DE NOVO CLASSIFICATION REQUEST FOR
CURVE™ POSITIVE AIRWAY PRESSURE SYSTEM

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Positive airway pressure delivery system.** A positive airway pressure delivery system is a prescription noninvasive ventilatory device that delivers expiratory positive airway pressure for patients suffering from obstructive sleep apnea. The system also provides positive airway pressure during incipient apnea. The system may include a dedicated flow generator and a patient interface.

NEW REGULATION NUMBER: 21 CFR 868.5273

CLASSIFICATION: Class II

PRODUCT CODE: QBY

BACKGROUND

DEVICE NAME: CURVE™ Positive Airway Pressure System

SUBMISSION NUMBER: DEN170089

DATE OF DE NOVO: December 14, 2017

CONTACT: FRESCA Medical, Inc.
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INDICATIONS FOR USE

The CURVE™ Positive Airway Pressure System is intended to treat Obstructive Sleep Apnea by delivering a therapeutic breathing pressure to a patient. It provides positive airway pressure during expiration and also during an incipient apnea. The system includes a dedicated flow generator and a patient interface, and is intended for use in the home environment. This system is to be used by adult patients weighing more than 66 lbs (30 kg).

LIMITATIONS

For prescription use only.

The CURVE™ Positive Airway Pressure System should only be used with the dedicated flow generator (CURVE™ System Airbox) and patient interface (CURVE™ Mask, Hose and Accessories). The flow generator and patient accessories of the CURVE™ Positive Airway Pressure System are not compatible with any other respiratory systems or accessories.

The CURVE™ Positive Airway Pressure System is not to be used with supplemental oxygen.

The CURVE™ Positive Airway Pressure System should not be used in patients with severe bullous lung disease, a pneumothorax, pathologically low blood pressure, dehydration and cerebrospinal fluid leak, recent cranial surgery or trauma.

Not for use in an MR environment.

PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The CURVE™ Positive Airway System is comprised of five components: a Nasal Pillow, Headgear, Valve, Hose, and Flow Generator.

The CURVE™ System Airbox is a flow generator that provides airflow and pressure to the mask and delivers therapeutic pressure to the patient's airway during disordered breathing. The valve allows positive airway pressure to be generated during expiration but at the same time it (1) reduces the airflow required to provide positive airway pressure during inspiration and expiration, and (2) utilizes the patient's own breathing effort during both normal inspiration and expiration. During disordered breathing events, such as apnea or hypopnea, the valve opens to allow positive airway pressure to be provided to the patient directly from the flow generator. In addition, the valve is designed to channel excess airflow directly into the room, thereby minimizing spikes in pressure and preventing carbon dioxide rebreathing from the hose.

The CURVE™ System patient interface consists of a nasal pillow mask, headgear and a hose. The nasal pillow mask includes the valve and the mask is held in contact with the patient's nares via the headgear. The nasal pillow mask is available in three sizes (small, medium and large). The hose connects the flow generator to the valve in the mask to deliver air from the flow generator to the mask.

The CURVE™ System is designed to have pressurized air from the flow generator always available to provide airway support. During treatment, the flow generator is never "off" or paused. Pressurized air is always being delivered through the hose to the valve, and flows into the mask whenever there is a drop in pressure or flow rate.

The CURVE™ System flow generator can only be used with the CURVE™ System patient interface and vice versa. The size and configuration of the Curve System hose and

flow generator connectors are designed to prevent connection to a standard Continuous Positive Airway Pressure (CPAP) hose, mask or flow generator.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The CURVE™ Positive Airway System includes components that have externally communicating patient contact via gas pathway for permanent duration. The flow generator, mask, hose and valve of the subject device also have contact with the dry gas pathway.

The complete device in its final, finished form was subjected to biocompatibility testing in accordance with the FDA guidance document, "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process.'" The following tests were conducted to assess biocompatibility of the device for the externally communicating components for permanent duration:

- Cytotoxicity
- Sensitization
- Intracutaneous reactivity
- Extractables and leachables testing with a risk assessment

The following additional tests were conducted for the dry gas contacting components:

- Volatile organic compounds (VOC) (EPA Compendium Method TO-15) to demonstrate that Total VOCs < 5,000 ppb,
- Particulate matter EPA PM2.5 to demonstrate that the device shall not emit more than 12 ug/m^3 of particulates smaller than 2.5 microns,
- Ozone gas analysis (U.S. Department of Labor, Occupational Safety and Health Administration (OSHA) – Test Method ID-214) to demonstrate ozone concentration < 0.050ppm,
- Carbon monoxide and carbon dioxide gas analysis to demonstrate carbon monoxide concentration < 9 ppm and carbon dioxide concentration <10,000 ppm

All tests passed. The results demonstrated the biocompatibility of the device.

SHELF LIFE/REPROCESSING/STERILITY

The CURVE™ Positive Airway System is a single patient, multi-use device and is not provided sterile. All components are reusable for up to 90 days. The device is provided with cleaning and disinfection instructions.

The cleaning procedures for the reusable main unit were validated following the recommendations of the FDA Guidance Document "Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling", AAMI TIR30 "A compendium of processes, materials, test methods, and acceptance criteria for cleaning reusable medical devices", and AAMI TIR12:2010 "Designing, testing, and labeling reusable medical devices for reprocessing in health care facilities: A guide for medical device

manufacturers." The cleaning validation study included 6 simulated use cycles of soiling and cleaning of the device. After 6 cycles, the test results showed no visible soil on the device components and analysis of the extract showed that residual soil, as shown by the carbohydrate and protein markers, was reduced to levels below the specified endpoints. The 6 simulated use cycles were shown to reflect that accumulation of soil will be limited over the recommended 90-day use period.

ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY

The CURVE™ Positive Airway System was tested in accordance with the following consensus standards and conformed with the following electromagnetic compatibility (EMC), electrical, mechanical and thermal safety standards:

- IEC 60601-1-2:2014: Medical Electrical Equipment - Part 1-2: General Requirements for Basic Safety and Essential Performance - Collateral Standard: Electromagnetic Compatibility-Requirements and Tests.

- AAMI / ANSI ES60601-1:2005/(R) 2012 and A1:2012, Medical Electrical Equipment - part 1: General Requirements for Basic Safety and Essential Performance.

- IEC 60601-1-11 Edition 2.0 2015-01: Medical electrical equipment - Part 1-11: General requirements for basic safety and essential performance - Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment

The device was also tested for static magnetic field testing to characterize the strength and safe exposure distance of the magnet present in the device.

MAGNETIC RESONANCE (MR) COMPATIBILITY

The device has not been tested for MRI compatibility and should not be used in an MRI suite.

SOFTWARE

The De Novo request provided adequate software documentation consistent with a "Moderate" level of software concern as discussed in the FDA Guidance Document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," issued May 11, 2005.

Software validation and verification testing demonstrated that the device met its design, implementation, and cybersecurity specifications.

PERFORMANCE TESTING – BENCH

The non-clinical testing for the device consisted of verification and validation testing of hardware and software.

The following bench tests were performed

- Device integrity testing to verify the hose crush force and confirm that the hose is crush resistant and can maintain an adequate flow rate to fill the airway.
- Hose torsion force testing to confirm the hose can spin freely without disconnecting during normal use by measuring peak torque at each interface with a torque wrench.
- Verification of appropriate hose removal force at the mask-valve interface and at the generator interface to ensure unintentional disconnection does not occur, but patients can easily disconnect hoses when necessary.
- Testing of valve removal force (force required to remove the valve from nasal pillow), pillow crush force, side strap removal force, backstrap removal force to ensure unintentional disconnection does not occur, but patients can easily disconnect components when necessary.
- Acoustics test was performed by measuring the noise level of the mask. The noise level was measured to be ≤30dB at 10cmH_2O setting, in accordance with ISO 17510 and 3744.
- Carbon dioxide rebreathing test measured carbon dioxide rebreathing in accordance with ISO 17510. Per that standard, under normal conditions the increase in carbon dioxide from baseline was ≤ 20%. For single fault conditions, the increase in carbon dioxide from baseline was ≤ 60%.
- System testing:
    - Flow rate: delivered airflow to mask at various generator settings was measured. Flow rate of ≥ 10 l/minute confirmed that airflow path is not occluded or restrictive.
    - Maximum expiratory pressure: the pressure drop into the mask was measured. A ≤2 cm H_2O pressure greater than the measured flow generator pressure confirmed sufficient ease of exhalation.
    - Inhalation pressure: the pressure drop into the mask was measured. A ≥ -1.0 cm H_2O pressure drop at an inhalation flow rate of 25 l/minute confirmed ease of inspiration.
    - Intra-mask static pressure: the measured pressure in the mask resulted in therapeutic pressure to the patient.
    - Air bolus testing: an air bolus of 2 liters over 1 second was applied. No impact on specifications for generator and mask pressures, airflow, exhaust pressure and inspiratory resistance was recorded.
- Packaging testing subjected devices to simulated shipping challenges (as per the International Safe Transit Association Standards 2A) with no impact on specifications for the flow generator, mask pressures, minimum airflow, exhaust pressure and inspiratory resistance.
- Use Life Testing was conducted to verify the recommended use life of the mask for up to 90 days. Testing included 712,800 simulated breathing cycles and 100 cleaning cycles and the device continued to meet the performance specifications following testing.
- Maximum limited pressure testing was performed. Under normal use conditions, testing confirmed that the maximum pressure output of the flow generator did not exceed 20 cm H_2O. Under simulated fault conditions, testing confirmed that the maximum pressure output of the flow generator did not exceed 30 cm H_2O.

- Maximum output temperature testing of humidified gas was not required for this submission because the device does not output humidified gas.
- Waveform testing was conducted during simulated breathing conditions for evaluating pressure and airflow response over a range and combination of high and low breath rates and tidal volumes and a quantitative analysis of differences in waveform characteristics (e.g. shape; periodicity; inflection points; slope; and magnitude) to support pressure and flow responses were equivalent between clinical device configuration and final device configuration. Four simulated "patients" were defined for purposes of evaluating the pressure and airflow response over a range and combination of high and low breath rates and tidal volumes. Waveforms were obtained for each of the four simulated "patients" at set pressures of 4, 12 and 20 cmH_2O during the following simulated breathing conditions:
    - Normal breathing.
    - Hypopnea (with an airflow reduction of 30-40%).
    - Hypopnea (with an airflow reduction of 50-60%).
    - Hypopnea (with an airflow reduction of 70-80%).
    - Apnea (at end of expiration).
    - Apnea (mid-inspiration)

SUMMARY OF CLINICAL INFORMATION

A clinical study in adults was used to support a reasonable assurance of safety and effectiveness for the use of this device for treatment of Obstructive Sleep Apnea.

Purpose/Study Design

Obstructive sleep apnea (OSA) is effectively treated using continuous positive airway pressure (CPAP) devices. This prospective, controlled, randomized, cross-over clinical study was designed to demonstrate whether the resultant OSA treatment with the subject device (clinical study configuration, referred as FRESCA) mask is non-inferior to treatment with the patient's prescribed CPAP mask**.**

Materials and Methods

Patients that were being successfully treated for OSA with a commercial CPAP device were randomized to Sequence 1 (polysomnography (PSG) control night with their existing CPAP mask followed by a PSG treatment night with the FRESCA mask) or Sequence 2 (PSG treatment night with the FRESCA mask followed by a PSG control night using their existing CPAP mask). Both nights were conducted in the sleep lab up to 14 days apart. Both nights utilized the same in-lab CPAP blower.

If the patient completed both study nights (i.e. sleeping >4 hours without technical PSG difficulty), then their apnea-hypopnea index (AHI) and oxygen desaturation index (ODI) data were entered into the database to determine whether the mean results of all FRESCA mask treatment nights were non-inferior (difference < 5 units) to those mean results from all the control nights with the patients' CPAP mask.

Inclusion Criteria
Prior to study enrollment, subjects were assessed to determine if they met the following inclusion criteria:

- Male or Female 18-70 years old;
- Qualifying diagnostic PSG/HSAT (Home Sleep Apnea test) resulting in AHI > 5 events/h of sleep;
- Qualifying titration PSG: In lab titration within the past 12 months and therapeutic pressure resulting in AHI < 5 events/h;
- Primary medical diagnosis of OSA/ Hypopnea syndrome and on CPAP treatment > 1 month;
- Current user of nasal mask or nasal pillow mask;
- Have regular usage of their CPAP machine (sufficient amount of mask use to enable tolerance of at least 4 hours of mask use for study nights) confirmed by SD card download;
- No significant changes in the subject's general health and no change in weight greater than ±10 lbs since titration PSG was performed and CPAP therapy initiated (confirmed from medical records);
- BMI < 35 kg/m^2;
- Must be able to be fit properly with FRESCA mask;
- Must be able to comply with all study requirements as outlined in the protocol;
- Must be able to understand English and be willing to provide written informed consent.

Exclusion Criteria
The following criteria excluded subjects from possible participation in this clinical study:

- Subjects with non OSA sleep disorders;
- Substantial central or mixed apneas (Central and Mixed apnea index ≥ 5 events/h);
- Subjects actively using bi-level PAP or require oxygen therapy;
- Subjects using a full face mask or chin strap;
- History of severe cardiovascular disease, including NYHA Class III or IV heart failure, CAD with angina or MI/stroke within past 6 months;
- Subjects who are medically complicated or who are medically unstable (i.e. cancer, dementia, unstable cardiac or respiratory disease, or unstable psychiatric illness);
- Potential sleep apnea complications that in the opinion of the investigator may affect the health and safety of the participant including: uncontrolled hypertension or hypotension, low blood oxygen (oxygen desaturations nadirs below 75% on their diagnostic PSG), or use of medication or other treatment which may pose additional risk to the subject;
- Subjects exhibiting any flu-like or any upper airway tract infection symptoms at time of assessment;
- Subjects with ongoing severe nasal allergies or sinusitis or difficulty breathing through the nose; persistent blockage or one or both nostrils; or any nasal or facial abnormalities that would not allow adequate placement of the device;
- Subjects with prior surgical intervention for obstructive sleep hypopnea/ apnea syndrome;
- Currently working nights, rotating night shifts, planned travel across two or more time zones required during study period, or within two weeks prior to study enrollment, or sleep schedule not compatible with sleep lab practices;

- Unstable use of medications or other agents that may affect sleep or PSG (sedatives or hypnotics);
- Consumption of > 500mg caffeine per day (e.g. > 8 cola-type beverages, > 5 cups of coffee);
- Pregnant (confirmed verbally);
- Currently enrolled in any other research study.

Selection of Doses in The Study
The FRESCA mask is intended to be used with positive airway pressure devices, such as CPAP, operating at or above 4 cm H2O and up to 20 cm H2O (i.e. ranges of pressure across which CPAP machines are titrated). The pressure used for each patient was the same as their prescribed pressure as determined by his/her historical titration PSG study. Each patient's prescribed pressure setting was used for all nights of treatment.

Primary Efficacy Variable(s)
The co-primary efficacy assessments are AHI and ODI as determined by a valid PSG study. These primary assessments are compared between the control CPAP mask and the FRESCA mask treatments, and both AHI and ODI assessments needed to be non-inferior for primary study success.

Results
Of the 47 subjects enrolled in the study, thirty-six (36) patients (26 men; mean age 51years, range 32 - 69) completed both study nights with valid PSG results. Prior to being treated for their OSA, the patients were documented in a diagnostic PSG with a mean AHI of 26.1 events/h (range: 5.7 – 74.4) and a mean ODI of 16.4 events/h (range: 0.0-74.4).
The summary of the results is presented in Table 1.

Table 1: AHI and ODI endpoint analyses

N=36 patients	**FRESCA** Mean Range	**Commercial CPAP Mask** Mean Range	**Difference between the means**	**p-value of non-inferiority test**
AHI results (events per hour)	3.0 0.0 – 23.5	2.4 0.0 – 33.7	0.6	p<0.001
ODI results (events per hour)	1.4 0.0 – 6.5	1.1 0.0 – 10.2	0.3	p<0.001

Both the AHI and the ODI endpoint analyses demonstrated the FRESCA mask results were non-inferior to the results with the commercial CPAP mask. All adverse events were mild or moderate in nature and were resolved by the time of the PSG completion. There were no serious adverse events. The adverse events reported are displayed below in Table 2.

Table 2: Adverse events listingAdverse event	Number of subjects (n=47)
Difficulty breathing through study device	4 (8.5%)
Skin/nose irritation	2 (4.3%)
Difficulty sleeping due to study device	1 (2.1%)
EKG irregularity	1 (2.1%)
Headache	1 (2.1%)
Pain in the nose	1 (2.1%)
Unable to tolerate mask	1 (2.1%)

Conclusion:
The clinical study was a prospective, controlled, randomized, cross-over clinical study designed to demonstrate whether the resultant OSA treatment with the FRESCA mask is non-inferior to treatment with the patient's prescribed CPAP mask.

Baseline characteristics support use of the FRESCA mask in all AHI severities (mild, moderate, severe) with an equivalent number of subjects in each severity successfully completing study requirements. Minor adverse events were resolved without medical intervention or other action, and without clinical sequelae. This study demonstrated that there are no significant clinical differences between typical commercial CPAP nasal or nasal pillow masks and the FRESCA mask.

The clinical device configuration was modified to produce the final finished device. This was mitigated by in vitro bridging using waveform testing to demonstrate there were no significant differences in performance characteristics that would affect clinical function between the device tested in the clinical trial and the final finished device.

Pediatric Extrapolation
In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

LABELING

The labeling (User Instructions) meets the requirements of 21 CFR 801.109 for prescription devices. The user instructions include the following:

a. A description and function of all components of the system and instructions regarding how to use each component for therapy;
b. A description of pressure settings range available with the system;
c. The available flow provided by the system at different pressure settings;
d. A warning that the device should not be used with supplemental oxygen;
e. Contraindications listing patient comorbidities that would preclude use of the system; and
f. A warning stating that device should only be used with the CURVE System Airbox and the CURVE Mask, Hose and Accessories are not compatible with any other respiratory systems or accessories.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of the positive airway pressure delivery system and the measures necessary to mitigate these risks.

Identified Risk	Mitigation Measures
Adverse tissue reaction	Biocompatibility evaluation Labeling
Electromagnetic interference with other devices	Electromagnetic compatibility testing Labeling
Infection	Reprocessing validation Labeling
Device software failure leading to ineffective treatment	Software verification, validation, and hazard analysis
Device hardware failure/malfunction leading to high airway pressure, carbon dioxide rebreathing or ineffective treatment	Non-clinical performance testing Labeling
Electrical shock injury or thermal injury	Electrical safety, thermal safety, and mechanical safety testing Software verification, validation, and hazard analysis Labeling
Use error leading to ineffective therapy or patient injury	Labeling

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the positive airway pressure delivery system is subject to the following special controls:

1. The patient-contacting components of the device must be demonstrated to be biocompatible.
2. Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use, including the following:
    a. Waveform testing must simulate breathing conditions and evaluate pressure and airflow response over a range and combination of high and low breath rates and tidal volumes.
    b. Use life testing must demonstrate adequate device performance over the labeled use life of the device.
    c. Device integrity testing must demonstrate the device can withstand typical forces expected during use.
    d. Carbon dioxide rebreathing testing must be performed.
    e. System flow rate, maximum expiratory pressure, inhalation pressure, and intra-mask static pressure testing must be performed.

f. Air bolus testing must demonstrate that the device can withstand worst-case scenario air pressures.
g. Maximum limited pressure testing of the flow generator in single fault condition must be performed.
h. Maximum output temperature testing of delivered gas, if humidified, must be performed.

3. Performance data must validate reprocessing instructions for any reusable components of the device.
4. Performance data must demonstrate the electrical, thermal, and mechanical safety and the electromagnetic compatibility of the device.
5. Software verification, validation, and hazard analysis must be performed.
6. Labeling must include the following:
    a. Therapy pressure range;
    b. Use life and replacement schedule for all components;
    c. Cleaning instructions; and
    d. Instructions for assembly and connection of device components.

BENEFIT/RISK DETERMINATION

The risks of the device are based on nonclinical laboratory studies as well as data collected in the clinical studies described above. The device exhibited an acceptable safety profile in the clinical study which was conducted. No device-related serious adverse events were observed.

The CURVE™ Positive Airway Pressure System risks include device failure, air leaks due to poor adjustment of headgear or detachment of headgear during use, air leaks due to incomplete or improper seals of nasal pillow, poor flapper performance resulting in difficult inhalation or lack of therapy and carbon dioxide rebreathing due to lack of a proper seal of the flow generator. Although these risks are associated with all positive airway pressure therapies, these device malfunctions or device related adverse events were not seen in the clinical studies. The probability of a harmful event with the use of this device is relatively low. As the system interacts only with the nasopharynx, the patient can breathe using the mouth or discontinue use if any discomfort is experienced.

The sponsor conducted a prospective, controlled, randomized, cross-over clinical study to demonstrate the device can treat OSA and that treatment with the subject device is non-inferior to treatment with CPAP, the standard of care for OSA. OSA is a sleep disorder characterized by snoring, repetitive apneas, sleep disruption due to frequent arousals, and, for some, daytime sleepiness. Untreated OSA is associated with adverse health outcomes, including decreased quality of life, psychological symptoms, insulin resistance, and increased risk for cardiovascular disease and mortality.

Patient Perspectives

The conducted clinical study showed that patients could use the subject device with comfort with minor adverse events that were resolved quickly by the time of PSG completion. No specific patient related outcome scales were evaluated.

Benefit/Risk Conclusion

In conclusion, given the available information above, the data support that the probable benefits outweigh the probable risks for the CURVE™ Positive Airway Pressure System to provide OSA treatment. The device provides benefits and the risks can be mitigated using general controls and the identified special controls.

CONCLUSION

The De Novo request for the CURVE™ Positive Airway Pressure System is granted and the device is classified under the following:

Product Code: QBY
Device Type: Positive airway pressure delivery system
Class: II
Regulation: 21 CFR 868.5273