CBG MEB

# PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

# Lucht synthetisch medicinaal SOL, 21.75% v/v, medicinal gas, compressed SOL SpA, Italy

## 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/2264/001/MR**
**Registration number in the Netherlands: RVG 33760**

**11 July 2011**

| | |
|---|---|
| Pharmacotherapeutic group: | medical gases |
| ATC code: | V03AN01 |
| Route of administration: | inhalation |
| Therapeutic indication: | prevention of hypoxia, where treatment with atmospheric air is indicated |
| Prescription status: | non prescription |
| Date of authorisation in NL: | 9 December 2009 |
| Concerned Member States: | Mutual recognition procedure with BE, DE, LU, UK |
| 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 Lucht synthetisch medicinaal SOL, 21.75% v/v, medicinal gas, compressed, from SOL SpA. The date of authorisation was on 9 December 2009 in the Netherlands.

Lucht synthetisch medicinaal SOL is considered a drug, i.e. it is used for medicinal purposes. The indication of Lucht synthetisch medicinaal SOL is prevention of hypoxia where treatment with atmospheric air is indicated. The deprivation of oxygen (hypoxia) leads to death within minutes. This application concerns synthetic air in cylinders for medicinal use only and does not cover compressed ambient air or the use of air for non-medicinal purposes.

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

Lucht synthetisch medicinaal SOL provides an alternative air source that can be of use if special requirements are to be met with regard to purity; synthetic air is a mixture of pharmaceutical oxygen and pharmaceutical nitrogen and therefore does not contain any impurities and contaminations, as in compressed environmental 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.

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 Lucht synthetisch medicinaal SOL. 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 oxygen, an established substance described in the European Pharmacopoeia (Ph.Eur.*). It is a colourless, odourless and insipid gas. In solid and liquid form it has a pale blue colour.

Manufacturing process
Oxygen is prepared in air separation plants from atmospheric air. It is produced by distillation of liquefied air. Sufficient information has been provided on the production process. The elimination of the major part of the impurities occurs in the molecular sieves which strongly absorb all polar compounds (moisture, carbon dioxide, nitrous oxide, hydrogen sulphide, sulphur oxide, and nitrogen dioxide).

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur.; this specification is acceptable. Analysis results of the drug substance don't refer to a batch as the production process is continuously supplying the storage tank. Results of analysis have been provided with reference to date/time when tested. From both sites results of three time points have been given. All results comply with the Ph.Eur. requirements.

Stability of drug substance
The drug substance is packed in insulated containers dedicated for the storage of oxygen. The pressure in storage and transport vessels is always above atmospheric pressure. The complete tank content is regularly checked on purity. No stability tests have been performed and a re-test has not been laid down. This is acceptable as the active substance is tested 3 three times a day for compliance with Ph.Eur.

* *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
Lucht synthetisch medicinaal SOL 21.75% v/v contains as active substance 21-22.5% v/v of oxygen, and is a colourless, odourless and tasteless gas.

The medicinal gas is packed in a white high-pressure cylinder with black markings on the shoulders, constructed from steel or aluminium. Valve types are "standard" (handwheel operated with either pin index or threaded connection) or integrated reducers. The cylinders and cylinder valves comply with the national Dutch requirements on the construction of high-pressure cylinders and cylinder valves and relevant European requirements.
The capacity ranges between 1 and 50 litres and bundles of these cylinders. The pressure of the end product is always 200 Bar, regardless of the pack size or the material of the valve.

The product contains 78.25% v/v nitrogen as excipient.

Pharmaceutical development
Oxygen has been used for medicinal purposes for many years. The choice for the cylinder is based on the pressure requirements of the final product. The choice for the material and the valve is based on their compatibility for use with mixtures containing oxygen. The development of the product is satisfactory

performed and explained. The product is intended to replace air. The packaging cylinders are usual and suitable for the product at issue.

Manufacturing process
The cylinders are subsequently filled with oxygen and nitrogen. Both components are filled one after the other by weight. Calculation/formulae on this process has been provided, relating the manufacturing processing (weights and pressure) to the composition of the drug product (% v/v). The manufacturing process has been adequately described and validated for the proposed site.

Control of excipients
Nitrogen complies with its Ph.Eur. requirements. This specification is acceptable. The mixture of nitrogen and oxygen is a very stable gas mixture. There is no reaction between the oxygen and nitrogen at the temperatures and pressures the medicinal air is exposed to.

Quality control of drug product
The product specification includes tests for appearance and labeling of the product, and for pressure, oxygen content, identity (oxygen, nitrogen), water content and fill volume. The requirements are in line with the Ph.Eur.
Results of batch analysis have been provided, demonstrating compliance with Ph.Eur. requirements.

Container Closure System
A general overview on cylinders and legislation has been provided, together with information on typical cylinders. It is indicated that the pressure of the end product is always 200 Bar, regardless of the pack size or the material of the valve. Cylinders at any pack size can be steel or aluminium; valve types are “standard” (handwheel operated with either pin index or threaded connection) or integrated reducers.
The MAH has indicated that the cylinders and cylinder valves comply with the national Dutch requirements on the construction of high-pressure cylinders and cylinder valves at the moment of purchase. Since 1999 cylinders and cylinder valves can be bought in accordance with the Council directive 1999/36/EC on transportable pressure equipment, known as the TPED or pi-mark directive. The dedicated use of cylinders is guaranteed by the color coding as stipulated in the normative EN 1089. The MAH has also stated compliance with the standard EN 1089-3

Stability of drug product
The product is packaged in gas cylinders complying with current regulations. Results of stability studies have not been provided. Air is a stable gas, surrounding us also in normal, ambient conditions. The manufacturing process does not change the raw materials, *i.e.* there is no sterilisation in the process, no heat transfer, no chemical treatment, no irradiation, no wet treatment, and no polymorphic transformation. A shelf life of 3 years has been sufficiently justified. The applicable storage conditions are stated in section 6.4 of the approved SPC.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Not applicable.

## II.2 Non-clinical aspects

Oxygen containing products have been available on the European for many years. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

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

## II.3 Clinical aspects

Since the use of synthetic air is considered 'well established', a bibliographic application is acceptable. There have been many publications over the years concerning both its safety and efficacy. The safety and efficacy sections are based on clinical experience of the use of synthetic air as published in the literature.

**Clinical efficacy and safety**

Medicinal air 21.75% by SOL contains oxygen, a component of the normal atmosphere and a gas which is essential to human life. For aerobic organisms, oxygen is the main oxidant (the ultimate electron acceptor) used by the cell to convert nutrients (electron donors) such as glucose and fatty acids to energy. Supplemental medicinal air synthetic is useful or necessary for life in several situations of hypoxia that interfere with normal oxygenation of the blood or tissue.

Oxygen is the active ingredient in air. As one of the three basic essential for life (oxygen, water and food) there is no substitute for oxygen. Death follows within minutes of its absence. Medicinal air synthetic is used for a variety of applications as a source of oxygen and a source of clean air.
Oxygen is absorbed in the blood by the normal activity of the respiratory system. Most oxygen is carried in the blood reversibly bound to haemoglobin. Oxygen is not stored in the body; therefore a continuous supply at a rate that precisely matches changing metabolic requirements is of vital importance.

There are no specific undesirable effects of breathing air. Overdose cannot occur. However, as contraindicated in the Summary of Product Characteristics, medicinal air synthetic must not be administered at pressure as it may cause decompression sickness ('the bends' due to nitrogen effects) and oxygen toxicity.
Medicinal air synthetic has not been found to have any impact on pregnancy and can be used during lactation without risks to the infant. With regards to other special groups, no specific precautions are required for children or the elderly.

Sufficient information to inform physicians and patients to warrant the safe use of the product is included in the SPC.
The therapeutic indication (prevention of hypoxia) for Lucht synthetisch medicinaal SOL, 21.75%, Medicinal gas, compressed, is consistent with the spectrum of activity reported in standard references and published literature, and also with the currently established clinical use of the drug.

The data related to the clinical properties of the product are collected from and based upon a careful and extensive literature search. The information presented confirms the suitability and efficacy of the product when used as recommended.

Pharmcovigilance plan

The member states consider that 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 have been identified. There is no need for a risk minimisation plan.

**Product information**

SPC

The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for MRP NL/H/1074/001, concerning a comparable product.

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, followed by two rounds with 10 participants each. Thirteen questions were asked. The questions covered the following

areas sufficiently: traceability, comprehensibility and applicability. Overall, each and every question meets criterion of 81% correct answers. The readability test has been sufficiently performed.

## III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Based on the submitted dossier and further literature, Lucht synthetisch medicinaal SOL, 21.75% v/v, medicinal gas, compressed can be considered effective in situations of prevention of hypoxia. Except for nitrogen, there are no other excipients and there are no known incompatibilities. With regard to special groups, no special precautions are required for children, women who are pregnant or breast-feeding, or the elderly.

There are no specific undesirable effects of breathing air. Overdose cannot occur, but Lucht synthetisch medicinaal SOL must not be administered at pressure as it may cause decompression sickness and oxygen toxicity.

The SPC contains sufficient information to inform physicians and patients about the safe use of the product under the conditions stipulated. The SPC adequately warns of the problems that can occur with air therapy, including the risk of burns. The SPC, package leaflet and labelling are in the agreed templates.

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

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that the 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, and has therefore granted a marketing authorisation. Lucht synthetisch medicinaal SOL, 21.75% v/v, medicinal gas, compressed was authorised in the Netherlands on 9 December 2009. The other member states mutually recognised the Dutch evaluation for marketing authorisation. The mutual recognition procedure was finished on 20 March 2011.

The PSUR submission cycle is 3 years. The first PSUR will cover a period from 20 March 2011 until 8 June 2013.

The date for the first renewal will be: 28 November 2012.

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 |
|---|---|---|---|---|---|---|
| | | | | | | |