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Physician Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT

Medical Carbon Dioxide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Medical Carbon Dioxide specification is: Carbon Dioxide Purity 99.0%

The Medical Carbon Dioxide specification complies with the USP Pharmacopeia monograph [124-38-9].

3. PHARMACEUTICAL FORM

Medicinal gas, liquefied

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

-Carbon Dioxide may be insufflated into the abdominal cavity to distend it to allow the investigation and treatment of intra-abdominal disease

-Carbon Dioxide may be administered through a metered supply, fed into the oxygenator of an extracorporeal circulation of a cardio-pulmonary by-pass system, and when the gas is used for laparoscopic surgery.

4.2 Posology and method of administration

Carbon Dioxide is usually administered through the lungs by inhalation. The major exceptions are when a metered supply is fed into the oxygenator of an extracorporeal circulation of a cardio-pulmonary by-pass system, and when the gas is used for laparoscopic surgery. There are no distinctions between the use of Carbon Dioxide in any age group.

Carbon Dioxide should only be given under the direct supervision of a clinician. Except under special circumstances (e.g. physiological investigations), the inspired concentration should not exceed 5%. However, 100% Carbon Dioxide may be insufflated into the abdominal cavity to distend it to allow the investigation and treatment of intra-abdominal disease,.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Carbon Dioxide is contra-indicated:

- in acidosis
- in respiratory obstruction, the administration of Carbon Dioxide may be dangerous since any further increase in respiratory effort increases negative intra-thoracic pressure
- during resuscitation, where it can be dangerous and should be avoided

4.4. Special warnings and precautions for use

Carbon Dioxide is stored in high pressure gas cylinders as a liquid under pressure. Rapid opening of the valve can cause the discharged gas to re-liquefy. This liquid can cause cold burns if in contact with the skin. Cylinders should only be used in the vertical position with the valve uppermost.

Care is needed in the handling and use of Carbon Dioxide gas cylinders.

4.5. Interaction with other medicinal products and other forms of interaction

Carbon Dioxide interacts with anaesthetic agents when the concentration is raised and gives rise to cardiac dysrhythmias. The threshold for dysrhythmias varies with different anaesthetic drugs.

Carbon Dioxide, by altering pH, influences uptake distribution and action of many drugs including neuromuscular blocking agents, and hypotensive agents. Carbon Dioxide interacts with adrenergic substances such as adrenaline. They should not be used together.

4.6. Pregnancy and lactation

The use of Carbon Dioxide is not recommended in pregnancy but is unlikely to influence lactation.

4.7. Effects on ability to drive and use machines

Inhalation of Carbon Dioxide is not compatible with driving or use of machinery.

4.8. Undesirable effects

Carbon Dioxide may produce unconsciousness in concentrations over 10%. Cardiac dysrhythmias have been reported in patients undergoing laparoscopy as a result of high blood Carbon Dioxide levels. Cardiac arrest due to gas embolism has been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffect@moh.gov.il>

4.9. Overdose

Moderate overdose of Carbon Dioxide less than 5% stimulates breathing. If excessive this may cause extreme respiratory difficulty, raise the blood pressure and lead to nausea and vomiting and occasionally unconsciousness.

In concentrations above 10%, Carbon Dioxide possesses anaesthetic properties.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Medical Gases

The characteristics of Carbon Dioxide are:

- odourless, colourless gas
- molecular weight 44.00
- sublimation point -78.5°C (at 1 bar) .
- density 1.872 kg/m³ (at 15°C)

Carbon Dioxide occurs at approximately 350 vpm in the atmosphere.

The effect of inhaling Carbon Dioxide, or of its accumulation in the body through breathing defects, varies with the tension achieved in the blood, the duration and condition of the exposure and the susceptibility of the individual concerned.

If a normal, conscious individual inhales 5% Carbon Dioxide, the rate and depth of breathing rise and the minute volume increases 2 to 5 fold. The skin becomes pink and warm and there may be sweating and a sense of discomfort. There is no effect on consciousness or mental function, even with long exposures. After a prolonged exposure when the return to breathing air takes place, an "off effect" may develop with malaise, pallor, headache and occasional nausea and vomiting, probably due to the metabolic disturbances as a result of breathing a volatile acid.

As the inspired concentration rises, these effects become exaggerated in proportion to the concentration. At around 8-9% dizziness may develop, and at 10% some subjects become unconscious. Most people will become unconscious at 12.5% and all subjects lose consciousness within 1-2 minutes at 20%. When the concentration is raised to 30% consciousness is lost rapidly, the blood pressure may rise to 27 kpa (200 mm Hg) or higher and there is intense vasoconstriction, a reduction in heart rate to 40-50 beats per minute and ECG changes. All anaesthetic agents reduce these responses to Carbon Dioxide.

5.2. Pharmacokinetic properties

When inhaled, Carbon Dioxide is rapidly distributed throughout the body.

Physiologically, it regulates the rate and depth of breathing and normally there is a constant tension of 5 kpa (40 mm Hg) in arterial blood. The concentration of Carbon Dioxide in the plasma is three times greater than that in red blood cells. The gas is carried partly in solution (2.4 - 2.7 vol %), but mostly either as bicarbonate (42.9 - 46.7 vol %), or as carbamino compound (3.0 - 3.7 vol %). The relative quantities in solution and as bicarbonate regulate the reaction of the blood and buffer changes in pH produced by stronger organic acids.

Carbon Dioxide produced by metabolism plays an integral part in the supply of oxygen to the tissues, since the amount released by haemoglobin at any given oxygen tension is directly related to the Carbon Dioxide tension in the blood. This in turn is governed by tissue activity

in the concentration inhaled. Thus the rate at which oxygen is given up to the tissues is increased when the Carbon Dioxide tension is raised. When a patient becomes apnoeic, Carbon Dioxide produced in the tissues, accumulates in blood at a rate of about 0.7 kpa (5 mm Hg) per minute

5.3. Preclinical safety data

None stated

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Inert gases

6.2. Incompatibilities

Carbon dioxide should not be given when adrenaline is used.

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store below 52 ° C in a well ventilated place

Carbon Dioxide cylinders should be:

- stored under cover, preferably inside, kept dry and clean, and not subjected to extremes of heat or cold and away from stocks of combustible material.
- stored separately from industrial and other non-medical cylinders.
- stored to maintain separation between full and empty cylinders.
- used in strict rotation so that cylinders with the earliest filling date are used first.
- stored separately from other medical cylinders within the store

6.5 Nature and contents of container

A summary of Medical Carbon Dioxide cylinders, their size and construction, type of valve fitted is detailed below:

Cylinders

Cylinder size	Content quantity	Structure material	Valve type	Valve material
0.5-50 liter	0.5-32 kg	Aluminum/ Steel	pin , 4496UNI ,CO2 index DIN6/UNI11144	brass

Cylinders Bundles

Cylinders Bundles size	Content quantity	Structure material	Valve type	Valve material
24m ³ -480m ³	162-700 kg	Steel	UNI/ 4496 DIN 6/UNI11144	brass

All cylinders used for the storage of Carbon Dioxide are manufactured from high tensile steel with a designed working pressure of at least 137 bar g. All cylinders require an appropriate regulator to be fitted prior to use.

The colour coding of the cylinder body according Israeli standard ISO 712 . Cylinders also carry the carbon dioxide name on the body of the cylinder.

Cylinder Valves

Medical Carbon Dioxide cylinders are supplied with two main types of cylinder valves.

Medical Carbon Dioxide small cylinders are fitted with valves with outlet connections pin index/Din 6

Big size cylinders are fitted with outlet connections W21.7X1/14" (DIN6) and are filled with liquid to a specified weight.

6.6 Special precautions for disposal (and other handling)

All personnel handling Carbon Dioxide cylinders should have adequate knowledge of:

- properties of the gas
- correct operating procedures for the cylinder
- precautions and actions to be taken in the event of an emergency

Preparation for Use

To prepare the cylinder for use:

- remove the temper evident seal the valve outlet protection cap. Ensure cap where fitted, is retained so that it can be refitted after use.
- do not remove and discard any batch labels fitted to the cylinder.
- ensure that an appropriate regulator is selected for connection to the cylinder.
- ensure the connecting face on the regulator is clean and the sealing washer fitted is in good condition.
- connect the regulator, using moderate force only and connect the tubing to the regulator / flowmeter outlet. Only the appropriate regulator should be used for the particular gas concerned.
- ensure that the cylinder valves and any associated equipment is not lubricated and kept free from oil and grease

- open the cylinder valve slowly and check for any leaks.

Leaks

Having connected the regulator or manifold yoke to the cylinder check the connections for leaks using the following procedure:

- Should leaks occur this will usually be evident by a hissing noise.
- Should a leak occur between the valve outlet and the regulator or manifold yoke, depressurise and remove the fitting and fit an approved sealing washer.

Reconnect the fitting to the valve with moderate force only, fitting a replacement regulator or manifold tailpipe as required.

- Sealing or jointing compounds must never be used to cure a leak.
- If leak persists, label cylinder and return to Maxima Company

Use of Cylinders

When Medical Carbon Dioxide cylinders are in use ensure that they are:

- only used for medicinal purposes.
- turned off, when not in use, using only moderate force to close the valve
- only moved with the appropriate size and type of trolley or handling device.
- handled with care and not knocked violently or allowed to fall.
- firmly secured to a suitable cylinder support when in use.
- not allowed to have any markings, labels or batch labels obscured or removed
- not used in the vicinity of persons smoking or near naked lights.

After use

When the Medical Carbon Dioxide cylinders are empty ensure that the:

- cylinder valves is closed using moderate force only and the pressure in the regulator or tailpipe released.
- valve outlet cap, where fitted, is replaced
- empty cylinders are immediately returned to an empty cylinder storage area for return to Maxima.

ADMINISTRATIVE DATA

7. MARKETING AUTHORISATION HOLDER

Maxima Air Separation Center LT

10 Haogen st. P.O.B.4124, Ashdod 7714101 . Israel

8. MARKETING AUTHORISATION NUMBER

161-27-35179-00