DE NOVO CLASSIFICATION REQUEST FOR CERÊVE SLEEP SYSTEM

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Thermal System for Insomnia. A thermal system for insomnia is a prescription device for use in patients with insomnia that is used to apply a specified temperature to the skin surface.

NEW REGULATION NUMBER: 882.5700

CLASSIFICATION: CLASS II

PRODUCT CODE: PLU

BACKGROUND

DEVICE NAME: CERÊVE SLEEP SYSTEM

SUBMISSION NUMBER: DEN140032

DATE OF *DE NOVO*: OCTOBER 20, 2014

CONTACT: CERÊVE, INC.
333 ALLEGHENY AVE, SUITE 201
OAKMONT, PA 15139

REQUESTER'S RECOMMENDED CLASSIFICATION: CLASS II

INDICATIONS FOR USE

The Cerêve Sleep System is indicated to reduce sleep latency to Stage 1 and Stage 2 sleep in patients with primary insomnia.

LIMITATIONS

The sale, distribution, and use of the device are restricted to prescription use in accordance with 21 CFR 801.109.

Other than reduction of sleep latency to Stage 1 and Stage 2 sleep, the efficacy of other sleep measures associated with insomnia has not been established by the Cerêve Sleep System in controlled clinical trials.

Limitations on device use are also achieved through the following statements included in

the Directions for Use manual:

Warning:

- If the patient has a skin condition on his/her forehead that may make wearing the Cerêve Sleep System uncomfortable, the physician will need to evaluate the skin condition prior to use of the Sleep System.
- Patients with cold sensitivity reactions such as Raynaud's Disease should not use cooling therapies in order to avoid cold sensitivity reactions that may include cold sensations, color changes in their skin in response to cold, and a numb, prickly feeling or stinging pain upon warming.

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

DEVICE DESCRIPTION

The Cerêve Sleep System is a cooling device comprised of three components: the bedside unit, the forehead pad, and headgear. The device pumps chilled fluid through the forehead pad, at patient selectable temperatures in a narrow range between 14 and 16 °C. An illustration of the device is provided in Figure 1 below.

Figure 1. Cerêve Sleep System (left) and schematic of device in home use environment (right).

The Cerêve Sleep System bedside unit provides the means to cool the fluid and transport the fluid from the unit to the forehead pad. The bedside unit utilizes solid state thermoelectric devices to cool a thermal transfer fluid consisting of purified water and isopropyl alcohol. The unit has a user interface that allows the user to turn the unit on and off, and adjust the temperature within the range of 14 to 16 °C. The unit contains a pump for circulating the thermal transfer fluid through the tubing and forehead pad. The bedside unit is powered by a DC electrical power supply and is controlled by an integral control unit (CU) and its firmware. The Cerêve Sleep System Headgear and Forehead pad contain the wearable portion of the sleep

system. It is comprised of a multi-use urethane forehead pad that is in contact with the patient's head, the Lycra® headgear that holds the forehead pad in place, and a 6 foot section of insulated tubing that connects to the Cerêve Bedside Unit.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The forehead pad is constructed of urethane and is in direct contact with the patient's skin. Each use of the device results in a limited contact duration of less than 24 hours. Therefore, per ISO 10993-1 (Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing), cytotoxicity, sensitization, and irritation testing were performed on the forehead pad and the results were found to be acceptable.

The thermal fluid is not intended to contact the patient; however, if the forehead pad is damaged, there could be potential for the fluid to come in contact with the patient during use. Therefore, the thermal fluid also was tested per ISO 10993-1 for cytotoxicity, oral toxicity, and ocular irritation and the results were found to be acceptable.

The headgear is constructed of clothing grade Lycra®, which is commonly used to fabricate clothing in contact with intact skin. In lieu of biocompatibility testing, justification was provided that the same material has a demonstrated history of safe use.

STERILITY

The Cerêve Sleep System is a non-sterile, reusable device. It is intended only for external use. Cleaning instructions for the bedside unit and forehead pad are provided in the labeling.

ELECTROMAGNETIC COMPATIBILITY (EMC) AND ELECTRICAL SAFETY

The Cerêve Sleep System was tested for and found to be in compliance with the following standards for electromagnetic compatibility and electrical safety:

Table 1 – Summary of EMC and Electrical Safety Testing

Standard	Title
AAMI ANSI ES60601-1:2005/(R)2012 and A1:2012, C1:2009/(R)2012 and a2:2010/(r)2012	(Consolidated Text) Medical Electrical Equipment - Part 1: General Requirements For Basic Safety And Essential Performance
AAMI ANSI IEC 60601-1-2:2014	Medical Electrical Equipment -- Part 1-2: General Requirements For Basic Safety And Essential Performance -- Collateral Standard: Electromagnetic Disturbances -- Requirements And Tests
IEC 60601-1-11 Edition 1.0 2010-04	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

SOFTWARE

The Cerêve Sleep System bedside unit is powered by a DC electrical power supply and is controlled by an integral control unit (CU) and its firmware.

The Level of Concern of the software for the Cerêve Sleep System was assessed using the FDA guidance document, "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices" and resulted in a determination of a **Moderate** level of concern.

- The software regulates the temperature of thermal fluid at the output of the bedside unit to the temperature set point selected by the patient, and maintains the temperature set point without requiring additional patient adjustment by pulse-width modulation (PWM).
- The software will allow for variation of the fluid temperature set point at the output of the bedside unit in preset increments based on patient adjustment.
- The software also includes additional safety features that provide for automatic shutdown for fault conditions. All of the fault conditions are backed up by hardware controls in the case of software loss of control.

Software validation was performed on all key performance characteristics for temperature control. Additionally, software validation was performed on all safety critical performance features for the following requirements: unit temperature (thermistor control), unit temperature (thermal cut-out), fluid temperature (thermistor control), and fluid temperature (thermal cut-out).

PERFORMANCE TESTING – BENCH

The Cerêve Sleep System was tested to characterize the device outputs at each temperature setting on the controller of the bedside unit. The non-clinical bench tests performed to support the performance and safety of the Cerêve Sleep System are summarized in the table below:

Table 2 – Summary of Non-clinical Testing

Test	Test Summary
Fluid flow rate	The fluid flow rate through the forehead pad was evaluated and verified to be within specification.
Time to reach target temperature	The time for the device to reach the target temperature was verified to be within specification.
Maintenance of target temperature	The ability of the device to maintain the target temperature setting for 8 hours was verified while operating at an ambient temperature of b(4) GCI/ and applying heat to the forehead pad.
Sound level	The sound level generated from the device during use was verified to be in an acceptable range.
Temperature drop across forehead pad	The temperature difference between the outlet of the forehead pad and inlet of the forehead pad was verified to be less than or equal to b(4)) while applying heat to the forehead pad.

Test	Test Summary
Temperature drop from bedside unit and forehead pad	The temperature difference between the forehead pad and bedside unit was verified to be less than or equal to b(4) CCI/
Tubing and connector strength	The tubing connection strength was verified to withstand a minimum tensile force.
Puncture load on forehead pad	The forehead pad integrity was verified to withstand a minimum puncture load force without rupture.
Kinked/occluded tubing and leakage testing	The device was verified not to leak when the tubing was simulated in a kinked or occluded condition. The forehead pad assembly was also verified not to leak when exposed to tensile forces beyond those anticipated during use conditions.
Simulated distribution and conditioning	The packaged device was confirmed to be undamaged and in operable condition following simulated distribution conditions in accordance with ASTM D4169-14 (Standard Practice for Performance Testing of Shipping Containers and Systems) and conditioning in accordance with ASTM D4332-14 (Standard Practice for Conditioning Containers, Packages, or Packaging Components for Testing).

SUMMARY OF CLINICAL INFORMATION

Three clinical studies were conducted with the Cerêve Sleep System in patients with primary insomnia. The studies are further summarized below.

1. **CIP-006:**

   Design: This was the pivotal study in support of the Cerêve Sleep System. This was a randomized, multi-center (7 U.S. sites), sham-controlled study of 116 primary insomnia adult subjects.

   Eligible subjects were provided with information about the study design and risks and signed the informed consent document. Criteria for inclusion included:

   - Age ≥ 22 years
   - Diagnosis of insomnia that meets criteria for Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM IV) diagnosis of primary insomnia and International Classification of Sleep Disorders (ICSD) general insomnia and Research Diagnostic Criteria (RDC) insomnia disorder criteria
   - Agreement to remain alcohol free and avoid drugs that could affect sleep during the study
   - >14 on the Insomnia Severity Index
   - Sleep-Wake diary that demonstrated sleep efficiency <85% on at least 50% of nights over a 7 day consecutive period

   Criteria for exclusion included:

   - Neuropsychiatric disorders that may affect sleep, brain function or cognition, such as current major syndromal psychiatric disorders, including DSM-IV mood, anxiety, psychotic, and substance use disorders

- Specific exclusionary diagnoses included major depressive disorder, dysthymic disorder, bipolar disorder, panic disorder, obsessive compulsive disorder, generalized anxiety disorder, any psychotic disorder, and any current substance use disorder. Unstable medical conditions including severe cardiac, liver, kidney, endocrine (e.g., diabetes), hematologic (e.g., porphyria or any bleeding abnormalities), other impairing or unstable medical conditions or impending surgery, central nervous system disorders (e.g., head injury, seizure disorder, multiple sclerosis, tumor), active peptic ulcer disease, inflammatory bowel disease, and arthritis (if the arthritis impacts sleep)
- Raynaud's disease
- Irregular sleep schedules including shift workers
- Latency to persistent sleep < 15 minutes on either the sleep disorder screening night or baseline polysomnograph (PSG)
- A sleep efficiency >85% on either the sleep disorder screening night or baseline PSG
- An AHI (apnea hypopnea index) >10 and/or a periodic limb movement arousal index (PLMAI)>15 from screening night
- Body mass index >34
- Use of medications known to affect sleep or wake function
- Consumption of more than one alcoholic drink per day
- Consumption of caffeinated beverages >4 per day

Following completion of 2 nights baseline PSG recordings in a sleep lab setting, subjects were randomized to receive 2 additional nights PSG sleep studies using either the Cerêve Sleep System or the sham device. There were 2 co-primary endpoints for the study, including (1) latency to persistent sleep (time to the first epoch of sleep sustained for 10 minutes) based on PSG and (2) sleep efficiency (total sleep time / time in bed) based on PSG. The two secondary endpoints for the study were Stage 3 non-rapid eye movement (NREM) sleep based on PSG and subjective sleep quality based on response to a self-reported questionnaire (Pittsburgh Sleep Diary) following each night of sleep.

Results: There were no statistically significant differences between the Cerêve and sham groups for the primary endpoints (latency to persistent sleep and sleep efficiency), nor for the secondary endpoints (Stage 3 NREM sleep and sleep quality). However, additional data analysis of the study showed there was a 12 minute reduction in the sleep latency to Stage 1 sleep (p=0.004) and Stage 2 sleep (p=0.008) in the Cerêve group compared to the sham. The measures of sleep latency to Stage 1 and Stage 2 sleep did not require sustained sleep. There was no statistically significant difference between the Cerêve and sham groups for reduction in sleep latency to Stage 3 sleep.

Adverse Events: There were a total of 3 adverse events (AEs) in the Cerêve group and 1 in the sham group that were deemed possibly or probably related to the device. The 3 AEs in the Cerêve group included headache. There were an additional 2 AEs in the Cerêve group and 1 AE in the sham group that were not device related. No serious AEs were observed in either group.

2. **CIP-003:**
   Prior to conducting CIP-006, the sponsor conducted a multi-center, controlled, within subjects cross-over study comparing the effects of 2 different temperature modes of the Cerêve Sleep System on subjects with primary insomnia. This was a multi-center (9 U.S. sites) study of 145 subjects with inclusion and exclusion criteria that were similar to those in CIP-006. Following screening and baseline PSG measurements, subjects had two sequential nights in each condition with the Cerêve Sleep System separated by 3-5 nights at home. There were 2 co-primary endpoints for the study, including (1) latency to persistent sleep based on PSG and (2) sleep efficiency based on PSG.

   Similar to CIP-006, there were numerical improvements in latency to persistent sleep and sleep efficiency in both groups, but there were no statistically significant differences between the two modes. The rate of adverse events was low and further supported the overall safety of the Cerêve Sleep System. The most common AE was headache, with a total of 11 headache AEs in 10 subjects that were deemed possibly, probably or definitely related to the device. Other AEs were deemed not to be device-related. No serious AEs were observed.

3. **CIP-004:**
   Following CIP-003, the sponsor conducted a non-randomized home-use study to evaluate long-term use effects of the Cerêve Sleep System in 32 subjects from CIP-003. Subjects used the Cerêve Sleep System in their home for 30 days and up to 5 months for safety assessments. The subjects had similar numerical improvements in latency to persistent sleep and sleep efficiency measures at 30 days as those observed in prior measurements obtained in CIP-003. The subjects reported improved self-reported sleep quality scores after 30 days use. These results demonstrate that the Cerêve Sleep System effect is durable over 30 days of use in the home in these subjects. No serious device-related AEs were reported and further supported the safety of the Cerêve Sleep System for extended use.

LABELING

The Cerêve Sleep System User Manual is consistent with the clinical data and covers all of the hazards and other clinically relevant information that may impact use of the device. Patient labeling is also provided, which includes a warning for patients to consult with their physician if they have a skin condition that may make use of the device uncomfortable. The labeling includes the following caution statement noting the limitation of the established device effectiveness:

> Other than reduction of sleep latency to Stage 1 and Stage 2 sleep, the efficacy of other sleep measures associated with insomnia has not been established by the Cerêve Sleep System in controlled clinical trials.

The labeling satisfies the requirements of 21 CFR § 801.109 Prescription devices.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of the Thermal System for Insomnia and the measures necessary to mitigate these risks.

Table 3 – Identified Risks to Health and Mitigation Measures

Identified Risk	**Mitigation Method**
Adverse Skin Reaction	Biocompatibility Assessment Labeling
Electromagnetic Interference with Other Devices	Electromagnetic Compatibility Testing Labeling
Electrical Safety (e.g., shock)	Electrical Safety Testing Labeling
Thermal Injury	Non-clinical Performance Testing Software Verification, Validation, and Hazard Analysis Labeling

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the Thermal System for Insomnia is subject to the following special controls:

1. The patient-contacting components of the device must be demonstrated to be biocompatible.
2. Performance testing must demonstrate electromagnetic compatibility and electrical safety.
3. Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be evaluated:
    a. Thermal performance of the device, including maintenance of the target temperature, must be evaluated under simulated use conditions.
    b. Mechanical testing to demonstrate the device can withstand forces under anticipated use conditions.
    c. Mechanical testing to demonstrate the device is resistant to leakage under anticipated use conditions.
4. Software verification, validation, and hazard analysis must be performed.
5. Patient labeling must be provided to convey information regarding safe use of the device, including instructions for assembly.

BENEFIT/RISK DETERMINATION

The risks of the device are based on data collected in the clinical studies described above. There were no serious adverse events associated with the use of the device.

The probable benefits of the device are also based on data collected in the clinical studies described above. Although the clinical studies do not support that the device is effective for improvement of primary insomnia symptoms in general (including latency to persistent sleep,

sleep efficiency, and sleep quality), the probable benefit is a reduction in the time to reach stage 1 and stage 2 sleep.

Additional factors to be considered in determining probable risks and benefits for the Cerêve Sleep System include: risks, such as headache, will be apparent to the individual user of the device with use. Similarly, if there is benefit to the individual user it should be apparent. One alternative low-risk treatment includes cognitive behavioral therapy. A second alternative therapy includes pharmacologic therapy which may carry greater risk. There are no similar medical devices on the market for this proposed indication for a reduction in the time to reach Stage 1 and Stage 2 sleep.

In conclusion, given the available information above, the data support that for reducing latency to Stage 1 and Stage 2 sleep in patients with primary insomnia, the probable benefit outweighs the probable risks for the Cerêve Sleep System. The device provides probable benefit for reducing time to Stage 1 and Stage 2 sleep and the risks can be mitigated by the use of general and the identified special controls.

CONCLUSION

The *de novo* request for the Cerêve Sleep System is granted and the device is classified under the following:

Product Code: PLU
Device Type: Thermal System for Insomnia
Class: II
Regulation: 21 CFR 882.5700