DE NOVO CLASSIFICATION REQUEST FOR PORTABLE NEUROMODULATION STIMULATOR (PONS)

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Neuromuscular tongue stimulator to treat motor deficits. A neuromuscular tongue stimulator to treat motor deficits is a prescription device that consists of a non-implantable apparatus to generate electrical pulses for stimulation of the nerves in the tongue to provide treatment of motor deficits.

NEW REGULATION NUMBER: 21 CFR 882.5889

CLASSIFICATION: Class II

PRODUCT CODE: QCF

BACKGROUND

DEVICE NAME: Portable Neuromodulation Stimulator (PoNS)

SUBMISSION NUMBER: DEN200050

DATE DE NOVO RECEIVED: August 4, 2020

SPONSOR INFORMATION:

Helius Medical, Inc.
642 Newtown Yardley Road, Suite 100
Newtown, Pennsylvania 18940

INDICATIONS FOR USE

:

The PoNS device is indicated for use as a short term treatment of gait deficit due to mild to moderate symptoms from multiple sclerosis and is to be used as an adjunct to a supervised therapeutic exercise program in patients 22 years of age and over by prescription only.

LIMITATIONS

Prescription use only.

The device is not to be used while eating, drinking, or driving to avoid risk of physical injury.

The device should be used with caution in patients who:

- Have implanted electronic devices, including:
    - Cardiac pacemakers
    - Cardioverter defibrillators
    - Deep Brain Stimulators
    - Vagal Nerve Stimulators
    - Sacral nerve stimulators
    - Cochlear Implants
- Have metal in the mouth (e.g. piercings, braces, retainers, or other orthodontic appliance)
- Have seizure disorders (e.g., epilepsy)

Use of the device does not replace the need for follow-up testing to determine the initial and ongoing effectiveness of the therapy as recommended by clinical practice guidelines.

Warnings

The intensity should only be adjusted while the Mouthpiece is on the tongue. The patient should be the one who adjusts the intensity level. In case the patient needs assistance in pressing the buttons on the Controller, the person assisting should use care to adjust the intensity by small increments. Check with the patient each time you press the INTENSITY UP/DOWN buttons, before pressing them again.

Portable Radio Frequency (RF) communications equipment (including peripherals such as antenna cables and external antennas) should be used no closer than 30 cm (12 inches) to any part of the PoNS System, including cables supplied with the PoNS System. Otherwise, degradation of the performance of this equipment could result.

Device should not be used by persons under the age of 22.

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

DEVICE DESCRIPTION

The PoNS™ device is a non-implantable tongue stimulator that delivers neuromuscular electrical stimulation to the trigeminal and facial nerves for use as a short-term treatment of gait deficit due to mild to moderate symptoms from multiple sclerosis and is to be used as an adjunct to a supervised therapeutic exercise program. The device is for use in patients over 22 years of age by prescription only.

The PoNS™ mouthpiece is held lightly in place by the lips and teeth around the neck of the tab that goes into the mouth and rests on the anterior, superior part of the tongue. The control unit is worn around the neck during session usage. It has 5 user-controlled buttons: power, information, intensity up, intensity down, and start/stop/pause. The control unit also records usage data including session duration and general activities performed which are captured by an accelerometer. During a patient's visit with a therapist, the therapist is able to connect the control unit to a computer and, using software developed specifically for the PoNS™, view the usage data. The purpose of the usage data is to give the therapist information on how to improve a patient's execution of therapy by identifying potential areas of missed or shortened sessions. The PoNS™ System is comprised of a Controller, a Mouthpiece, a Mouthpiece Retainer Case, a Charger, a Product Carry Case and the PoNS™ Software. Accessory components, also supplied, include a cable for connection to a computer running the PoNS™ software.

Controller: The Controller includes the primary user interface and drive electronics for providing the electronic stimulation waveform. Through the user interface, the intensity of the stimulation waveform can be adjusted, the stimulation can be started and stopped, and the Controller can be powered on and off. The Controller user interface consists of a visual display, audio feedback and vibration feedback.

Mouthpiece: The Mouthpiece houses the electrode array through which the stimulation waveform is applied to the patient's tongue. Electronics and software within the Mouthpiece control the timing of the stimulation waveform. The Controller sends commands to the Mouthpiece and receives status messages from the Mouthpiece via a cable that forms an integral part of the Mouthpiece assembly.

Mouthpiece Retainer Case: The Mouthpiece Retainer Case is used to store the Mouthpiece between uses. The cable of the Mouthpiece wraps around the base of the Mouthpiece Retainer Case. There is a pocket in the Carry Case sized to house the Mouthpiece Retainer Case during storage.

Charger: The Charger consists of a mains power adaptor that connects to the Controller via a standard USB Type-C connector and provides a low voltage power supply to recharge the Controller battery. Stimulation is disabled while the Charger is connected to the Controller.

Summary of Mouthpiece Materials of Construction and Type of Patient Contact

Mouthpiece Component	Material	Patient Contact
Electrode Printed Circuit Board	Polyimide	Mucosal Membrane (mouth, tongue, lips)
Electrodes on Printed Circuit Board	Gold Plated Nickel	
Overmolded Bite Pad	Thermoplastic elastomer	
Mouthpiece Cap	Polycarbonate	
Potting Resin (internal)	Polyurethane Resin	Potentially Mucosal Membrane

Output parameters and other electrical specifications of the PoNS™ device are presented below in Table 1.

General Device Characteristics	
Mode or Program Name	Portable Neuromodulation Stimulator (PoNS™)
Waveform (e.g., pulsed monophasic, biphasic)	Pulsed biphasic (unbalanced)
Shape (e.g., rectangular, spike, rectified sinusoidal)	Rectangular
Maximum Output Voltage (volts) (+/- 5%)	17.5V @ 500 Ω 20V @ 5 kΩ
Maximum Output Current (specify units) (+/- 5%)	3.5 mA @ 500 Ω (channel: 26 mA) 440 µA @ 5 kΩ (channel: 3.85 mA)
Duration of primary (depolarizing) phase (µsec)	60 µsec
Pulse Duration (µsec)	312.5 µsec
Frequency (Hz) [or Rate (pps)]	triplets at 200 Hz intervals, repeating every 50 Hz channel pulses stimulating different tongue locations at 3.2 kHz; groups of 16 channel pulses delivered in triplets at 200 Hz; repeats every 50 Hz
Net Charge (microcoulombs (µC) per pulse) (If zero, state method of achieving zero net charge.)	-0.002 @ 500 Ω (channel: -0.016) -0.0041 @ 5 kΩ (channel: -0.036)
Maximum Phase Charge, (µC)	0.21 @ 500 Ω (channel: 1.56)
Maximum Current Density, (mA/cm², rms)	18.79 @ 500 Ω 2.36 @ 5 kΩ
Maximum Average Current (average absolute value), (mA)	0.082 @ 500 Ω 0.009 @ 5 kΩ
Maximum Average Power Density, (W/cm²)	0.025 @ 500 Ω 0.0041 @ 5 kΩ

Summary of Nonclinical/Bench Studies

Biocompatibility/Materials

The biocompatibility evaluation for PoNS™ mouthpiece was conducted in accordance with the International Standard ISO 10993-1 :2009 "*Biological Evaluation of Medical Devices Part-1: Evaluation and Testing Within a Risk Management Process*". The PoNS™ mouthpiece and components is categorized as a surface device in prolonged (24 hours to 30 days) contact of the mucosal membrane (i.e. mouth, tongue lips). Assessment of the device included the following tests which met the prespecified acceptance criteria:

- Cytotoxicity (ISO 10993-5:2009)
- Sensitization Test (ISO 10993-10:2010)
- Intracutaneous Reactivity (ISO 10993-10:2010)
- Oral Mucosa Irritation (ISO 10993-10:2010)
- Acute Systemic Toxicity (ISO 10993-11:2006)
- Material-mediated pyrogenicity (ISO 10993-11:2006)
- Extractables & Leachables Study (ISO 10993-17:2002
- Chemical Characterization of medical device materials (ISO 10993-18:2005)
- Genotoxicity (ISO 10993-3:2014)

SHELF LIFE/REPROCESSING/STERILITY

The PoNS™ device is not provided sterile and is not intended to be sterilized prior to use. The device is a single- patient, reusable device and instructions have been provided to dispose of the mouthpiece portion of the device after fourteen weeks from first use.

The PoNS Controller is programmed such that it ceases to provide stimulation after (b) (4) weeks and a patient must return to their Healthcare Professional to reset the Controller for additional time. This mechanism is intended to control long-term and unchecked patient usage, and to ensure Healthcare Professional oversight.

The PoNS™ device consists of the following components: a mouthpiece, a controller, and a retainer case. Cleaning instructions have been provided for each of the three components.

ELECTROMAGNETIC CAPABILITY & ELECTROMAGNETIC SAFETY

The PoNS™ system was tested according to the following FDA-recognized consensus standards:

- IEC 60601-1:2005 (Modified to be equivalent to (AAMl/ANSI ES60601-1:2005/(R)2012 and C1:2009/(R)2012 and, A2:2010/(R)2012) "Medical Electrical Equipment; Part 1: General requirements for basic safety and essential performance." Results demonstrated that the device is compliant to this standard.
- 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 60601-1-11:2015 "Medical electrical equipment: 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."

- IEC 60601-2-10: 2012 and A1:2016 "Medical Electrical Equipment Part 2-10: Particular requirements for the basic safety and essential performance of nerve and muscle stimulators."

SOFTWARE

A failure or latent flaw in the software of the PoNS™ device could indirectly result in minor injury to the patient or operator; therefore, the software of this device is considered to have a "Moderate" level of concern.

The submission contained all the elements of software documentation corresponding to a "Moderate" level of concern, as outlined in the FDA guidance document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices." issued May 11, 2005 (https://www.fda.gov/media/73065/download). Adequate documentation describing the software, firmware, software specifications, architecture design, software development environment, traceability, revision level history, unresolved anomalies and cybersecurity provides the foundation that the software will operate in a manner as described in the specifications. A hazard analysis was performed to characterize software risks including device malfunction and measurement related errors. The submission included verification and validation (V&V) testing to address the potential hazards with satisfactory result.

PERFORMANCE TESTING - BENCH

LITHIUM-ION BATTERY TESTING:

The PoNS™ controller is powered by a rechargeable 3.7V Lithium-Ion battery. The battery complies with IEC 62133-2 (Standard for lithium batteries), and IEC 60601-1 (Basic Safety).

ELECTRICAL STIMULATION OUTPUT

Testing was performed to characterize the stimulation output waveform, the functionality of the PoNS™ as a system, and the requirements of the output stimulation parameters. Results demonstrated that the system meets specifications.

ELECTRODE BENCH TESTING:

Testing was performed to assess the mechanical measurements, the design of the electrodes (and tolerances) and the electrical characteristics (impedance and current distribution) of the electrodes under the expected worst-case conditions of normal operation. Results demonstrated that the electrodes passed all testing.

SUMMARY OF CLINICAL INFORMATION

The following clinical information was provided to evaluate the safety and effectiveness of the PoNS™ device:

- Two Clinical Studies:
  - A randomized, double blind controlled trial in (b) (4) subjects with gait deficits due to Multiple Sclerosis (Tyler et. al, 2014)
  - A pilot study intended to investigate the effects of PoNS™ with cognitive rehab and physical rehab, on the primary outcome of improvement in sensory organization tasks (Leonard et. al, 2017)
- A retrospective analysis of real-world data ("RWD") collected with the PoNS™ in MS patients in clinical rehabilitation settings in Canada
- Post-hoc re-analysis of studies by Tyler et. al, 2014 and Leonard et. al, 2017, pooling results with RWD.
- 6-patient case series poster presentation.

The clinical information provided is summarized below.

1. **Summary of the study by Tyler et. al (2014):**
   A Randomized, double blind controlled trial in (b) (4) subjects with gait deficits due to Multiple sclerosis. (b) (4) subjects used Active PoNS™ device, (b) (4) subjects used a control device that did not deliver stimulation. The intervention consisted of (b) (4) weeks of gait training in the laboratory while simultaneously using the device to provide stimulation during gait training. This was followed by (b) (4) weeks of home use of the device while performing gait training for a total of (b) (4) weeks of treatment. The primary outcome measure was the Dynamic Gait Index (DGI, clinician scored index of (b) (4) gait tasks). DGI was performed at baseline week (b) (4) . Results showed the active group on average achieved improvement in DGI score of (b) (4) at (b) (4) weeks while the control group improved (b) (4) points. Compared to baseline, the active group achieved a statistically significant and clinically significant ((b) (4) change in DGI) by the end of the study, while the control group did not.

Table 19-4: DGI Over Time in Tyler Active vs. Control Groups

	Active					Control				
Week	N	Mean	SD	Lower CI	Upper CI	N	Mean	SD	Lower CI	Upper CI
(b) (4)										

Figure 19-1: Change in DGI Score from Baseline

(b) (4)

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Table 19-5: Responder Analysis (Tyler, et al. DGI Data)

Change in DGI at Week 14 versus Baseline	Active Group	Control Group
(b) (4)		

2. **Summary of the study by Leonard et. al (2017):**
Patient blinded, randomized, controlled trial in (b) (4) subjects with MS assessing effects of PoNS+cognitive and physical rehabilitation (n=7), vs sham device+cognitive and physical rehabilitation (n=7). Baseline evaluations including structural and fMRI, balance tests (sensory organization tests ("SOT")), DGI, and a neuropsychological assessment. Participants received physical therapy and working memory training for (b) (4) weeks. For the first (b) (4) weeks, an in- lab training program was completed with twice-daily training sessions, followed by (b) (4) weeks of at- home training with the same exercises. During both stages, subjects completed three sessions per day: morning, afternoon and evening. Participants returned every (b) (4) weeks for re-evaluation and to progress their training. Results: SOT scores measured baseline stability under six progressively difficult conditions. The composite scores showed a trend of improvement over time for both the Control and Active groups, although more consistent for the Active group. The Active group showed a statistically significant improvement at (b) (4) weeks compared to baseline values. The DGI tasks included: steady state walking, walking with changing speeds, walking with head turns horizontally and vertically, stepping over and around obstacles, pivoting and stair climbing. Analysis of DGI scores after (b) (4) weeks revealed a non-significant trend towards the Active group.. This study also examined functional magnetic resonance imaging (fMRI) during a gait imagery task.

Figure 6. Dynamic Gait Index showing average scores for baseline and following (b) (4) and (b) (4) weeks of training

Series 1 = Active Group in red
Series 2 = Sham Group in green

3. **Real World Data**

The sponsor also provided a retrospective analysis of real-world data ("RWD") collected with the PoNS™ in MS patients in clinical rehabilitation settings in Canada. Patients who agreed to treatment were given 1-hr consultation, consented, and given baseline assessments of gait function using FGA (Functional Gait Assessment (FGA). The primary outcome for effectiveness was defined as the mean change from baseline to week (b) (4) in FGA. At Week (b) (4) the mean improvement in baseline functional gait assessment GA) score was (b) (4) points (b) (4) (n=36). No serious safety AE were reported. Of note, (b) (4) of the (b) (4) real world patients had baseline Expanded disability status scale (EDSS) scores (b) (4) These results suggest that the PoNS™ may not be as effective for subjects with more severe baseline disability.

A post-hoc re-analysis of Tyler and Leonard studies, pooling results with RWD was also provided by pooling the DGI results from Tyler and Leonard studies with the RWD to provide a larger data set on which to evaluate the evidence supporting the effectiveness of PoNS™ for the proposed indications for use. Comparison was facilitated by creating from the RWE an "adjusted DGI" with the same range as the 8-item DGI; this entailed summing the 7 items in common across the DGI and FGA scales and multiplying by 8/7. Although the sponsor provides a rationale for why one can multiply the FGA results by 8/7ths to convert the score to a surrogate DGI score, this practice is not validated according to any published literature.

The mean improvement from baseline to Week (b) (4) pooling over all three groups is (b) (4) (b) (4) when time points in common (Weeks (b) (4) and (b) (4) are used. The mean improvement is (b) (4) ((b) (4)) when all possible

data at all weeks are used. However, as noted in the Tyler and Leonard studies, there are differences in the sub-type of MS included in Tyler, et al, Leonard et al, and RWD, differences in baseline DGI score, and differences in medication's used by subjects in each group. Furthermore, he demonstrated improvement in the RWE pooled with Tyler and Leonard et al (b) (4) improvement from baseline), is not much better than the demonstrated improvement in the control group of the Tyler et. al, study (b) (4) improvement).

Figure 19-5: Adjusted DGI Scores in RWE Analysis Dataset

(b) (4)

Figure 19-6: Pooling Analysis – RWE + Tyler

(b) (4)

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 Part 801.109 for prescription devices.

The following contraindications, warnings, and precautions are included within device labeling:

Contraindications:
The PoNS device delivers electrical stimulation directly to the surface of the tongue. Precautions for use are similar to those for transcutaneous electrical nerve stimulation (TENS).

Electrical stimulation SHOULD NOT be used:

- if there is an active or suspected malignant tumor
- in areas of recent bleeding or open wounds
- in areas that lack normal sensation

The PoNS has not been tested on, and thus should not be used by individuals who are pregnant. Do not use the PoNS if you are sensitive to nickel,
gold or copper.

Precautions:
The device should be used with caution in patients who:

- Have implanted electronic devices, including:
  - Cardiac pacemakers
  - Cardioverter defibrillators
  - Deep Brain Stimulators
  - Vagal Nerve Stimulators
  - Sacral nerve stimulators
  - Cochlear Implants
- Have metal in the mouth (e.g. piercings, braces, retainers, or other orthodontic appliance)
- Have seizure disorders (e.g., epilepsy)

Warnings:

- DO NOT connect the Mouthpiece to the Controller before seeing your PoNS™ therapist, to avoid premature expiration of the Mouthpiece.
- DO NOT place the Mouthpiece in your mouth while the Controller is charging or connected to your PoNS™ therapist's computer.
- DO NOT use a power adapter other than the one provided with your PoNS™ to charge the Controller. Always charge the Controller indoors.
- DO NOT wet the Controller or use your PoNS™ in the rain or snow.
- DO NOT wet the connector on the end of the Mouthpiece cord when cleaning the Mouthpiece. Always check and ensure the connector is dry before connecting and using the Controller.
- DO NOT use the PoNS™ if you are sensitive to nickel, gold or copper. The PoNS™ Mouthpiece contains nickel, gold and copper.
- DO NOT use your PoNS™ if you have open mouth sores, ulcers or tongue piercings.
- DO NOT eat, drink or smoke while using your PoNS™.
- If the materials on the Mouthpiece cause any allergic reactions or undesirable effects, discontinue using the PoNS™ immediately and contact your healthcare provider.

- DO NOT bite down on the Mouthpiece with excessive force.
- DO NOT use your PoNS™ if it has been dropped and broken.
- DO NOT use your PoNS™ while driving or operating machinery.
- DO NOT connect the Mouthpiece to any other device or modify any part of the equipment.
- Keep your PoNS™ out of Magnetic Resonance Imaging (MRI) field.
- Keep your PoNS™ out of the sight and reach of children.
- BE AWARE: the long-term effects of electrical stimulation are unknown.
- Only use specified charger and cable.
- The PoNS™ Controller contains a rechargeable lithium battery.

The labeling also includes:

- Information on how the device operates and the typical sensations experienced during use
- Information in the Instructions for Use regarding how to place the device on the user
- Storage and cleaning instructions for the device
- Physical limitations of the device including suitable temperature range, duration of use, and expected product life.
- Charging instructions; and
- Disposal instructions.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of the neuromuscular tongue stimulator to treat motor deficits and the measures necessary to mitigate these risks.

Identified Risk	**Mitigation Measures**
Adverse tissue reaction	Biocompatibility evaluation
Thermal, electrical, or mechanical fault, or system malfunction resulting in tissue damage due to overstimulation or thermal injury (e.g. burn/shock) to user	Electrical, mechanical, and thermal safety testing Electromagnetic compatibility (EMC) testing Battery safety testing Non-clinical performance testing Software validation, verification & hazard analysis Labeling
Use error that may result in user discomfort or injury	Labeling
Device contamination resulting in patient illness	Labeling
Adverse events involving the mouth, tongue, or gums such as irritation and discomfort	Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the neuromuscular tongue stimulator to treat motor deficits is subject to the following special controls:

(1) Performance data must demonstrate that all patient-contacting components of the device are biocompatible.

(2) Performance data must demonstrate the electromagnetic compatibility, battery safety, and electrical, mechanical, and thermal safety of the device.

(3) Non-clinical performance testing must characterize the electrical stimulation parameters of the device.

(4) Software verification, validation, and hazard analysis must be performed. Software documentation must include an assessment of the impact of threats and vulnerabilities on device functionality and end users as part of cybersecurity review.

(5) Labeling must include:
   a) A detailed summary of the device's technical parameters;
   b) Instructions for use;
   c) Cleaning, storage, and charging instructions; and
   d) Disposal instructions.

BENEFIT-RISK DETERMINATION

The known probable risks of the device are based on the data collected in the clinical study described above. The device exhibited an acceptable safety profile in the clinical studies which were conducted, and any adverse events that occurred were temporary and had complete resolution. No device-related serious adverse events were observed, such as electrical injury, burns, or permanent injury to tongue nerve or muscle function. The results of the nonclinical testing demonstrated that the device performed as per specifications and the results did not raise concerns regarding risks to the patients.

The probable benefits of the device are also based on data collected in clinical studies as described above. From the Tyler et al. study, there is evidence of a clinically meaningful treatment effect on Dynamic Gait Index (DGI) scores, a clinician scored index of (b) (4) gait tasks. DGI was performed at baseline week (b) (4) and (b) (4) wks. Results showed the active group on average achieved improvement in DGI score of (b) (4) at (b) (4) weeks while the control group improved (b) (4) points. Compared to baseline, the active group achieved a clinically significant (4-point change in DGI) by the end of the study, while the control group did not.

Thus, PoNS™ device provides clinically meaningful relief improvement treatment of gait deficit due to mild to moderate symptoms from multiple sclerosis when used as an adjunct to a supervised therapeutic exercise program.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

Benefit/Risk Conclusion

In conclusion, given the available information above, for the following indication statement:

> The PoNS™ device is indicated for use as a short-term treatment of gait deficit due to mild to moderate symptoms from multiple sclerosis and is to be used as an adjunct to a supervised therapeutic exercise program in patients over 22 years of age by prescription only.

The probable benefits outweigh the probable risks for the Portable Neuromodulation Stimulator (PoNS™). 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 Portable Neuromodulation Stimulator (PoNS™) is granted and the device is classified as follows:

Product Code: QCF
Device Type: Neuromuscular tongue stimulator to treat motor deficits
Regulation Number: 21 CFR 882.5889
Class: II