swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

PulmoProDiff

International non-proprietary name:	carbon monoxide, helium
Pharmaceutical form:	medicinal gas, compressed
Dosage strength(s):	0.25% / 18%
Route(s) of administration:	inhalation use
Marketing authorisation holder:	Messer Schweiz AG
Marketing authorisation no.:	69970
Decision and decision date:	approved on 17 March 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
EN	European standard (Euronorm)
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ISO	International Organization for Standardization
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
Ph. Eur.	European Pharmacopeia
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
V	Volume

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for carbon monoxide and helium in the above-mentioned medicinal product.

Authorisation in accordance with article 14 paragraph 1 a^{bis} TPA
The applicant requested a simplified authorisation procedure in accordance with article 14 paragraph 1 a^{bis} TPA.

2.2 Indication and dosage

2.2.1 Requested indication

This medicinal gas is for diagnostic use only.
It is used for the diagnostic testing of pulmonary function (determination of the diffusion capacity / transfer factor as the main parameter and determination of the lung volume as an additional parameter).
PulmoProDiff medicinal gas may only be used in patients capable of performing the test, irrespective of age.

2.2.2 Approved indication

This medicinal gas is for diagnostic use only.
It is used for the diagnostic testing of pulmonary function (determination of the diffusion capacity / transfer factor as the main parameter and determination of the lung volume as an additional parameter).
PulmoProDiff medicinal gas may only be used in patients capable of performing the test, irrespective of age.

2.2.3 Requested dosage

Single-breath inhalation, up to 5 times per diagnostic session (repeat measurements).

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	03 July 2024
Formal control completed	19 July 2024
Preliminary decision	15 November 2024
Response to preliminary decision	12 January 2025
Final decision	17 March 2025
Decision	approval

For the application for the authorisation of the medicinal product PulmoProDiff, medicinal gas, compressed, Swissmedic has reviewed the quality exclusively on the basis of primary data. The authorisation of PulmoProDiff, medicinal gas, compressed, is based primarily on the medicinal product ProMED pul-g He/CO 18% (V/V) / 0.25% (V/V), medicinal gas, compressed, which contains the same active substance and has been authorised in Germany for more than 10 years. Apart from the quality-related aspects for which Swissmedic has conducted an independent scientific review, this SwissPAR refers to the authorisation of the foreign medicinal product ProMED pul-g He/CO 18% (V/V) / 0.25% (V/V), medicinal gas, compressed.

3 Quality aspects

3.1 Drug substances

3.1.1 Drug Substance: CO in N_2

INN: carbon monoxide
Chemical name: carbon monoxide
Molecular formula: CO
Molecular mass: 28.01 g/mol
Molecular structure:

Physicochemical properties: Carbon monoxide is a toxic, flammable gas. Carbon monoxide is a metastable molecule. It is almost inert under mild conditions. For safety reasons the drug substance is handled as an API mix containing 5% (V/V) CO in nitrogen (molecular formula N_2), as it may form explosive mixtures in the presence of oxygen, e.g. with air. The physical properties of both CO as pure gas and the API mix CO in N_2 are provided.

Synthesis: For safety reasons, carbon monoxide is handled as a premix (API mix) of carbon monoxide in nitrogen containing 5% (V/V) of carbon monoxide. The manufacturing process of this API mix consists of filling gaseous carbon monoxide and nitrogen by weight. The gas mixture in the cylinders is then homogenised.

Specification: The specifications of CO are in line with the Ph. Eur. monograph No. 2408 “Carbon monoxide”. The specifications of the API mix of carbon monoxide in nitrogen are in line with the Ph. Eur. monograph No. 2904 “Carbon monoxide intermix (5 per cent) in nitrogen”.

Stability: No retest period is defined for carbon monoxide, as it will be analysed directly before manufacturing the API mix. Appropriate stability data have been generated for the API mix of carbon monoxide in nitrogen, resulting in a suitable retest period.

3.1.2 Drug Substance: Helium (He)

INN: helium
Chemical name: helium
Molecular formula: He
Molecular mass: 4.00 g/mol
Molecular structure:
He

Physicochemical properties: Helium is a monoatomic noble gas. It is colourless, odourless, tasteless and non-toxic. The physical properties of helium are provided.

Synthesis: Helium obtained from natural gas sources is used and tested according to Ph. Eur., and filled into gas cylinders and cylinder bundles of different sizes and filling pressures.

Specification: The specifications of helium are in line with the Ph. Eur. monograph No. 2155 “Helium”.

Stability: The drug substance is chemically inert due to its electronic configuration. Therefore, no stability studies have been carried out. A suitable retest period is defined.

3.2 Drug product

Description and composition: The drug product is a compressed gas mixture for medicinal use. The gas mixture is provided in gas cylinders with a filling pressure of 150 bar, at 15 °C. The route of administration is inhalation. The active ingredients are carbon monoxide and helium. The excipients are oxygen and nitrogen. The medicinal product is supplied as a non-sterile dosage form.

Pharmaceutical development: The justification of the chosen composition is based on the literature. Physico-chemical properties are described. The techniques used for the manufacturing process of the medicinal product represent the state-of-the-art and do not require specific developments.

Manufacture: The drug product is provided in gaseous, compressed form and consists of a mixture of single gases which are filled into gas cylinders by the gravimetric filling technique.

Specification: For the control of the finished product, adequate tests and acceptance criteria for release and end of shelf-life have been established. The specifications include relevant physicochemical characteristics, identification of the drug substances, assay and purity tests. The applied test methods are adequately validated according to the recommendations of the current scientific guidelines.

Container closure system: The container closure system consists of seamless gas cylinders made of aluminium equipped with suitable valves. Design, construction, manufacturing and testing of the components of the container closure system are specified in EN and ISO standards relevant for the gas industry.

Stability: Appropriate stability data have been generated in the packaging material intended for commercial use and according to the relevant international guidelines.

3.3 Quality conclusions

Satisfactory and consistent quality of the drug substances and drug product has been demonstrated.

4 Nonclinical aspects

In accordance with Art. 14 para. 1 a^{bis} TPA, Swissmedic has only reviewed the nonclinical overview for the authorisation of PulmoProDiff, medicinal gas, compressed. The approval is based on the medicinal product ProMED pul-g He/CO 18% (V/V) / 0.25% (V/V), medicinal gas, compressed, which contains the same active substances and has been authorised in Germany for more than 10 years.

5 Clinical aspects

For the application for the authorisation of the medicinal product PulmoProDiff, medicinal gas, compressed, Swissmedic has conducted only a summary review of efficacy and safety. The authorisation of PulmoProDiff, 0.25% / 18%, medicinal gas, compressed, is based primarily on the medicinal product ProMED pul-g He/CO 18% (V/V) / 0.25% (V/V), medicinal gas, compressed, which contains the same active substances and has been authorised in Germany for more than 10 years. This SwissPAR refers to the authorisation of the foreign comparator medicinal product ProMED pul-g He/CO 18% (V/V) / 0.25% (V/V), medicinal gas, compressed.

6 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for PulmoProDiff was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

PulmoProDiff 0,25 %/18 % (V/V)

Medicinial gas, compressed

The safety and efficacy of PulmoProDiff 0,25 %/18 % (V/V) medicinal gas, compressed were only checked summarily. The marketing authorisation of PulmoProDiff 0,25 %/18 % (V/V) medicinal gas, compressed is based on PulmoProDiff 0,25 %/18 % medicinal gas, compressed, from May 2023, which is approved in Austria with the same active substance.

Composition

Active substances

Carbon monoxide, helium

Excipients

Oxygen 21% (v/v), nitrogen

Pharmaceutical form and active substance quantity per unit

Medicinial gas, compressed
Carbon monoxide (CO) 0.25% (v/v) and helium 18% (v/v)
at a pressure of 150 bar **(**at 15°C**)**
Colourless, odourless and tasteless gas.
A 10 litre gas cylinder filled under a pressure of 1 bar at 15°C has a volume of 1.46 m^3 gas (1460 litre).

Indications/Uses

This medicinal gas is for diagnostic use only.
It is used for the diagnostic testing of pulmonary function (determination of the diffusion capacity / transfer factor as the main parameter and determination of the lung volume as an additional parameter).
PulmoProDiff medicinial gas may only be used in patients capable of performing the test, irrespective of age.

Dosage/Administration

Adults and paediatric patients

This medical gas is only for inhalation in connection with diagnostic testing for pulmonary function.

Dosage

The medicinal gas is inhaled for a single-breath, which may be repeated at intervals for a maximum of five times per session.

Administration

It must be used in accordance with the operating instructions for the measuring equipment. Measurements may only be performed by qualified medical personnel trained in the performance of pulmonary function tests.

Contraindications

- Presence of CO toxicity
- Dangerous levels of carboxyhaemoglobin

Warnings and precautions

In case of repeated inhalations of the medicinal gas within a short period of time, the risk of an increase in the carboxyhaemoglobin level should be considered. If the medicinal gas is inhaled continuously or repeatedly at short intervals over a longer period of time, an increase in the carboxyhaemoglobin level may occur. This should be controlled with a blood gas test.

Patients with a history of coronary artery disease may be at risk for ST segment depression induced by CO.

Paediatric population

This medicinal gas should be used with caution in children because of the lack of systematic toxicity data for this mixture.

Occasionally symptoms of weariness have been reported, especially in younger children, when spirometry and measurement of diffusing capacity was performed in a single setting.

Interactions

None known.

Pregnancy, lactation

Pregnancy

The safety of inhalation of this medicinal gas during pregnancy has not been assessed. However, no adverse effects are expected when used as directed. PulmoProDiff can be used during pregnancy

when clearly needed, but the maximum number of testing sessions that should be performed is three per trimester.

Breastfeeding

No effects on the breastfed newborn/infant are anticipated. This medicinal gas may be used during breastfeeding.

Fertility

No data available. There are no known effects on fertility.

Effects on ability to drive and use machines

This medicinal gas has no effect on the ability to drive or to operate machines.

Undesirable effects

No undesirable effects are known.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Signs and symptoms
Carbon monoxide poisoning is characterized by signs of reduced oxygen intake, which include impaired consciousness or neurobehavioral symptoms, headache, dizziness, nausea, vomiting and blurred vision; chest pain, dyspnoea, weakness or other vague symptoms.
The use of this medicinal gas in diagnostic lung function tests is associated with a small increase in the blood concentration of carboxyhaemoglobin.

Management of overdose
If an excessive increase in blood carboxyhaemoglobin concentrations is suspected, the patient should immediately receive oxygen treatment via a mask. A blood gas analysis should be performed and the carboxyhaemoglobin concentrations should be less than 5%.
If signs of severe hypoxia, angina pectoris, impaired consciousness or other neurobehavioral symptoms occur, the patient must receive immediate medical attention.

Properties/Effects

ATC code

V03AN

Mechanism of action

Pharmacodynamics

The product is intended for diagnostic purpose only. No biological effects should be expected. Brief exposure in combination with concentration of carbon monoxide and helium used is unlikely to cause any biological effects irrespective of age when used as indicated. See also a special warning for children in Section Warnings and precautions.

Clinical efficacy

No data available.

Pharmacokinetics

Carbon monoxide

Absorption

Inhaled carbon monoxide is rapidly and extensively absorbed into blood. Inhaled carbon monoxide is transported to lung alveoli as a result of convective forces in the respiratory tract and diffusion. At the alveolar gas-blood interface, carbon monoxide dissolves into pulmonary capillary plasma and, from plasma, diffuses into erythrocytes and other tissue. Carbon monoxide binds to haemoglobin to form carboxyhaemoglobin.

Distribution

80% of carbon monoxide is bound to haemoglobin in circulating erythrocytes, 15% to myoglobin and less than 5% to other compounds.

Metabolism

Elimination

Absorbed carbon monoxide is eliminated from the body primarily by exhalation and oxidative metabolism. Oxidative metabolism of carbon monoxide has been estimated to be a relatively small fraction (<10%) of endogenous carbon monoxide production.

Helium

Helium is an inert and insoluble gas which is, after inhalation, exhaled without any absorption in the lung.

Kinetics in specific patient groups

No data available.

Preclinical data

No preclinical data of relevance to the safety assessment are available except as referenced above in the information for healthcare professionals.

Other information

Incompatibilities

None known.

Effects on diagnostic methods

None known

Shelf life

Do not use this medicinal gas after the expiry date which is stated on the gas cylinder after EXP.

Special precautions for storage

Store below 50°C.

All regulations concerning handling of pressure vessels must be followed.

Store in original gas cylinder. Do not transfer contents from original gas cylinder to another gas cylinder.

Store gas cylinders indoors in well-ventilated rooms or outdoors in ventilated sheds where they are protected from rain and direct sunlight.
Protect the gas cylinders from shocks, falls, oxidising and flammable materials, moisture, sources of heat or ignition.

Storage in the pharmacy department

The gas cylinders should be stored in an airy, clean and locked place, for storage of medicinal gas only. Inside this place, a separate premise should be dedicated to the storage of PulmoProDiff gas cylinders.

Storage in the medical department

The gas cylinder should be put in an equipped site with appropriate material in order to hold the gas cylinder vertically.

Transport of gas cylinders

The gas cylinders should be transported with appropriate material in order to protect them from risks of shocks and falls. A particular attention should be also turned to the fastening of the pressure regulator so as to avoid the risks of accidental failures.

Special precautions for disposal and other handling

General

Never use oil or grease, even if the cylinder valve sticks or if the regulator is difficult to connect.
Handle valves and devices belonging to them with clean and grease-free (hand-cream, etc.) hands.
Use only standard devices that are designed for medicinal use.
Check that the cylinders are sealed before they are taken into use.

Preparation for use

Remove the seal from the valve before use.
Use only regulators designed for medicinal purposes. Check that the regulator is clean and that the gaskets are in good condition.
Open the cylinder valve gently and pressurize the regulator, close the valve. Depressurise the regulator.
Check for leakage according to instructions that accompany the regulator. Do not attempt to remedy leakage from the valve or device in any way other than by changing the gasket or O-ring.
In the event of leakage, close the valve and uncouple the regulator. Label defective cylinders, put them aside, and return them to the supplier.

Using the gas cylinder

Smoking and naked flames are absolutely forbidden in areas when gas therapy is given.
Close down the equipment in the event of fire or if it is not being used.
Carry to safety in the event of fire.
When the cylinder is in use, it should be secured in an appropriate support.
Precautions should be taken to prevent blows or falls during storage and transport.
The package must be returned with a minimum residual pressure. This residual pressure protects the cylinder from potential contamination.
After use, the cylinder valve should be closed with normal force. Depressurise the regulator or connection.

Instruction for disposal of gas cylinder

When the gas cylinder is empty, it should not be discarded. Empty gas cylinders will be collected by the supplier.

Authorisation number

69970 (Swissmedic)

Packs

A 10 litre gas cylinder filled under a pressure of 150 bar contains 1.46 m^3 gas at 1 bar and 15 °C (1460 litre).
The aluminium gas cylinder (identification with bright green shoulder and white body) is equipped with a residual pressure valve made of brass with a specific outlet connection.

Marketing authorisation holder

Messer Schweiz AG
Seonerstrasse 75
5600 Lenzburg

Date of revision of the text

Foreign reference product: May 2023
Without safety relevant amendments by Swissmedic: November 2024