, DE
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 member states have granted a marketing authorisation for Zuurstof YES 100% v/v, medicinal gas, compressed from Yes Pharmaceutical Development Services GmbH. The date of authorisation was on 31 July 2013 in the Netherlands.

The product is indicated for:

Normobaric oxygen therapy (Oxygen therapy at normal pressure)
- Treatment or prevention of hypoxia and hypoxaemic conditions.
- Treatment of cluster headache.

Hyperbaric oxygen therapy (Oxygen therapy at high pressure)
- Treatment of serious carbon monoxide poisoning irrespective of the COHb content in the blood (in particular essential in patients who after exposition to carbon monoxide have lost consciousness, have neurological symptoms, cardiovascular failure or serious acidosis or pregnant patients).
- 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 constitutes approx. 21% of air. Oxygen is vital to living organisms, and all tissues must be oxygenated continuously in order to maintain the energy production of the cells. Oxygen enters the lungs in inhaled air, where it diffuses along the walls of the alveoli and surrounding blood capillaries and then enters the system circulation (mainly bound to haemoglobin), which transports it to the peripheral tissues of the body. This is a normal physiological process that is essential to the body's survival.
By increasing the oxygen fraction in the inhaled air/gas mixture, the partial pressure gradient that controls the transport of oxygen to the cells increases.
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. Hyperbaric oxygen therapy counteracts growth of anaerobic bacteria.

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.

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.*). Oxygen is a colourless, odourless and tasteless gas at normal temperature and pressure. In liquid form it is a pale blue liquid.

For five air separation plants full details of the manufacture are included in the dossier. For one air separation unit the CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
The manufacture comprises seven stages. The starting material is naturally occurring atmospheric air. The purification of the oxygen from atmospheric air is a purely physical process based on fractional distillation of liquid air. This involves, after removal of unwanted particulates and contaminants, compression and cooling of the air at room temperature and then at lower temperatures to produce liquefied air from which oxygen is obtained by fractional distillation. The manufacturing process has been adequately described. Also information regarding production capacity at the different air separation plants is provided. The characterization (impurity profile/removal) of the starting material was sufficiently discussed.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. with the exception of the description of the appearance. Appearance is not described in the specification as the drug substance is stored as in a liquidised form and the Ph. Eur. Monograph describes the gaseous form. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the purity and impurities criteria have been provided for three consecutive batches of each air separation plant.

Stability of drug substance
No stability data have been provided. Bibliographic data have been provided. The re-test period of 6 months is acceptable. The storage tanks must be located at temperatures below 50°C in well ventilated areas installed according specific technical specifications.

** 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 YES 100% v/v is is a compressed, colourless and odourless inhalation gas for medical use within a pressurised cylinder. The drug product consists of 100% oxygen.

The drug product is stored in gas cylinders that are made of steel alloy, aluminium and composite materials without welding seams. The packaging is usual for this type of dosage form.

No excipients are present.

Pharmaceutical development
The manufacturing process is a well-established method. The choice of packaging is justified. 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. These requirements are common among manufacturers of oxygen.
The product is supplied as a non-sterile dosage form. Although no microbiological specification test or limits are specified for the finished product it is evident that pure oxygen in liquid form during manufacture and in compressed form during filling will not promote microbial growth. Pressurised cylinders will not permit the ingress of microbes into the primary container during its storage and use. Despite this, microbiological validation has been done as part of process validation.

Manufacturing process
Liquid oxygen is evaporated, the gaseous oxygen is compressed and filled in cylinders. Sufficient data regarding the process validation is included.

Quality control of drug product
The product specification includes tests for content, appearance of the cylinder, labeling and pressure, solubility and impurities. The analytical methods are acceptable. No validation data is required since pharmacopoeial methods are applied. Batch analytical data from all manufacturing sites have been provided on three batches, demonstrating compliance with the specification.

Stability of drug product
Bibliographic data regarding the stability of gaseous oxygen in cylinders have been provided. The proposed shelf-life of 36 months is justified.
The proposed storage conditions among which a temperature storage condition of *Store below 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 member states agreed that no further clinical studies are required.

Pharmacokinetics
Pharmacokinetic studies with oxygen have not been performed in humans. The pharmacokinetics of oxygen reflects in most aspects the physiology of "normal breathing". Data on pharmacokinetics of oxygen were, therefore, derived mainly from reviews and textbooks.
The available literature permits having a clear understanding of the clinical pK and pD of this active substance.

Pharmacodynamics
Oxygenation of the tissues is essential for live. Oxygen takes part in the cellular metabolism and catabolism and allows the production of energy (ATP). In case of hypoxemia the administration of supplemental oxygen will improve tissue oxygen delivery. Hypoxemia generally implies a failure of the respiratory system to oxygenate arterial blood. Most frequently hypoxaemia is defined as PaO2 <60 mm Hg (8 kPa) or as arterial oxygen saturation SaO2 <90%.
Variation of the blood oxygen partial pressure (PaO2) influences the cardiovascular system, respiratory system, cellular metabolism and CNS.

Clinical efficacy
Introduction
The use of oxygen for the treatment of hypoxemia is well established. The efficacy of oxygen in most of the proposed indications has been demonstrated by randomised controlled trials or by long term experience. The use of oxygen is included in many protocols for routine use and can be viewed as symptomatic therapy and efforts should be made to correct the primary cause of hypoxemia.
The clinical overview provides a concise overview of the claimed indications, dosages, and safety.

Normobaric oxygen therapy
Since the introduction of oxygen therapy in clinical practice in early 1920, its use has been extensively recognised for several diseases of the respiratory, cardiovascular, and central nervous systems. As previously demonstrated, when oxygen therapy is applied according to the SmPC recommendations, and patients receiving the therapy being monitored continuously, the benefits became obvious. From the reduction to total clearance of the symptoms in some cases, oxygen has been showing through the last century its value and appropriate therapeutic use.

Hyperbaric oxygen therapy
The use of oxygen at increased pressure is close to a true pharmacological application of the gas. Hyperbaric oxygen is administered in a pressure chamber. Hyperbaric oxygen therapy has, therefore, two inseparable components: increased hydrostatic pressure and increased oxygen tension.

Clinical safety
Oxygen is elemental for life, and its use in clinical practice has been proved to be effective and safe. The possible adverse reactions are minimal and easily avoided or overcome.
Given the toxicity of pure oxygen when administered for longer periods of time at high flow rates, the FiO2 level in breathing support should as a rule not exceed 60-70%. Oxygen therapy is proved to be very well tolerated, when administered within the recommended doses. In fact, in all clinical studies reported, there were no serious adverse reactions in patients, and all the few adverse reaction were overcome by simply decreasing the dose of oxygen inhalation or if necessary interrupting the oxygen therapy. Oxygen therapy has been clearly proved to be safe and practical.
As cited above, oxygen inhalation is primarily used to reverse or prevent the development of hypoxia; other consequences usually are minor. However, when oxygen is breathed in excessive amounts or for prolonged periods, secondary physiological changes and toxic effects can occur, though they can be

easily minimized.
In the respiratory system inhalation of oxygen at 1atm or above causes a small degree of respiratory depression in normal subjects, presumably as a result of loss of tonic chemoreceptor activity. However, ventilation typically increases within a few minutes of oxygen inhalation because of a paradoxical increase in the tension of carbon dioxide in tissues. This increase results from the increased concentration of oxyhaemoglobin in venous blood, which causes less efficient removal of carbon dioxide from the tissues.

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
Concerning the need for a risk management plan the MAH declares no such plan is deemed necessary. The application concerns a product for which no safety concerns requiring additional risk minimisation activities have been identified. This is considered acceptable.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with those accepted for other compressed oxygen products approved in the member states.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 5 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The majority of questions in the readability test could be answered without any significant problems. Overall, more than the required 90% (i.e. 18 out of 20 respondents) were able to find the requested information and thereof more than the required 90% were able to understand it. The readability test has been sufficiently performed. Furthermore, during the procedure the PIL has been adequately adapted in line with the SPC information and the comments of the member states involved.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Zuurstof YES 100% v/v, medicinal gas, compressed 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.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that well-established use has been demonstrated, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 2 May 2013. Zuurstof YES 100% v/v, medicinal gas, compressed was authorised in the Netherlands on 31 July 2013.

The date for the first renewal will be: 2 May 2018.

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