DE NOVO CLASSIFICATION REQUEST FOR
CERENA TRANSCRANIAL MAGNETIC STIMULATOR (TMS) DEVICE

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Transcranial Magnetic Stimulator for Headache.** A transcranial magnetic stimulator device for headache is a device that delivers brief duration, rapidly alternating, or pulsed, magnetic fields that are externally directed at spatially discrete regions of the brain to induce electric currents for the treatment of headache.

NEW REGULATION NUMBER: 882.5808

CLASSIFICATION: CLASS II

PRODUCT CODE: OKP

BACKGROUND

DEVICE NAME: CERENA TRANSCRANIAL MAGNETIC STIMULATOR (TMS) DEVICE

SUBMISSION NUMBER: K130556

DATE OF DE NOVO: MARCH 5, 2013

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REQUESTER'S RECOMMENDED CLASSIFICATION: CLASS II

INDICATIONS FOR USE

The eNeura Therapeutics® Cerena™ Transcranial Magnetic Stimulator is indicated for the acute treatment of pain associated with migraine headache with aura.

LIMITATIONS

For prescription use only.

Patients must not have any metals or conductive materials or metal containing implants in the head, neck, or upper body that are attracted by a magnet.

Patients must not use the device if they have a cardiac pacemaker, deep brain stimulator (DBS), vagus nerve stimulator (VNS), spinal cord stimulator (SCS), or other implanted neurostimulator, implanted cardioverter defibrillator (ICD), or any active implanted medical device.

Patients with implants that are affected by a magnetic field must not use the device.

The device is only intended for use by patients experiencing the onset of pain associated with a migraine headache with aura.

The device should not be used on headaches due to underlying pathology or trauma.

The device should not be used for medication overuse headaches.

The device has not been demonstrated as safe or effective when treating cluster headache or chronic migraine headache.

The device has not been shown to be effective when treating during the aura phase.

The device has not been demonstrated as effective in relieving the associated symptoms of migraine (photophobia, phonophobia, and nausea).

Safety and effectiveness have not been established in pregnant women, children under the age of 18, and adults over the age of 65.

The device should not be used in patients with suspected or diagnosed epilepsy or a personal or family history of seizures.

The recommended daily usage of the device is not to exceed one treatment per 24 hours.

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

DEVICE DESCRIPTION

The Neuralieve Cerena Transcranial Magnetic Stimulator (TMS) is a portable, hand-held, AC-powered device that delivers a brief pulse of magnetic energy at 0.9 Tesla to the back of the head to induce an electrical current in a portion of the brain (occipital cortex). This stimulation to the occipital cortex is intended to stop or lessen the effects of migraine headaches (with aura). The device is designed to be used in a home or office setting.

The device exterior is made of polycarbonate, a plastic routinely used in consumer medical products. Additionally, the device includes an AC/DC power adapter, a separate power cord for a standard 120V wall outlet and an Operator's Manual.

The device has a display on the top surface consisting of two 7- segment LEDs and a row of LEDs that light in sequence to indicate progress when stimulator's capacitors are charging. There is no separate ON-OFF button. When the stimulator is plugged into the power adapter and the power adapter is plugged into a standard wall outlet, the power indicator light turns on and the display lights up. There are two actuation buttons. The button labeled "Charge" is used to begin the capacitor charging process. The button, labeled "Treat," discharges the fully charged capacitors through the coil to generate the single magnetic pulse.

A complete treatment consists of two independent pulses delivered separately. After the patient delivers the first pulse, the device buzzes to alert the user to press the charge button again. The patient has two minutes to press the charge button after delivering the first pulse or the device will deliver an error code. After the device discharges the second pulse, it does not allow the device to charge for 5 minutes. The device cannot be discharged before completing the charging cycle.

When the user successfully presses the "Treat" button as instructed, the device generates a single magnetic field pulse (<1Tesla). The user hears a brief sound when the magnetic pulse occurs. The stimulator also buzzes and vibrates for two seconds to provide additional feedback that a pulse has occurred.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The device is intended to only contact intact skin for a limited duration (< 24 hours). The housing of the device is the only patient contacting material and is made from polycarbonate, a plastic routinely used in consumer medical products. In lieu of biocompatibility testing, the sponsor provided a justification that the identical material has a demonstrated long history of safe use in legally marketed devices with the same type and duration of contact.

SHELF LIFE/STERILITY

This is a non-sterile, reusable device. It is intended only for external use and the user manual includes appropriate cleaning instructions for the external surface of the device. The device does not have a stated shelf life, which based upon the nature of the device components is acceptable.

ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY

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

Standard	Title

Standard	Title
IEC 60601-1	Medical electrical equipment – Part 1: General requirements for safety and essential performance.
IEC 60601-1-2	Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral standard: Electromagnetic compatibility - Requirements and tests

SOFTWARE

Software for the device consisted of proprietary software that controls the user interface and energy delivery to the stimulation coil. The software was reviewed, and the provided documentation was found adequate and consistent with a 'MODERATE' level of concern as discussed in the FDA document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, " issued May 11, 2005.

PERFORMANCE TESTING – BENCH

Device output – Testing was conducted to characterize the device magnetic field output and the magnetic field pulse. The magnetic field was measured to find the contour plots of various field levels along each axis of the device. The magnetic field pulse was also measured and graphed to show the magnetic field over time and the rate of change for the magnetic field over time.

Sound level – Testing was performed to determine the loudness of the sound generated by the device to demonstrate that the device is within the OSHA safety limits for noise exposure.

SUMMARY OF CLINICAL INFORMATION

One clinical trial was performed with the device to demonstrate the safety and effectiveness of the device for the treatment of migraine headache with aura.

Design

The study was a prospective, randomized, double blind, multi-center, sham-controlled trial. The sham device used provided a similar auditory and vibratory output to mimic the treatment device.

The study consisted of a one month, lead-in phase to establish the subjects' baseline frequency and severity of migraine followed by a randomized, double-blind treatment phase consisting of three treatments or three months, whichever happened first. Subjects were required to have at least one aura episode during the lead-in phase to enter the migraine treatment phase.

Subjects were instructed to treat their migraine headache during the aura phase and to record their pain severity, severity of associated migraine symptoms (photophobia, phonophobia, nausea), presence of vomiting, and use of rescue medications at the time of treatment as well as at 1, 2, 24, and 48 hours after treatment.

Population

The study population was limited to subjects aged 18 to 65 years who had an International Classification of Headache Disorders, 2nd edition (ICHD-II) diagnosis of migraine with aura, at least one migraine with aura episode during the one month lead-in phase, and an average of one to eight migraine episodes per month.

Subjects were required to have a history of an aura preceding more than 30% of their headaches but were not required to have aura during every migraine episode. Headache severity must have been moderate or severe for approximately 90% of migraine attacks. Key exclusion criteria included subjects with an aura that lasted more than 60 minutes, headaches due to underlying pathology or trauma, and overuse of medication for headaches.

Results

A total of 201 subjects were enrolled in the study at a 1:1 ratio (102 used Cerena, 99 used the sham control). A total of 164 subjects (82 in each group) recorded at least one treatment of a migraine attack with aura using the device (or sham). A total of 113 subjects (53 with Cerena, 60 with Sham) recorded at least one treatment of a migraine when there was pain of any severity (pain score of 1-3) at the time of the treatment. Pain was measured on a scale of 0-3 with 0 representing no pain and 3 representing severe pain. These 113 subjects were used to evaluate the primary and secondary effectiveness end points.

With a post-hoc analysis of these 113 subjects, the primary endpoint (proportion of subjects who were free of pain 2 hours after treatment) analysis demonstrated a statistically significant 21.07% difference in favor of the device over the sham device (37.74% for Cerena and 16.67% for sham, p=0.0181).

The secondary endpoints were evaluated, and the data demonstrated non-inferiority of the Cerena device to sham for the proportion of subjects free of photophobia, meaning that the device does not worsen these associated symptoms. The data did not demonstrate non-inferiority for the proportion of subjects free of nausea and phonophobia.

The data also supported device effectiveness in the proportion of subjects who were pain free after 24 hours (33.96% for Cerena and 10% for sham, p=0.0025).

The study was not designed to necessarily demonstrate effectiveness on successive treatments because subjects did not need to treat more than one migraine when they did not experience more than one in the 3-month trial period.

Adverse Events

There were 7 AEs in 5 subjects (9.43%) of the Cerena group and 11 reported in 7 subjects (11.67%) of the sham group. Events possibly related to the use of the device include dizziness (N=2). Other reported events included sinusitis, aphasia, and vertigo (N=1 each). No seizures were reported.

LABELING

The *Cerena* physician and patient manuals are consistent with the clinical data and cover all the hazards and other clinically relevant information that may impact use of the device. The labeling is sufficient and 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 transcranial magnetic stimulator devices for headache and the measures necessary to mitigate these risks.

Identified Risk	**Mitigation Method**
Failure to identify correct population	Clinical testing Labeling
Ineffective treatment	Clinical testing Non-Clinical Testing Software Verification, Validation, and Hazard Analysis Labeling
Risk of seizure	Clinical Testing Non-Clinical Testing Labeling
Scalp discomfort, scalp burn, dizziness, nausea, or other adverse effects	Clinical testing Non-Clinical Testing Thermal Safety Software Verification, Validation, and Hazard Analysis Labeling
Adverse tissue reaction	Biocompatibility Labeling
Electrical shock, burn	Electrical Equipment Safety Thermal Safety Labeling
Interference with other electrical equipment	Electromagnetic Compatibility Labeling
Noise Irritation and Hearing Loss	Non-Clinical Testing Labeling

SPECIAL CONTROLS:

1. Appropriate analysis/testing must demonstrate electromagnetic compatibility (EMC), electrical safety, and thermal safety.

2. Appropriate verification, validation, and hazard analysis must be performed on the device software and firmware.
3. The elements of the device that contact the patient must be assessed to be biocompatible.
4. Non-clinical testing data must demonstrate that the device performs as intended under anticipated conditions of use. This includes full characterization of the magnetic pulse output and resulting magnetic field map. This also includes characterization of the sound level of the device during use.
5. Clinical testing must demonstrate that the device is safe and effective for treating headache in the indicated patient population.
6. The physician and patient labeling must include the following:
    a. A summary of the clinical performance testing, including any adverse events and complications.
    b. The intended use population in terms of the types of headaches appropriate for use with the device.
    c. Information on how to report adverse events and device malfunctions.
    d. A diagram or picture depicting the proper placement of the device on the user.

BENEFIT/RISK DETERMINATION

The risks of the device are based on data collected in the clinical studies described above. No serious device-related adverse events were reported in the clinical performance data. The majority of adverse events were minor and all resolved on their own shortly after discontinuation of device use. Based on this information, the risk associated with this device is considered low.

The probable benefits of the device are also based on data collected in clinical study of subjects with migraine with aura described above. A post-hoc analysis of the subgroup of subjects with any pain at the time of treatment was performed. The analysis demonstrated effectiveness in treating pain associated with migraine headaches both at the 2 and 24 hours after treatment. However, the study did not demonstrate effectiveness on treating the associated symptoms of migraine (photophobia, phonophobia, nausea).

Additional factors to be considered in determining probable risks and benefits for the device include: (1) There are no legally marketed devices available for patients with migraine. There are approved drug treatments, but these have known adverse effects that are more common and more severe than those seen in the Cerena trials. (2) Long-term safety and effectiveness data for the Cerena are not available. The clinical data are limited to 3 months in duration and limited to evaluation of the first treated migraine.

Given the available information, the data support that the probable benefits outweigh the probable risks for the Cerena device for treating migraine pain. The device risks can be mitigated by the use of general and the identified special controls.

CONCLUSION

The *de novo* for the Cerena TMS device is granted and the device is classified under the following:

Device Type: Transcranial magnetic stimulator device for headache
Regulation: 21 CFR 882.5808
Class: Class II
Product Code: OKP