

Public Assessment Report

Scientific discussion

**Lung test gas CO (He) AGA,
0.28%, inhalation gas, compressed
(carbon monoxide, helium)**

SE/H/1154/01/MR

This module reflects the scientific discussion for the approval of Lung test gas CO (He) AGA, 0.28%, inhalation gas, compressed. The procedure was finalised at 2011-07-07. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

AGA Gas AB has applied for a marketing authorisation for Lung test gas CO (He) AGA, 0.28%, 9.3% inhalation gas, compressed. The active substances are carbon monoxide and helium. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Lung test gas CO (He) AGA is presented in the form of medicinal gas, compressed containing 0.28% of CO.

The finished product is packaged in gas cylinders, made of aluminium equipped with a cylinder valve.

II.2 Drug Substance

Carbon monoxide is a flammable colourless gas which is soluble in water at 0 °C and 1 bar 35 mL/L . The physico-chemical properties are sufficiently described. The manufacturing process of carbon monoxide has been adequately described and satisfactory information has been provided for the materials used.

The active substance specification includes relevant tests and the limits for impurities/ degradation products have been justified. The analytical methods applied are suitably described and validated.

II.3 Medicinal Product

Lung test gas CO (He) AGA contains 0.28% carbon monoxide, 9.3% helium, oxygen, and the remaining part is nitrogen.

The product development has taken into consideration the physico-chemical characteristics of the active substance and ingredients used.

The manufacturing process has been sufficiently described and critical steps have been 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.

III. NON-CLINICAL ASPECTS

The Lung test gas CO (He) AGA, is intended for diagnostic use only and indicated for testing of the pulmonary function, determination of the diffusion capacity/transfer factor and lung volume estimation

Pharmacodynamic, pharmacokinetic and toxicological properties of carbon monoxide, helium, oxygen and nitrogen are sufficiently known. The gases are well-known substances and sufficient non-clinical data is available in the scientific literature. Thus, the non-clinical safety aspects are covered. Whereas the literature on carbon monoxide and oxygen is extensive with numerous reviews, the literature on the toxicity of helium and nitrogen in animals is less extensive but still sufficient.

As all the substances are widely used, well-known active substances, no further studies are required. Overview based on literature review is, thus, appropriate.

Given the concentrations of the gases present in this mixture, the very short exposure periods needed for diagnostic purposes and their clinical use today, no safety concerns are to be expected.

IV. CLINICAL ASPECTS

IV.1 Introduction

Lung test gas CO (He) AGA, 0.28%, is intended for the diagnostic testing of pulmonary function only. A national marketing authorisation was granted on 2009-08-21.

The clinical part of the application was based on bibliographic data only. No clinical development program was conducted. This is acceptable as there is extensive clinical experience with lung test gases for the assessment of pulmonary function, and their use can be considered well established.

During the procedure, the indications, as suggested by the Applicant, were modified to enhance clarity. Furthermore, He was reclassified as active substance as it is used for the diagnostic indication "estimation of lung volume. The indication below was agreed upon finalisation of the procedure:

This medicinal product is for diagnostic use only

For diagnostic testing of pulmonary function (Determination of the diffusion capacity/transfer factor as main parameter and the estimation of lung volume as additional parameter).

IV.2 Pharmacodynamics

The gases are indicated for diagnostic purposes only, no therapeutic effects are sought. The pharmacodynamics of lung test gas CO/He is well known and specific studies were not conducted. Lung test gas CO (He) AGA contains 0.28% carbon monoxide, 9.3% helium, 20.9% oxygen, and the remaining part is nitrogen.

The various components are to be used as markers for different physiological aspects of lung function:

- Carbon monoxide is intended as a marker for the uptake of gas from the aerated lung/alveolar space to the blood (diffusion capacity). Carbon monoxide is a more suitable marker than oxygen itself due to its high affinity for haemoglobin in the erythrocytes. The partial pressure of carbon monoxide in the capillaries can be assumed to be zero (at baseline level), which simplifies the calculation of diffusion capacity.
- The helium tracer gas component is intended as a marker for the aerated lung volume. Helium is an inert gas that is highly diffusible (similar to carbon monoxide) but has very low solubility and thus does not leave the lung via the bloodstream.

IV.3 Clinical efficacy

Determination of diffusion capacity or lung transfer factor for carbon monoxide (TLCO) and lung volume are frequently used pulmonary function test for the evaluation of obstructive and restrictive lung diseases.

The TLCO is influenced by numerous physiological variables, such as alveolar oxygen tension and altitude, haemoglobin concentration, carboxy-haemoglobin level (smoking), exercise, age, gender, height, and possibly ethnicity. This should be taken into consideration when interpreting results. Assessment of the diffusion capacity of carbon monoxide, can be done using various techniques.

The single-breath (single breath holding) technique has become the gold standard and is the most widely accepted. In this test, the subject inhales a vital capacity breath of a test gas (usually 0.3% carbon monoxide) and an insoluble gas (helium or another inert gas such as methane), holds it in the lungs for 10 seconds, then exhales, during which time a sample of alveolar gas is taken for analysis. The concentration of the helium in the expired sample will be lower than that inspired by an amount that reflects the dilution of the test gas in the lung. The same dilution factor is applied to the carbon monoxide in the test gas in order to obtain the initial alveolar concentration; the final alveolar concentration is that in the expired alveolar sample. The 2 concentrations together with the time of breath holding and the inspired volume are used for the calculation of TLCO, which is done automatically by monitoring equipment.

Another technique is the steady-state method. Here, the subject breathes a low concentration of carbon monoxide (0.1 to 0.2%) for several minutes or until a steady state of carbon monoxide exchange is achieved (according to the monitoring equipment). A mixed expired gas sample is then gathered over several more minutes and the rate of carbon monoxide uptake is estimated as the difference between the quantities of inspired and expired carbon monoxide per unit of time. Partial pressure for pulmonary alveolar carbon monoxide ($P_A\text{CO}$) needs to be estimated either by analysis of end-tidal gas for carbon monoxide or by calculation from the pressure in the mixed expired gas and the dead space to tidal volume ratio measured for carbon dioxide. Sometimes this can require an arterial blood gas to be drawn during the gas collection. The test is more reproducible during low-level exercise than it is at rest but even so may yield falsely high or falsely low results. Advantages of the steady-state technique are that it requires less equipment and less calculation. Furthermore, only minimal patient cooperation is required because measurements are made during tidal breathing and it can be performed, for example, in an intensive care unit setting and during general anaesthesia.

Measuring lung volume may be done statically or dynamically. Static lung volume or capacity can be examined by spirometry or body plethysmography. The inert gas technique using helium or methane is a classic alternative method to spirometry and/or plethysmography and their use to measure the lung volume is considered well established.

IV.4 Clinical safety

The lung test gases are intended for diagnostic purposes only, and individual patients will therefore be infrequently exposed.

Carbon monoxide at concentrations up to 0.3% administered by the single breath or repeated breath technique for diagnostic purposes is not considered to present a risk to patients. In perspective, tobacco smoke has about 4% carbon monoxide content and car exhaust fumes can contain up to 10%.

Helium is passive marker of the air space within the lungs and airways. It is an inert gas with low solubility and therefore considered to be biologically inactive when inhaled in the present concentration.

The oxygen and nitrogen components of the lung test gases resemble the composition of ambient air.

IV.5 Discussion on the clinical aspects

Lung test gas CO (He) AGA, 0.28%, is intended for the diagnostic testing of pulmonary function. There is extensive clinical experience with these gases and their use can be considered well established. Thus, the clinical part of the application was based on bibliographic data only, which is considered sufficient.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The lung test gas CO/He is indicated only for the diagnostic testing of pulmonary function and should be used in combination with appropriate equipment and handled by adequately trained medical personnel. To date, there is extensive clinical experience with the use of lung test gases for assessment of TLCO and lung volume and their use can be defined as well-established.

In conclusion, the benefit/risk evaluation is favourable if the products are used in accordance with the recommendations in the SPC.

User consultation

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Helontix medicinal gas, compressed Helium 79%, Oxygen 21%, PL00735-5011R-0012. The differences between the package leaflets were tested in a focus test. With this focus test, the bridging report submitted by the applicant has been found acceptable.

The risk/benefit ratio is considered positive.

VI. APPROVAL

The Mutual recognition procedure for Lung test gas CO (He) AGA, 0.28%, inhalation gas, compressed, was successfully finalised on 2011-07-07.

During the procedure, the indications, as suggested by the Applicant, were modified to enhance clarity. Furthermore, He was reclassified as active substance as it is used for the diagnostic indication “estimation of lung volume”. A commitment to submit supportive new drug substance documentation was included at the end of the procedure.

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)