CBG MEB

Public Assessment Report

Scientific discussion

Apulco Acometh 0.30%/0.30%/0.30%, medicinal gas, compressed

(carbon monoxide, methane, acetylene)

NL/H/2971/001/DC

Date: 8 March 2016

This module reflects the scientific discussion for the approval of Apulco Acometh 0.30%/0.30%/0.30%, medicinal gas, compressed. The procedure was finalised on 23 January 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

A list of literature references is given on pages 16-18.

List of abbreviations

AARC	American Association for Respiratory Care
ASMF	Active Substance Master File
ATS	American Thorax Society
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CF	Cystic fibrosis
CMS	Concerned member state
CO	Carbon monoxide
COHb	Carboxyhaemoglobin
COPD	Chronic obstructive pulmonary disease
DLCO	Lung Diffusion Capacity
ERS	European Respiratory Society
FRC	Functional residual capacity
GTN	Glyceryl Trinitrate
He	Helium
MAH	Marketing authorisation holder
MBW	Multiple breath washout (method)
NIOSH	National Institute of Occupational Health and Safety of the United States
O_2	Oxygen
Ph.Eur.	European Pharmacopoeia
PL	Package leaflet
ppm	parts per million
RMS	Reference member state
SmPC	Summary of product characteristics
TLC	Total lung capacity
VC	Vital capacity

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Apulco Acometh 0.30%/0.30%/0.30%, medicinal gas, compressed from Air Products Nederland B.V.

The product is for diagnostic use only. It is used for diagnostic testing of lung function with determination of the lungs' diffusion capacity (or transfer factor) as the main parameter, and of lung volumes and pulmonary blood flow, as additional parameter.

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

Lung function gases are always administered through a lung function gas machine. The machines can work with gas mixtures which slightly differ in the range of the individual components within the gas mixture composition, but the type and number of gas components in the gas mixture is defined by the machine manufacturer.
In addition to this variety of gases, the doctor can also decide to use slightly different lung function gas mixtures, within the tolerances allowed by the machine.
The demand for lung function gas mixtures is therefore changing constantly.
Each lung function gas mixture is a stable mixture and is filled and supplied in dedicated high pressure cylinders.
The doctor can use this gas cylinders for several patients, therefore the need for gas cylinders per year is very low, typically 2 to 10 cylinders per year per mixture, depending on the application.

This decentralised procedure concerns an application under Article 10(a) of Directive 2001/83/EC, well established use. This is according to current EU directives (EU, 2001a) on what defines a medicinal product, which includes "Any substance or combination of substances (...) administered to human beings (...) with a view (...) to making a medical diagnosis".

Also, inhaled gases for lung function tests should be considered as medicinal products of well established medicinal use as they meet the defining qualifications (EU, 2001b) relating to:

(i) "the time over which a substance has been used", which "must not be less than one decade from the first systematic and documented use",
(ii) "quantitative aspects of the use of the substance",
(iii) "the degree of scientific interest in the use of the substance (reflected in the published scientific literature)"
(iv) "the coherence of scientific assessments".

Therefore, the application is solely based on scientific literature data, and no new non-clinical or clinical studies were conducted.

The concerned member states (CMS) involved in this procedure were Germany and Spain.

II. QUALITY ASPECTS

II.1 Introduction

Apulco Acometh 0.30%/0.30%/0.30% is a colourless, odourless and tasteless gas.
It contains 0.3% of each of the active substances carbon monoxide, methane and acetylene, and 21% and 78.1% of the excipients oxygen and nitrogen, respectively.

The gas cylinders are made of aluminium, equipped with a brass valve with a specific outlet connector. Gas cylinders are identified also by colour: the shoulder is painted in bright green and the cylinder body in white.

II.2 Drug Substances

Carbon monoxide
The active substance carbon monoxide (CO) is described in the European Pharmacopoeia (Ph.Eur.). No Active Substance Master File (ASMF) or Certificate of Suitability (CEP) was submitted; full information on carbon monoxide is included in the dossier.

Manufacturing process
The MAH defines industrial carbon monoxide as starting material. It is regarded as drug substance as soon as it is tested according to the Ph.Eur. by the active substance manufacturer. In order to justify this approach, the MAH provided sufficient evidence that carbon monoxide can be regarded as industrial commodity used in non-pharmaceutical markets.

Quality control of drug substance
The proposed drug substance specification is in accordance with the Ph.Eur. monograph on carbon monoxide. The MAH confirmed that the Ph.Eur. monograph is suitable for the control of impurities originating from the manufacturing process.
Industrial carbon monoxide and the drug substance carbon monoxide are filled in dedicated and product specific aluminium cylinders. The pressure inside the cylinders is 200 bar. Sufficient information was provided on the standards according to which the cylinders are tested and on the valves.

Stability of drug substance
Bibliographic evidence is provided on the stability of carbon monoxide which is considered sufficient. The proposed re-test period of six months is granted, with the storage conditions “Shall not be exposed to extreme heat. If at risk of fire, move to a safe place. Handle carefully. Shall be returned with a minimum residual pressure. Cylinders shall be stored and transported with valves closed.”

Methane
A Ph.Eur. draft monograph is available for the active substance methane. Full information is provided on this drug substance; no ASMF or CEP has been submitted.

Manufacturing process
The MAH defines industrial methane as starting material. It is regarded as drug substance as soon as it is tested by the active substance manufacturer. This approach can be accepted as no synthetic steps are involved in the manufacturing process of methane.
Industrial methane is produced by cryogenic distillation of natural gas. Sufficient information has been provided on the manufacturing process of the drug substance.

Quality control of drug substance
The proposed drug substance specification is in accordance with the draft Ph.Eur. monograph on methane. The draft monograph is applicable to methane obtained from natural gas. It is therefore expected that it covers all impurities which may be carried over to the drug substance during manufacture of industrial methane.
Industrial methane and the drug substance methane are filled in dedicated and product specific steel cylinders with a water capacity of 50 litres owned by the MAH. The pressure inside the cylinders is 175 bar. Sufficient information was provided on the standards according to which the cylinders are tested and on the valves.

Stability of drug substance
Bibliographic evidence is provided on the stability of methane which is considered sufficient. The proposed re-test period of six months and storage conditions “Shall not be exposed to extreme heat. If at risk of fire, move to a safe place. Handle carefully. Shall be returned with a minimum residual pressure. Cylinders shall be stored and transported with valves closed.” are acceptable.

Acetylene
The drug substance acetylene is not described in a pharmacopoeia. No ASMF or CEP has been submitted; full information is provided on acetylene.

Manufacturing process

The MAH defines industrial acetylene as starting material. It is regarded as drug substance as soon as it is tested by the active substance manufacturer. In order to justify this approach, the MAH provided sufficient evidence that acetylene can be regarded as industrial commodity used in non-pharmaceutical markets.

Industrial acetylene is produced by adding calcium carbide to water. Sufficient information has been provided on the manufacturing process of the drug substance.

Quality control of drug substance

The proposed drug substance specification has been set up in house. It covers all relevant impurities originating from the manufacturing process of industrial acetylene.

Industrial acetylene and the drug substance acetylene are filled in dedicated and product specific steel cylinders with a water capacity of 40 litres owned by the MAH. The pressure inside the cylinders is 19 bar. Sufficient information was provided on the standards according to which the cylinders are tested and on the valves.

Stability of drug substance

Bibliographic evidence is provided on the stability of acetylene which is considered sufficient. Acetylene is unstable, particularly when applying high pressure. In order to stabilise the drug substance and increase the gas content of the cylinders, acetylene is dissolved in acetone and a porous material is contained in the cylinders.

The proposed re-test period of six months and storage conditions “Shall not be exposed to extreme heat. If at risk of fire, move to a safe place. Handle carefully. Shall be returned with a minimum residual pressure. Cylinders shall be stored and transported with valves closed.” are acceptable.

Premixes of carbon monoxide and nitrogen

For safety reasons, carbon monoxide is handled as premixes of carbon monoxide in nitrogen containing either 3% or 5% of carbon monoxide. The manufacturing process consists of filling of gaseous carbon monoxide and nitrogen by weight. The specifications of the premixes include the determination of the contents of carbon monoxide nitrogen. Impurities are tested in the individual gases and are not expected to increase in the premixes.

The premixes are packed in aluminium cylinders. The pressure inside the cylinders is 200 bar. Sufficient information was provided on the standards according to which the cylinders are tested and on the valves.

On the basis of bibliographic evidence and supportive 12 months stability data obtained from cylinders stored under cover and at room temperature, a shelf life of 18 months is applied for the premixes. Moreover, the MAH provided bibliographical evidence on the homogeneity of the premixes under various conditions of use (e.g., extreme temperatures, cooling and heating cycles, cylinder utilisation, abrupt opening). Based on the provided bibliographical evidence and the supporting stability data, the claimed shelf life of 18 months is justified. Storage conditions are “Shall not be exposed to extreme heat. If at risk of fire, move to a safe place. Handle carefully. Shall be returned with a minimum residual pressure. Cylinders shall be stored and transported with valves closed.”

Premix of methane and nitrogen

For safety reasons, methane is handled as premix of 2.2% methane in nitrogen. The manufacturing process consists of filling of gaseous methane and nitrogen by weight.

The specification of the premix includes the determination of the contents of methane and nitrogen. Impurities are tested in the individual gases and are not expected to increase in the premixes.

The premix is packed in aluminium cylinders with a water capacity of 40 litres. The pressure inside the cylinders is 200 bar. Sufficient information was provided on the standards according to which the cylinders are tested and on the valves.

On the basis of bibliographic evidence and supportive 12 months stability data obtained from cylinders stored under cover and at room temperature, the MAH claims a shelf life of 18 months for the premix. Moreover, the MAH provided bibliographical evidence on the homogeneity of the premix under various conditions of use (e.g., extreme temperatures, cooling and heating cycles, cylinder utilisation, abrupt opening). Based on the provided bibliographical evidence and the supporting stability data, the claimed shelf life of 18 months is justified. Storage conditions are “Shall not be exposed to extreme heat. If at risk of fire, move to a safe place. Handle carefully. Shall be returned with a minimum residual pressure. Cylinders shall be stored and transported with valves closed.”

Premix of acetylene and nitrogen
For safety reasons, acetylene is handled as premix of 1.15% acetylene in nitrogen. The manufacturing process consists of filling of gaseous acetylene and nitrogen by weight.
The specification of the premix includes the determination of the contents of acetylene, acetone, nitrogen, and water. Apart from acetone, impurities are tested in the individual gases and are not expected to increase in the premixes.
The premix is packed in steel cylinders with a water capacity of 50 litres. The pressure inside the cylinders is 50 bar. Sufficient information was provided on the standards according to which the cylinders are tested and on the valves.
On the basis of bibliographic evidence and supportive 12 months stability data obtained from cylinders stored under cover and at room temperature, the MAH claims a shelf life of 18 months for the premix. Moreover, the MAH provided bibliographical evidence on the homogeneity of the premix under various conditions of use (e.g., extreme temperatures, cooling and heating cycles, cylinder utilisation, abrupt opening). Based on the provided bibliographical evidence and the supporting stability data, the claimed shelf life of 18 months is justified. Storage conditions are “Shall not be exposed to extreme heat. If at risk of fire, move to a safe place. Handle carefully. Shall be returned with a minimum residual pressure. Cylinders shall be stored and transported with valves closed.”

II.3 Medicinal Product

Pharmaceutical development
The MAH has explained that mixing of the premix CO, premix CH4, premix C2H2, oxygen, and nitrogen results in a homogeneous product. Lung test gas mixtures have been used as a medicinal gas for more than 10 years. The manufacturing steps do not result in any change of state. The choice of aluminium or aluminium hoopwrapped cylinders is based on the specific wishes of the customer/user of the final product. The choice of cylinder material and the valve is based on their specific compatibility for use with carbon monoxide, methane, acetylene and oxygen, because nitrogen is an inert gas, hence is compatible with all common materials.

Manufacturing process
The manufacturing process consists of filling of the acetylene premix, carbon monoxide premix, methane premix, oxygen, and nitrogen by weight. The manufacturing process was adequately described. A batch is defined as nine cylinders of the same size filled simultaneously using the same batch of premix C2H2, premix CO, premix CH4, oxygen, and nitrogen. The manufacturing process was successfully validated with a sufficient number of batches covering all cylinder sizes. The provided process validation data demonstrate reproducibility of this process.

Control of excipients
The excipients oxygen and nitrogen are tested according to the Ph.Eur. CEPs are available for both excipients. The specifications are acceptable.

Quality control of drug product
The drug product specification includes acceptance criteria for the contents of carbon monoxide, methane, acetylene, and oxygen (each cylinder), identification of nitrogen (one cylinder per batch), and pressure. The release and shelf life specifications are identical and are acceptable. Sufficient batch analysis data have been provided.

Stability of drug product
On the basis of bibliographic evidence, the MAH claims a shelf life of 36 months for the drug product. In addition, supporting stability data have been provided covering 18 months in all container sizes. Moreover, the MAH provided bibliographical evidence on the homogeneity of the drug product under various conditions of use (e.g., extreme temperatures, cooling and heating cycles, cylinder utilisation, abrupt opening). Based on the provided bibliographical evidence and the supporting stability data, the claimed shelf life of 36 months is justified. Appropriate storage conditions have been laid down, which are included in section 6.6 of the SmPC.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Apulco Acometh 0.30%/ 0.30%/0.30%, medicinal gas, compressed has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product.

The following post-approval commitment was made:
- The MAH committed to continue the stability studies up to the shelf life of 36 months.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

The components of the gas mixture are well known naturally occurring substances. The use of these gases in the single-breath carbon monoxide (CO) inhalation test is clinically well-established.
Besides the use as a diagnostic, carbon monoxide appears to have some cytoprotective, anti-inflammatory and neuroprotective effects in animal models. These effects have been investigated after prolonged exposure to CO, and are therefore likely not relevant for the current product. Possible effects of methane on intestinal motility and of both methane and acetylene as anaesthetic are only relevant at concentrations much higher than present in the current product.
With regard to safety pharmacology, although short term CO exposure is likely to increase COHb levels and therefore potentially induce hypoxia, adverse effects were only seen in animals after prolonged exposure or at COHb levels much in excess of clinically relevant levels for this diagnostic procedure (up to 3.2%).
Limited safety pharmacology data is available for methane and acetylene, and only at very high concentrations, showing no effects for methane and some cardiovascular and respiratory effects for acetylene. Due to the high concentrations (which caused anaesthesia), these effects are not likely relevant for Apulco Acometh.

III.2 Pharmacokinetics

The pharmacokinetics of O_2 in this product will follow the normal physiological kinetic properties of O_2.
Diffusion of CO into erythrocytes and binding of CO to Hb is rapid. The half-time for saturation in rats was approximately 25-35 minutes at different concentrations of inhaled CO, with equilibrium reached between 60 and 120 minutes exposure. The majority of CO is measured in blood. A small proportion of inhaled CO undergoes oxidative metabolism, through mitochondrial cytochrome oxidase. In humans, the rate of oxidative metabolism has been estimated to be 14 µmol/day. The half-time for CO desaturation after removal from CO exposure is approximately 32-35 minutes.
Methane is not absorbed after inhalation, and exhaled without modification. Acetylene is rapidly absorbed after inhalation and exhaled unchanged.

III.3 Toxicology

Both methane and oxygen are non-toxic at the concentrations in which they are present in the current product for diagnostic use.
Toxicology studies in rats, mice, rabbits, dogs and monkeys reveal changes in respiratory system, cardiovascular effects, changes in haematological parameters, and to a lesser extent neurological effects, after subacute and chronic exposure to carbon monoxide. These effects are of little relevance for the clinical setting of a single breath application of Apulco Acometh. Studies on acetylene have only been performed with very high concentrations. The information is not well documented, and references are very old in some instances. However, the data are reassuring, and no effect of acetylene is anticipated from the use of the current product.
Carbon monoxide appears to have genotoxic potential when inhaled for 10 minutes or more at clinically relevant concentrations. The relevance of this finding for the clinical setting of 10 seconds inhalation is not known, but unlikely. Considering this genotoxic potential, a local carcinogenic effect after prolonged inhalation of CO is to be expected. However, the application of the single breath inhalation test resulting in exposure of 10 seconds is very unlikely to result in an increased

carcinogenic risk. No data on methane are available, but a genotoxic potential is unlikely. Limited data on acetylene show no genotoxic potential.
A recent study in mice revealed a reduction in foetal growth and increased gestational deaths after exposure to carbon monoxide throughout pregnancy at the high dose resulting in COHb levels of 15.6% and 28.6% in maternal and foetal blood respectively. At the 'no observed adverse effect level' of 250 ppm, maternal and foetal blood COHb were around 13% and 23% respectively. As both duration of exposure and blood COHb are much in excess of those expected from clinical use of the product there is a large safety margin, and no effect on the foetus is expected from the use of this diagnostic product. Methane was shown to be teratogenic at very high concentrations. As methane is not absorbed, this effect is likely not directly related to methane, but rather to changes in the air composition and subsequent adaptive changes. Such effects are not likely after a single breath inhalation of 0.3% methane. No data is available for acetylene. Since this gas is readily absorbed, a risk for the foetus cannot be excluded.

III.4 Ecotoxicity/environmental risk assessment (ERA)

Since lung function tests are well-established medicinal products that have been used for decades, approval of Apulco Acometh will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.5 Discussion on the non-clinical aspects

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 member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

The application is based purely on bibliographic clinical evidence that the lung function test is a well-established procedure.

The applied indication is 'for diagnostic testing of lung function with determination of the lungs' diffusion capacity (or transfer factor) as the main parameter, and of lung volumes and pulmonary blood flow, as additional parameter.'
This is the most widely used mode of the single-breath test, as defined in international guidelines (Anon, 1999a). The inclusion of acetylene also allows the mixture to be used in the single-breath, constant exhalation maneuver (Zenger et al, 1993), for simultaneous measurement of DLCO and the pulmonary capillary blood flow (equivalent to cardiac output, QC), which is derived from the rate of alveolar absorption of acetylene. The oxygen and nitrogen are normal air constituents and are required as vital physiological substrate and as inert "filler", respectively. The inclusion of oxygen and nitrogen allows that the gas mixture can be used in the test without the need to connect additional gases. Although the use of the single-breath exhalation method is not always the method of choice for determining cardiac output, its continued clinical utility is also indicated by recent discussion in the literature (Hansen, 2013, Hughes, 2012, Hughes, 2013). It is considered a more amenable procedure than the single-breath test for lung function measurements during exercise (Anon, 1995, MacIntyre, 2005), which are more sensitive to the effects of cardiopulmonary functional deficits (Miller, 2009) and a standardised procedure has been described (Miller, 2009) that is based on documented evidence of its clinical validity and robustness. The inclusion of methane, rather than helium, is justified because, with acetylene, it allows simultaneous measurement of DLCO and QC, respectively (Ramage, 1987, Wilson, 1994) due to their common method of on-line detection. Moreover methane may be considered a better alternative to helium because of the bronchodilator effect of helium (Laude, 2006) that may cause an over-estimation of lung volumes.

Products and their composition
The concentrations of the individual test gases are standardised according to the American and European practice guidelines. The tracer gas should be relatively insoluble, chemically and biologically inert and the gaseous diffusivity should be similar to CO. Furthermore, it should not interfere with the measurement of CO concentration and the tracer gas should not ordinarily be present in alveolar gas or else be present at a known, fixed concentration (e.g. argon). Commonly used tracer gases are helium (He) and methane (CH4). The inspired CO should nominally be 0.3%. However, as ratios are more important than absolute values, exact concentrations are not critical.

Apulco Acometh 0.30%/0.30%/0.30% matches well with the applied gases, as listed by MacIntyre et al (2005) and can be considered acceptable.

IV.2 Pharmacokinetics

Carbon monoxide
Carbon monoxide (CO) is rapidly and extensively absorbed in the lung alveoli following inhalation. Because CO binds avidly to Hb, there is a relatively low free blood and cytosolic CO concentration in the erythrocyte and, therefore, a partial pressure gradient that drives CO transfer from alveolar air to blood.
The major factors that control absorption of CO include those that affect delivery of inhaled air to the alveolar region of the lung and those that affect the lung's CO diffusion capacity. Factors that may affect net CO absorption include health status (lung function), exercise, the supine position, age (increased in infancy and childhood, declines in adults with age), altitude, increasing the blood Hb concentration and decreasing the partial pressure of O_2 in inhaled air or blood and present COHb.

The adult human body is estimated to contain approximately 10 ml (448 mcmol) of CO. As a result of its affinity for hemoglobin and myoglobin the largest CO load after inhalation being found in blood, heart, skeletal muscle and spleen (Vreman et al, 2006).

Inhaled CO is eliminated from the body primarily by direct exhalation but also via oxidative metabolism. The mechanism of elimination of CO by exhalation is diffusion. The half-life for wash-out after exposure to CO was estimated to be 250-320 minutes (Peterson et al, 1975).

The metabolism of CO involves three major processes, (i) production of CO from endogenous and exogenous precursors, (ii) binding of CO to heme proteins, and (iii) oxidative metabolism of CO to CO_2. Endogenous CO is produced, primarily, from the enzymatic degradation of heme by the enzyme, heme oxygenase (HO).
A small proportion of inhaled CO undergoes oxidative metabolism, primarily due to the action of mitochondrial cytochrome oxidase (Young and Caughey, 1986). This is approximately 3% of endogenous carbon monoxide production.

Acetylene
Acetylene is rapidly absorbed and eliminated unchanged in the body. The rate of alveolar absorption of acetylene is proportional to the pulmonary capillary blood flow during a single-breath, constant exhalation maneuver. The expired volume of acetylene reflects the volume of gas taken up by the lungs.
Acetylene is a gas that is soluble in tissue and blood but does not bind to Hb. Its solubility in tissue and blood has been measured as, respectively, 0.76 and 0.74 mL acetylene (STPD)/mL blood/atmosphere (Cander, 1959).
Inhaled acetylene is rapidly excreted without any retention in the body, even after repeated exposure (Jibelian et al, 1981, Schrikker et al, 1989).

Methane
Inhaled methane is not absorbed and is exhaled unchanged. There are no interactions between CO, acetylene and methane: methane and acetylene are not metabolized and excreted unchanged by exhalation.

IV.3 Pharmacodynamics

Carbon monoxide may have a physiological role in the body, such as a neurotransmitter or a blood vessel relaxant.
Carbon monoxide produces tissue hypoxia by binding to Hb, displacing O_2 from it, and forming COHb, which has less O_2-carrying capacity of blood and impairs release of O_2 from Hb in tissues.
Carboxyhemoglobin blood saturations may range up to 8–10% in heavy smokers or persons extensively exposed to automotive exhaust gases. In symptomatic poisoned people they are often in the 10–30% range. The severity of symptoms ranges from mild (constitutional symptoms) to severe (coma, respiratory depression, and hypotension). It is important to recognize that carboxyhemoglobin levels do not correlate well with the severity of symptoms in a substantial number of cases. The duration of exposure appears to be an important factor mediating toxicity.

The tissues that have the highest O_2 demand, such as brain and heart, are considered especially vulnerable because of the carbon monoxide-induced hypoxia. During exercise, increased cardiac work and O_2 consumption increases the vulnerability of the heart to CO-induced hypoxic injury, particularly in patients with underlying coronary artery or myocardial disease (US Department of Health and Human Services, 2009).

Brain hypoxia induced by CO can result in various symptoms of impaired central nervous system function, e.g. headache, dizziness, nausea, vomiting, confusion, disorientation, convulsions and coma (Dolan, 1985, Ernst and Zibrak, 1998). Delayed development of neuropsychiatric and neurological impairment may occur within 1-4 weeks of exposure (reviewed in US, 2009).
The treatment of carbon monoxide poisoning is removal from the environment and/or the supplemental oxygen until the carbon monoxide level is below 5%.

The pharmacodynamic process of the CO uptake to measure the diffusing capacity involves several steps of the physiological pathway and impairment in every step can result in a decrease of the CO diffusion (Brusasco et al, 2005).

Early studies using different low concentrations of CO showed different results on inflammatory responses. Also the results on COHb show differences.

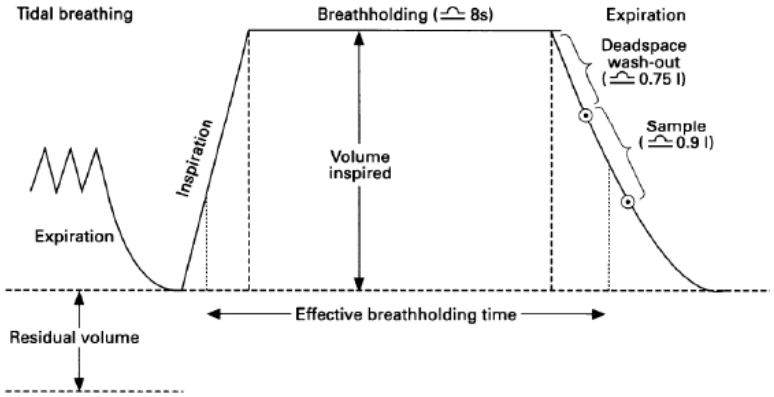
Acetylene is categorised as a simple asphyxiant (NIOSH, 2009) due to high ambient concentrations causing displacement of oxygen (International Uniform Chemical Information Database, 2000). In the past acetylene has been used as a human anaesthetic (Brandt, 1926, Davidson, 1925) at concentrations of about 70% (with 30% oxygen).

Methane is biochemically and biologically inert and has no significant pharmacodynamic effects.

IV.4 Clinical efficacy

Single-Breath Inhalation Test
A combined task force of ATS and European Respiratory Society has listed the test criteria that are acceptable for measurement of D_{LCO} by the single-breath procedure (Macintyre et al, 2005).
The procedure is summarised in Figure 1 showing a spirogram.

Figure 1: Spirogram of the single-breath inhalation procedure for determining D_{LCO} (from Cotes et al, 1997)



The single-breath inhalation test measures the diffusing capacity for the lungs measured using carbon monoxide, also known as transfer factor (D_{LCO}).

The significant clinical value of measuring D_{LCO} has led to widespread and evidently successful efforts to improve instrumentation and to refine and standardise the procedures and performance of D_{LCO} measurements across laboratories (Crapo and Jensen, 2003, Jensen et al, 2009). Jensen and Crapo have outlined the essential elements of the single-breath CO inhalation test. The measurement of the lungs' diffusion capacity depends on the measurement of the diffusion rate of CO which, after inhalation, follows the same diffusion path of oxygen, namely from the alveoli across the alveolar-capillary membrane and on to Hb within the erythrocytes. From the concentration of expired CO, the D_{LCO} can be calculated.

The calculation requires that there is a non-absorbable carrier gas, such as helium, present in the inhaled mixture in order to allow calculation of (i) the degree of dilution of CO on inhalation and (ii) the alveolar CO concentration.
The procedure for measuring D_{LCO} for diagnostic purposes has been standardized in expert guidelines (Anon, 1987, Anon, 1999a) and recommendations (Cotes et al, 1993, Macintyre et al, 2005).
The updated recommendations (Anon, 1995) formed the basis of the American Association of Respiratory Care (AARC) Clinical Practice Guidelines (Anon, 1999a).

Methane, present at a concentration of 0.3%, is used as a tracer gas in the single-breath inhalation test. As methane is not absorbed, it is used for measuring the long volumes, in addition to the measurement of DLCO with carbon monoxide.
Acetylene, present at a concentration of 0.3%, is absorbed. The presence of acetylene is introduced for use in the single-breath, for simultaneous measurement of DLCO and the pulmonary capillary blood flow (equivalent to cardiac output, QC), which is derived from the rate of alveolar absorption of acetylene.

Assessment of established use criteria

(i) "the time over which a substance has been used", which "must not be less than one decade from the first systematic and documented use",
(ii) "quantitative aspects of the use of the substance",
(iii) "the degree of scientific interest in the use of the substance (reflected in the published scientific literature)"
(iv) "the coherence of scientific assessments".

The single-breath exhalation test (Zenger et al, 1993) utilises both CO and acetylene for simultaneous measurement of DLCO and QC, respectively (Ramage et al, 1987, Wilson et al, 1994). Both procedures have been thoroughly validated and are employed to produce robust data, with standardised instrumentation, in many pulmonary diagnostic laboratories (i).

Apulco Acometh has been used for more than a decade in several European countries. Its established use is also reflected in the public assessment report of Lung test gas CO (C2H2, CH4) AGA, 0.3%,

0.3%, 0.3% (SE/H/1153/01/MR), registered in Sweden in 2011. Discussions regarding its use in the single-breath exhalation test were published in 2012 and 2013. Although its use cannot be quantified, it is assumed that this criterion is met (ii).

Scientific interest in the use of Apulco Acometh for the measurement of diffusion capacity is recognized in the submitted application (iii). Published scientific assessments are considered coherent (iv).

IV.5 Clinical safety

The MAH indicates that the single-breath inhalation test, the gas containing CO, CH4 and C2H2 is inhaled at concentrations that provide no safety concerns to the test subjects.

CO
The safety of inhaling CO is determined by the blood levels of COHb that it generates, and the possible consequent hypoxia. It is reported that the single-breath inhalation procedure, which entails inhalation of 0.3% (3,000 parts per million [ppm]) CO with 10 seconds breath-holding, raises COHb levels from 0.5% to approximately 1% (Vreman et al, 2000a). In 10 healthy non-smoking subjects, Frey and colleagues reported a mean (±sd) increase in blood COHb levels of 0.71 (±0.087)% per single-breath CO inhalation test (Frey et al, 1987).
In physiological studies in healthy subjects exposed to inhaled CO at 300 to 1,000 ppm for periods of between 30 minutes to one hour, COHb levels increased from about 3 to about 9% (Hausberg et al, 1997, Mayr et al, 2005). This compares to reported COHb levels of 3-8% in smokers and less than 3% in non-smokers (Marshall et al, 1995). In comparison, in experimental studies (Graham et al, 2002) in which healthy subjects performed 4 consecutive 0.3% CO inhalation manoeuvres, at 10 minutes intervals and including one 20 second breath-hold and one 9 second breath-hold, COHb levels increased from a mean basal of 1.2%, before the manoeuvres, to a mean of 3.2%, afterwards. The total period of breath-holding of this series of single-breath manoeuvres may be considered to be close to that of the single-breath CO inhalation procedure, which is, normally, repeated a maximum of 5 times (Jensen et al, 2009, Macintyre et al, 2005). Therefore, this data suggests that a series of standard single-breath CO inhalation manoeuvres may lead to an increase in COHb of about 3%. A blood COHb of about 3% appears to be a “threshold” level between non-smokers and smokers (Marshall et al, 1995). Of note, Graham and colleagues demonstrated that a single-breath CO inhalation manoeuvre did not significantly change alveolar CO levels, which might suggest a small effect on blood COHb levels.

Acetylene
In humans, acetylene is rapidly absorbed and rapidly excreted from the body (Jibelian et al, 1981, Schrikker et al, 1989). It is not acutely toxic below its lower explosive limit of 2.5% (25,000 ppm). Inhalation of 10% acetylene (100,000 ppm) for one hour does not cause acute toxicity while inhalation of 33% or 35% caused unconsciousness within 7 and 5 minutes, respectively (Davidson, 1925).
Two fatalities and a near-fatality have been reported after inhalation of 40% (400,000 ppm) acetylene during manufacture with calcium carbide (Carreon, 2000, Jones, 1960), but the cause of these deaths was attributed to the phosphate and amine impurities in crude acetylene and to CO present in the work area.
In the US, the National Institute of Occupational Health and Safety (NIOSH) has set an industrial exposure ceiling of 2,500 ppm for 15 minutes (NIOSH, 2009).
Acetylene at a concentration of 0.3% (3,000 ppm) is well below 2.5% (25,000 ppm). Non-clinical data supported the absence of an expected safety issue.

Methane
Methane, present at a concentration of 0.3%, is not absorbed. Methane does not have significant toxicological effects up to a concentration of 80%. Therefore, the concentration of methane in the mixture does not raise a safety concern.

Contraindications
Key contraindications for performing lung function test are described by the 1996 American Association for Respiratory Care (AARC).
Absolute contraindications are:

- Haemoptysis

- Pneumothorax
- Presence of CO toxicity
- Dangerous levels of oxyhemoglobin

Relative contraindications are:

- Patients with history of coronary artery disease may be at risk for ST segment depression induced by CO.
- Unstable cardiovascular status:
  - Recent Myocardial infarction – waiting time 1 week: Safety data on exercise testing post myocardial infarction show that most patients are stable after 7 days so it is reasonable to perform lung function test safely after this time.
  - Angina pectoris – administration of sublingual glyceryl trinitrate (GTN) prior to test is recommended: The need to perform lung function testing preoperatively in a patient with chronic angina is a common request on lung function departments. The administration of GTN prior to testing is often sufficient to avoid symptoms and permit useful lung function testing to be performed.
- Recent eye surgery – waiting time 2-3 weeks, but longer waiting times may be appropriate depending on the type of eye surgery. Increase of intraocular pressure might occur.
- Presence of acute illness or symptoms that might interfere with the test.
- Recent thoracic or abdominal surgery – waiting time 4 weeks: To avoid rupture site of injury, pain and discomfort.
- Inadequacy of the patient to follow the instructions for the specific test communicated by the technician due to mental or physical disorder.
- Large meal or vigorous exercise immediately before the test.
- Smoking within 24 hours of test administration.
- Reduced vital capacity not within the values needed to accurately interpret the gas transfer results.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Apulco Acometh.

- Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	Myocardial ischaemia
Missing information	Safety in paediatric population

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

The use of lung test gas containing 0.3% of each of the active substances carbon monoxide, methane and acetylene, and 21% of oxygen in the single-breath inhalation test is widely-used and described in guidelines. This test enables the measurement of lung diffusion capacity and also of pulmonary blood flow (cardiac output).
Measurements of lung diffusion capacity and of lung volumes are useful for the characterization of pathophysiological processes in lung disorders. The single-breath diffusion test is indicated to distinguish various conditions of airway obstruction and restriction, lung disease diagnostics and in testing the efficacy of pulmonary disease treatments and is used in clinical trials of inhaled drugs to monitor possible adverse effects on lung function. Generally accepted test criteria for measurement of DLCO by the single-breath procedure are described by a combined task force of ATS and European Respiratory Society.
Although not state-of-the-art in general, measurement of cardiac output through the single breath inhalation test is particularly useful in obese patients and patients who for other reasons are not suitable for ultrasound measurement of cardiac function.

V. USER CONSULTATION

The package leaflet (PL) 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. During the two test rounds, with 10 participants each, 100% of the requested information in the patient information leaflet was found and understood without any problem. This means that the formal success criteria are met: more than 90% of the participants were able to find the requested information, and of those, more than 90% were able to understand the information that was found and would act appropriately. Therefore, the conclusion of this readability test is that the PL can enable the patient to use the medicinal product safely and effectively.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Apulco Acometh 0.30%/0.30%/0.30%, medicinal gas, compressed has a proven chemical-pharmaceutical quality. The product can be considered effective and safe in diagnostic use, i.e. for diagnostic testing of lung function with determination of the lungs' diffusion capacity (or transfer factor) as the main parameter, and of lung volumes and pulmonary blood flow, as additional parameter.

The use of lung test gas containing 0.3% CO, 0.3% CH4, 0.3% C2H2, and 21% O in the single-breath inhalation test is established and described in guidelines. For this application, no original clinical trials or clinical study data were conducted or presented.

In the Board meeting of 2 October 2014, the application was discussed. The Board raised questions regarding the acceptability of industrial carbon monoxide as starting material. The MAH adequately justified that the starting material complies with ICH guideline Q11 'on development and manufacture of drug substances'. The substance is compliant to the European Pharmacopoeia monograph specification. Herewith the concern was adequately addressed. In addition the Board required further explanation about the choice of gas composition. The MAH provided sufficient justification for the presence of acetylene in the formulation, as well as for the use of methane instead of helium.

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 for Apulco Acometh based on literature, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 January 2015.

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

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