

**DE NOVO CLASSIFICATION REQUEST FOR
CLEARMATE**

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Isocapnic ventilation device. An isocapnic ventilation device is a prescription device used to administer a blend of carbon dioxide and oxygen gases to a patient to induce hyperventilation. This device may be labeled for use with breathing circuits made of reservoir bags (21 CFR 868.5320), oxygen cannulas (21 CFR 868.5340), masks (21 CFR 868.5550), valves (21 CFR 868.5870), resuscitation bags (21 CFR 868.5915), and/or tubing (21 CFR 868.5925).

NEW REGULATION NUMBER: 21 CFR 868.5480

CLASSIFICATION: Class II

PRODUCT CODE: QFB

BACKGROUND

DEVICE NAME: ClearMate™

SUBMISSION NUMBER: DEN170044

DATE OF DE NOVO: August 23, 2017

CONTACT: Thornhill Research, Inc.
5369 W. Wallace Ave
Scottsdale, AZ 85254

INDICATIONS FOR USE

ClearMate™ is intended to be used by emergency department medical professionals as an adjunctive treatment for patients suffering from carbon monoxide poisoning. The use of ClearMate™ enables accelerated elimination of carbon monoxide from the body by allowing isocapnic hyperventilation through simulated partial rebreathing.

LIMITATIONS

Intended Patient Population is adults aged greater than 16 years old and a minimum of 40 kg (80.8 lbs)

ClearMate™ is intended to be used by emergency department medical professionals. This device should always be used as adjunctive therapy; not intended to replace existing

protocol for treating carbon monoxide poisoning.

When providing treatment to a non-spontaneously breathing patient using the ClearMate™ non-spontaneous breathing patient circuit, CO₂ monitoring equipment for the measurement of expiratory carbon dioxide concentration must be used.

PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF WARNINGS AND CAUTIONS.

DEVICE DESCRIPTION

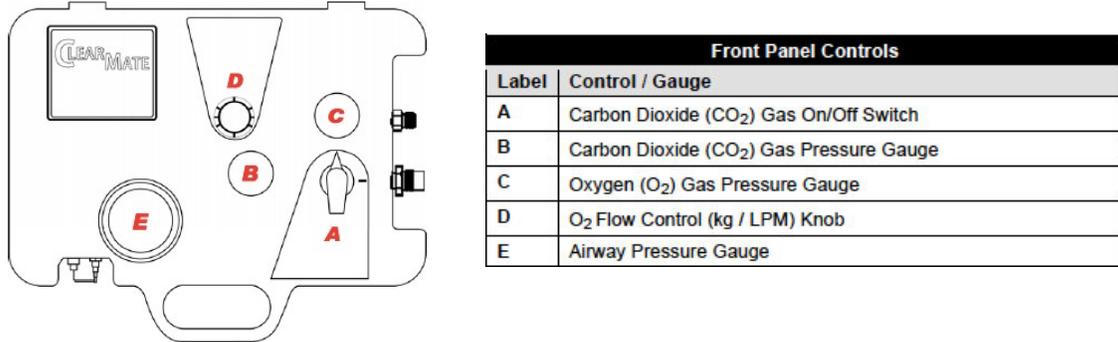
This device is intended to induce isocapnic hyperventilation in patients to speed up elimination of carbon monoxide (CO). Isocapnic hyperventilation can be defined as large increases in patient minute volume with minimal changes in arterial partial pressure of carbon dioxide (CO₂). This device replaces CO₂ levels in the airway, thereby maintaining CO₂ levels in the blood that ultimately causes hyperventilation. This pneumatic device initially provides 100% supplemental oxygen (O₂) at minute volumes selected based on patient weight. If the patient minute volume demand is more than the preset supplement O₂ volume, this device supplies a mixture of 94%/6% (O₂/CO₂), which maintains CO₂ levels in the airway to enable isocapnic breathing by partial simulated rebreathing (of CO₂). This device consists of:

1. The subject of this De Novo, the Control unit (“briefcase”), connects to sources of O₂ and CO₂ (neither gas is supplied with this device). The unit includes pressure gauges to read the source gas pressures. Internal components control supplemental gas flowrates, gas concentrations, and CO₂ diversion away from the gas delivery pathway should O₂ pressures be insufficient. This unit weighs about 2 kg and is pneumatically driven (i.e., no electronics).
2. Two breathing circuits, which are not the subject of this De Novo, can attach to the gas outlet ports of the control unit. These circuits are constructed of reservoir bags (21 CFR 868.5320, Class I), oxygen cannulas (21 CFR 868.5340, Class I), masks (21 CFR 868.5550, cleared under K953107), valves (21 CFR 868.5870, cleared under K142402), resuscitation bags (21 CFR 868.5915, cleared under K912203), and/or tubing (21 CFR 868.5925, cleared under K161420).

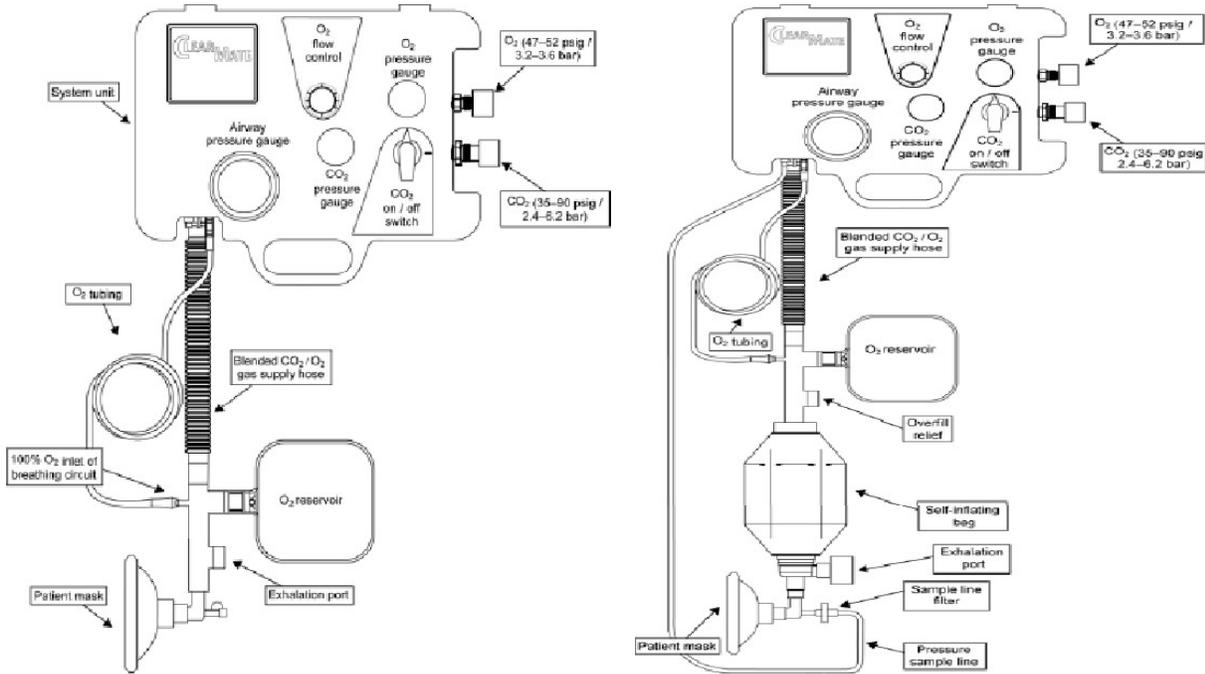
The circuits are described in greater detail below:

- a. The spontaneously breathing patient circuit has an O₂ cannula (for supplemental O₂ delivery) and corrugated cannula (for O₂/CO₂ delivery). The two cannulas deliver gases to the patient mask. An O₂ reservoir is in the pathway to contain excess gases not consumed by the patient.

Figure 1: Front Panel Layout



b. The non-spontaneously breathing patient circuit has an O₂ cannula (for supplemental O₂ delivery), corrugated cannula (for O₂/CO₂ delivery), and pressure sample line. The two cannulas deliver gases past the O₂ reservoir bag and self-inflating bag to the patient mask. Adjacent to the patient mask is the pressure sample line (monitored by the control unit).



Figures 2 and 3: Spontaneously Breathing Patient Circuit (above, left)
 Non-Spontaneously Breathing Patient Circuit (above, right)

3. Hoses for source gas connections and a device stand for steadying the device, which are a subject of this De Novo.

To use this device, O₂ and CO₂ source gases are connected to respective device input ports. A gauge identifies O₂ source gas pressure (expected to be between 47-95psi). Then, the user sets supplemental O₂ minute volume based on patient weight. After minute volume is set, CO₂ can be switched on, at which point the CO₂ gauge will show whether pressures are nominal (expected

between 35-95psi). Once the appropriate circuit is attached, the patient mask should be placed on the patient.

For the spontaneously breathing patient, when breathing exceeds supplemental O₂ minute volume negative pressure – as low as 2cmH₂O – this will cause the demand valve (corrugated tubing pathway) to deliver 94%/6% O₂/CO₂ mixture.

For the non-spontaneously breathing patient, the user manually compresses the self-inflating bag to facilitate the minute volume. Bagging at minute volumes greater than supplemental O₂ settings will cause the demand valve to deliver 94%/6% O₂/CO₂ mixture. The pressure sampling line (only in this circuit) meters the airway pressure.

During use, the device offers the following features:

1. If the O₂ gas supply drops below 40 psig / 2.75 bar, CO₂ gas is diverted from the blended gas pathway to drive an auditory pneumatic alarm.
2. If the CO₂ gas fails, or is exhausted, only O₂ will continue to be delivered to the patient. The device does not alarm in this case.
3. If the O₂ supply fails while the CO₂ source is attached, the system will shut off all gas to the demand valve and again, CO₂ is diverted to drive an auditory pneumatic alarm. The alarm will sound until CO₂ supply pressure is insufficient.

The device is designed such that the CO₂ will neither be connected to the supplement O₂ line nor the blended line in the event of O₂ supply failure.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

A biological risk assessment was performed and found to be in accordance with FDA guidance: *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process* (issued June 16, 2016). Based on the risk assessment:

- The face mask is a component with of the device with limited duration (\leq 24 hours) contact with intact skin. This mask is cleared under K953107 based on similar biocompatibility concerns. This mask is purchased without modification to be connected to the remaining components of this device.
- The face mask (K953107), elbow adapter (K161420), straight adapter (K161420) and resuscitation bag (K912203), and leaflet valve (K142402) recirculates humidified gas. These components are cleared based on similar biocompatibility concerns within the respective 510(k)s. K953107, K912203, and K142402 components are purchased without modification to be connected to the remaining components. K161420 is the

applicant's own device.

- The entire device (control system and breathing circuits) are subject to dry gas pathway concerns. To mitigate dry gas pathway concerns, the applicant conducted particulate matter testing and volatile organic compounds (VOCs) sampling with a toxicological assessment. These tests used acceptable extraction methods that simulated worst case conditions given the intended use of the device.

Based on the submitted testing and evaluations, the applicant has demonstrated device biocompatibility for this intended use.

PERFORMANCE TESTING – BENCH

Breathing Circuit Performance

Ten samples of spontaneously breathing and non-spontaneously breathing circuits (20 samples total) were tested. These tests include minimum pressures for reservoir bag inflation response. One-way valves (e.g., relief valves, demand valves) were individually tested for minimum pressure responses. Testing validated the worst case range of pressures experienced in the circuits, leakage rate of the circuit, and supplemental O₂ flowrate accuracy specifications. Circuits were tested to facilitate the correct gas concentrations output by the control unit. Circuit dimensions were also validated. Lastly, the resuscitation bag was tested to ensure ability to facilitate up to 80BPM. All predefined specifications were met.

Control Unit Performance

Ten control units were tested for specified operation after exposure to normal and excessive source gas pressures. Operation of supplemental O₂ concentration, blended gas concentrations, low O₂ pressures (upper and lower limits) that trigger the CO₂-driven alarm, CO₂ diversion to drive the alarm, blended gas pathway demand valve, blend gas pathway maximum flow rate, and supplemental O₂ flowrate accuracy. All predefined specifications were met.

Use life Performance

The applicant proposed a 5-year use life. Verification consisted of challenging 5 device samples at double the typical maximum breaths per minute and 1.4 times the typical adult tidal volume (per breath) for 10 hours. These conditions are sufficient to simulate 30 minutes of use (as labeled) for approximately 8 patients a year. 8 patients a year is double the anticipated number of cases emergency rooms across the US experience on average (based on 20000 reported cases of suspected CO poisoning by CDC and 5534 US hospitals per the American Hospital Association). After repeated use, there are validations of supplemental O₂ accuracy and CO₂ concentrations based on device settings. The results confirm supplemental O₂ output and O₂/CO₂ demand valve operating specifications, which are the components subjected to most repeated use over the use life.

PERFORMANCE TESTING – ANIMAL

The following animal models of carbon monoxide poisoning were used to confirm proof of principle that isocapnic hyperventilation increases the rate of carbon monoxide removal. The second animal study also supplies safety assurance.

- 1) Fisher JA et al. Isocapnic Hyperpnea Accelerates Carbon Monoxide Elimination. Am J Respir Crit Care Med 1999, 159:1289-1292.

This study investigated the use of isocapnic hyperpnea for treatment of CO poisoning in a dog model. The study concluded that isocapnic hyperpnea more than doubles the rate of carboxyhemoglobin (COHb) elimination induced by normal ventilation with 100% oxygen.

- 2) Krech T et al. Isocapnic Hyperventilation Increases Carbon Monoxide Elimination and Oxygen Delivery, Am J Respir Crit Care Med, 2001, Vol 163, pp458-462.

This animal study evaluated the effect of isocapnic hyperventilation on carbon monoxide elimination and oxygen delivery in mechanically ventilated sheep and concluded that isocapnic hyperventilation increased the rate of carbon monoxide elimination without adversely affecting cardiac output or oxygen delivery

SUMMARY OF CLINICAL INFORMATION

Published studies on healthy volunteers with carbon monoxide exposure were used to support a reasonable assurance of safety and effectiveness for the use of this device in the adjunctive treatment of carbon monoxide poisoning. Additionally, literature demonstrating the use of isocapnic hyperventilation to speed removal of anesthetic agents was used to support effectiveness of this device as anesthetic agents similarly undergo minute ventilation dependent elimination.

Below is the list of published studies used to support this marketing submission. In total, the studies support device safety during use as well as device effectiveness for lowering CO half-life and increased CO elimination. The specific findings of each study are detailed below:

- 1) Anand et al. Hyperventilation with Maintenance of Isocapnia. An “Old New” Method in Carbon Monoxide Intoxication. PLOS One DOI:10.1371/journal.pone.0170621, January 2017.

Thirteen volunteers that were chronic smokers and had baseline COHb levels near 5% were tested to compare non-isocapnic hyperventilation (i.e., 100% O₂ with voluntary hyperventilation) with isocapnic hyperventilation using the ClearMate device for reduction of COHb levels. The study found the elimination half-life of COHb to be significantly lowered when isocapnic hyperventilation was used. No serious adverse events were reported during use of the ClearMate device.

- 2) Rucker et al. Normocapnia Improves Cerebral Oxygen Delivery During Conventional Oxygen Therapy in Carbon Monoxide-Exposed Research Subjects. *Ann Emerg Med.* 2002;40:611-618.

A randomized single blind crossover study on 14 healthy volunteers with CO exposure causing 10-12% COHb evaluated CO elimination times and cerebral blood flow after treatment with hyperoxia with or without normocapnia. Maintaining normocapnia during hyperoxic treatment resulted in significantly higher cerebral blood flow and a 21% decrease in the elimination half-life of CO.

- 3) Takeuchi et al. A Simple “New” Method to Accelerate Clearance of Carbon Monoxide. *American Journal of Respiratory and Critical Care Medicine.*2000: Vol. 161, No. 6.

The purpose of this study was to evaluate the effect of minute ventilation on carbon monoxide elimination in humans. Healthy human volunteers were exposed to CO that caused carboxyhemoglobin levels of 10-12%, then treated with either 100% oxygen at normal minute ventilation or isocapnic hyperventilation at 2-6 times resting minute ventilation. The elimination half-life of COHb fell from 78 to 31 minutes in the treatment group.

- 4) Katznelson et al. Accelerated Recovery from Sevoflurane Anesthesia with Isocapnic Hyperpnoea. *Anesth Analg* 2008;106:486-91.

This randomized controlled trial compared elimination of anesthetic agents with standard ventilation versus isocapnic hyperventilation. Isocapnic hyperventilation increased the respiratory elimination of the anesthetic agents.

- 5) Kateznelson et al. Increased lung clearance of isoflurane shortens emergence in obesity: a prospective randomized-controlled trial. *Acta Anaesthesiol Scand* 2011;55:995-1001.

Forty-four obese elective surgical patients were randomized to conventional recovery vs. isocapnic hyperventilation. Minute ventilation preceding extubation was 22.6 L/min in the isocapnic hyperventilation group and 6.3 L/min in the conventional group. Anesthetic emergence was significantly accelerated in the isocapnic hyperventilation group.

The following study describes use of the ClearMate device (outside the US) in the treatment of severe carbon monoxide poisoning. The device use setting was different from the labeled indication for use (initiated at the scene instead of in the emergency room), and data collection is not consistent with US practice (carboxyhemoglobin levels not reported and EEG used for prognosis and outcome measure). Due to these differences, the study was not used to support efficacy for the current indication but was used to support safety of the device as it reflected real world use in a large number of patients.

Wu et al. A Clinical Study of Treatment for Delayed Neuropsychoneural Sequela Caused by Acute CO Poisoning with ClearMate Gas Poisoning First Aid Ventilator. Chinese Journal of Clinicians, January 2015, Vol. 12.24, No. 12.

Nonrandomized study of patients with acute CO poisoning, control group of 320 received standard treatment and the treatment group of 319 received early treatment with the ClearMate device.

Control group: hyperbaric oxygen (HBO) treatment. 0.22MPa, oxygen treatment for 60 minutes, 1-2 times/day, for 10 days as a therapeutic course.

Treatment group: ClearMate treatment. On site or after arrival in emergency centres, ClearMate treatment was immediately administered to patients once or twice (30 minutes to 1 hour earlier than first HBO treatment in control group), HBO and other treatment were followed afterwards, and a therapeutic course lasted for 10 days.

Endpoint was effective treatment, which was defined as:

Effective-Patient has clear consciousness, continence, major signs of CO poisoning disappearing, EEG shows minor abnormalities, and BI score is 40 - 60.

Noneffective: no improvement in consciousness and signs, exacerbation or death, moderate or serious abnormalities on EEG, and BI score < 40.

Results:

Groups	Patient Number (Case)	Cure (Case)	Effective (Case)	Ineffective (Case)	Total Effective Rate (%)
Treatment Group	319	296	20	3	99.05
Control Group	320	187	62	71	77.81

Although this large study concluded that the ClearMate device caused a significant reduction in neurological adverse events due to carbon monoxide poisoning, there are major limitations of the study that impact the ability to extrapolate these benefits to the requested indication for use:

- 1) Some of the device use was initiated at the scene (before hospital admittance); results from this early use of the device may not be generalizable to emergency room use of the device.
- 2) The study does not report carboxyhemoglobin levels of the subjects. Severity of the carbon monoxide poisoning for all subjects is unknown, and similarity of severity between groups is unknown.
- 3) The study does not describe whether patients receiving ClearMate treatment had spontaneous ventilation, and also does not describe the protocol used for assisted ventilation with the device.

Taking into account the limitations of this study, there is a moderate level of uncertainty for the benefits claimed. There is no device related adverse effects described in this study.

Pediatric Extrapolation

Treatment settings are based on estimated minute ventilation of the patient, which is based on weight. There are no factors other than weight that would limit the extrapolation of adult use to pediatric use.

This device is intended to be used in pediatrics greater than 16 years of age and 80.8 lbs in weight. The labeling limits the minimum weight to 80.8 lbs (40 kg), which is the lower boundary for the weight input setting.

LABELING

Based on the available animal and clinical data, labeling is required to inform proper use on the intended patient populations. The following information is included in the labeling for this device:

1. Age and weight restrictions based on device specifications.
2. Environment of use based on supporting evidence of effectiveness.
3. Use as adjunctive therapy based on demonstrated effectiveness in comparison to existing protocols for treating carbon monoxide poisoning.
4. Monitoring of pertinent patient vital signs during use.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of the isocapnic ventilation device and the measures necessary to mitigate these risks.

Identified Risks to Health	Mitigation Measures
Hypocapnia (lacking CO ₂)	Non-clinical performance testing Labeling
Hypercapnia (excess CO ₂)	Non-clinical performance testing Labeling
Hypoxemia (lacking O ₂)	Non-clinical performance testing Labeling
High airway pressure (e.g., barotrauma)	Non-clinical performance testing Labeling
Adverse tissue reaction	Biocompatibility evaluation

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the isocapnic ventilation device is subject to the following special controls:

- (1) Non-clinical performance testing data must demonstrate that the device performs as intended under anticipated conditions of use, including the following performance characteristics:
 - A. Gas concentration accuracy testing for the range of intended concentrations;
 - B. Airway pressure delivery accuracy testing;
 - C. Supplemental O₂ flowrate accuracy testing;
 - D. Alarm testing; and
 - E. Use life testing.

- (2) The patient-contacting components of the device must be demonstrated to be biocompatible.

- (3) Labeling must include the following:
 - A. Instructions for use;
 - B. A precaution that monitoring of capnography is necessary during treatment with non-spontaneously breathing patients; and
 - C. Use life specification.

BENEFIT/RISK DETERMINATION

The probable benefits are based on information from the nonclinical studies and clinical studies of healthy volunteers with carbon monoxide exposure. The probable benefit of the device is more rapid clearance of carboxyhemoglobin in patients with acute carbon monoxide poisoning. The benefits may be both short and long term. The probability of the subject experiencing a benefit from the device depends on many factors, including the severity of the CO poisoning, the underlying health of the patient and the availability/time to availability of hyperbaric oxygen therapy.

There were no adverse events reported in the literature review for this device. However, given this device delivers mixtures of carbon monoxide and oxygen, the risks associated with the use of the device are hypercapnia, hypocapnia, and hypoxemia. The probability of these outcomes occurring as a result of the device use are extremely small, due to the mitigation of risks by the general and special controls. Effective mitigations include bench testing and labeling that instructs on proper device use. Because this device is intended for use in the emergency room where standard of care – hyperbaric oxygen therapy – may not be available, and the device is essentially delivering the same gas blend that hyperbaric oxygen therapy would (94% O₂ vs 100% O₂) until hyperbaric treatment is available, the benefit risk analysis is highly favorable.

In conclusion, given the available information above, the data support that for emergency room treatment of carbon monoxide poisoning, the probable benefits outweigh the probable risks for the ClearMate device. The device provides benefits and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the ClearMate device is granted and the device is classified under the following:

Product Code: QFB
Device Type: Isocapnic ventilation device
Class: II
Regulation: 21 CFR 868.5480