February 6, 2023

Theranica Bioelectronics ltd
% Janice Hogan
Partner
Hogan Lovells US LLP
1735 Market Street, Suite 2300
Philadelphia, Pennsylvania 19103

Re: K223169
Trade/Device Name: Nerivio
Regulation Number: 21 CFR 882.5899
Regulation Name: Trunk and limb electrical stimulator to treat headache
Regulatory Class: Class II
Product Code: QGT
Dated: October 9, 2022
Received: October 11, 2022

Dear Janice Hogan:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's

requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Jitendra V. Virani -S

CDR Jitendra Virani, MS MBA
Assistant Director
DHT5B: Division of Neuromodulation
and Physical Medicine Devices
OHT5: Office of Neurological
and Physical Medicine Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2023
See PRA Statement below

510(k) Number *(if known)*

K223169

Device Name

Nerivio

Indications for Use *(Describe)*

The Nerivio is indicated for acute and/or preventive treatment of migraine with or without aura in patients 12 years of age or older. It is a prescription use, self-administered device for use in the home environment at the onset of migraine headache or aura for acute treatment, or every other day for preventive treatment.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) SUMMARY

Theranica Bio-Electronics LTD.'s Nerivio

Submitter

Theranica Bio-Electronics LTD.
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Phone: +972-72-3909755
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Contact Person: Dagan Harris
Date Prepared: October 9, 2022

Name of Device: Nerivio

Common or Usual Name: Nerivio

Classification Name: Trunk and limb electrical stimulator to treat headache

Regulatory Class: Class II

Product Code: QGT

Regulation Number: 21 CFR 882.5899

Predicate Device:

Device name: Nerivio

Manufacturer: Theranica Bio-Electronics LTD.

510(k) Number: K203181

Device Description:

The Nerivio is a wearable, battery-powered device that is controlled by a mobile application. The system delivers low energy electrical pulses to the upper arm for 45 minutes per treatment, after which the device turns off automatically.

The device is composed of a pair of UltraStim® electrodes (K130987) covered with hydrogel and removable protective film, an electronic circuitry that includes firmware, LED indicator and a power button for activating the device and for wireless connection with Android and iOS mobile platforms and a battery contained in a plastic case situated within thermoplastic elastomers ("TPE") shell. In addition, an armband that is wrapped over the device to secure the Nerivio position on the user's arm is included.

The device is operated and controlled via software that is installed and run on a user's personal mobile device such as a mobile phone or tablet. The device hardware communicates with the mobile application through a Bluetooth protocol. This mobile application software allows the user to control the stimulation intensity from 0 to 100% (representing intensity levels of 0-40mA), to start or stop the

stimulation program, and to view device status such as the device's connection state, stimulation duration, remaining number of treatments, and user notifications.

The user is instructed to adjust the intensity to the strongest stimulation level just below the perceived pain level. Treatments with Nerivio are intended to be self-administered by the user immediately after the onset of migraine headache or aura.

Intended Use / Indications for Use

The Nerivio is indicated for acute and/or preventive treatment of migraine with or without aura in patients 12 years of age or older. It is a prescription use, self-administered device for use in the home environment at the onset of migraine headache or aura for acute treatment, or every other day for preventive treatment.

Summary of Technological Characteristics

Both the subject device and the predicate device function as remote electrical neuromodulation (REN) devices that utilize electro-stimulation that relieves migraine headache, using equivalent output parameters. The basic pulse structure is biphasic, with symmetrical interleaving phases and rectangular shape. The amplitude shift signal alternates between a nominal maximum and a nominal minimum of the amplitude signal. The maximal output current is 40mA. The assumed impedance is 1K ohm +/- 500 ohms.

Table 1 provides a comparison between the key functional features of the Nerivio and predicate device.

Characteristic	**Subject Device**	**Predicate Device**	**Comparison**
Submission Number	K223169	K203181	N/A
Device Name	Nerivio	Nerivio	Same
Manufacturer	Theranica Bio-Electronics LTD.	Theranica Bio-Electronics LTD.	Same
Indications for Use	Nerivio is indicated for acute or preventive treatment of migraine with or without aura in patients 12 years of age or older. It is a prescription use, self-administered device for use in the home environment at the onset of migraine headache or aura for acute treatment, or every other day for preventive treatment.	Nerivio is indicated for acute treatment of migraine with or without aura in patients 12 years of age or older. It is a prescription use, self-administered device for use in the home environment at the onset of migraine headache or aura.	Additional indication for preventive treatment
Prescription or OTC	Prescription	Prescription	Same
Electrical waveform	Biphasic rectangular, modulated	Biphasic rectangular, modulated	Same
Electrical output			
Max output voltage 500 Ω	20V (measured)	20V (measured)	Same

2 KΩ 10 KΩ	60V (measured) 60V (measured)	60V (measured) 60V (measured)	
Max output current 500 Ω 2 KΩ 10 KΩ	 40 mA 30 mA 6mA	 40 mA 30 mA 6mA	Same
Maximum phase charge (500Ω)	8μC	8μC	Same
Maximum average current (500Ω)	1.76mA	1.76mA	Same
Maximum current density (peak) (500Ω)	1.6mA/cm2	1.6mA/cm2	Same
Maximum current density (r.m.s) (500Ω)	0.34mA/cm	0.34mA/cm	Same
Maximum average current density (abs value) (500Ω)	0.07mA/cm2	0.07mA/cm2	Same
Maximum average power density (500Ω) Frequency	1.41mW/cm2	1.41mW/cm2	Same
Primary phase duration [μSec]	200	200	Same
Pulse Duration [μSec]	400	400	Same
Electrode Area	25 cm^2	25 cm^2	Same
Treatment location	Upper arm	Upper arm	Same
Treatment duration	45 min.	45 min.	Same
Reusable	Yes	Yes	Same
# of treatments per one device	Up to 18 treatments	12 treatments	Additional 6 treatments
Power source	LiMnO2 cell battery	LiMnO2 cell battery	Same
On/off button	Power push-button	Power push-button	Same
Dimensions	Device – 12.0x7.5x1.5 cm Armband – 48.0x10.0x0.3 cm	Device – 12.0x7.5x1.5 cm Armband – 48.0x10.0x0.3 cm	Same
Weight	Device - 50 gr Armband – 33 gr	Device - 50 gr Armband – 33 gr	Same
Shelf life	24 months	24 months	Same
Mobile Application software	Yes	Yes	Same
Biocompatibility	Yes	Yes	Same
Sterile	No	No	Same
Processor control	Yes	Yes	Same
Wireless control	Yes	Yes	Same
Automatic overload trip	Yes	Yes	Same
Automatic no load trip	Yes	Yes	Same
Automatic shut off	Yes	Yes	Same
Mobile Application treatment control	Yes	Yes	Same

Table 1 – Comparison between subject and predicate devices

Performance Data

Non-Clinical Tests:

As the Nerivio is identical to the predicate in its hardware and components. The subject device presents a few minor upgrades and additions in the software and firmware, with the main reflection on the user being the increased number of treatments it provides. Accordingly, non-clinical bench tests addressed verification and validation of the software, firmware, battery, and device performance

The company conducted internal bench tests to verify and validate the device battery's lifetime reliability and safety, firmware verification testing, system specification and verification testing, mobile application software testing. In all instances, the Nerivio functioned as intended and expected.

Clinical Tests:

A Randomized, Controlled Trial (RCT) of the Nerivio device in migraine patients was performed to assess the Nerivio safety and clinical efficacy in prevention of migraine. Specifically, it assessed the capability of the Nerivio device to reduce the number of migraine days, number of headache days and number of moderate/severe headache days in patients with migraine. The study was in compliance with 21 CFR parts 50, 56, and 812.

The study was a prospective, randomized, sham-controlled, multicenter study conducted at 15 sites. Eligible participants were adults (18–75 years old) who met the International Classification of Headache Disorders (ICHD-3) criteria for migraine, with 6 to 24 headaches per month (with at least 4 days a month on which their headaches and associated symptoms meet diagnostic criteria for migraine).

Participants had a 4-weeks period of "Baseline" phase. During that phase, participants were asked to complete a daily migraine diary using the electronic diary application installed on the participants' smartphones, while continue with their standard practice for migraine. Following the baseline period, and if were qualified to continue according to the study requirements, participants went into an 8-weeks period of "Treatment" phase. During that phase, participants were asked to treat with the Nerivio device every other day with their optimal stimulation intensity and complete a daily migraine diary using the electronic diary application installed on the participants' smartphones, while continue with their standard practice for migraine. Participants were asked NOT to use the Nerivio for acute treatment during the Treatment phase, in order to reduce bias between the active and the sham groups. At the end of the treatment phase, participant went into a 4-weeks period of "follow-up" phase.

The primary efficacy endpoint was the mean change in number of migraine days per month comparing the 4-week baseline phase (weeks 1-4) with the last 28 days of the treatment phase (weeks 9-12). The main secondary endpoints were the mean changes in numbers of moderate/severe headache days, and headache days per month comparing the 4-week baseline phase (weeks 1-4) with the last 28 days of the treatment phase (weeks 9-12).

248 participants were eligible to be randomized into the treatment groups (Active 128. Sham 120), and made the ITT dataset.

The findings of the study show that treatment with Nerivio every other day is significantly more effective than sham.

There was a reduction of 3.97±0.41 Vs. 1.28±0.43 of migraine days in the active and sham groups, respectively (mean±SEM, p<0.001), with a therapeutic gain of -2.69 (95% C.I. -3.87, -1.51) migraine days. The results indicate significant clinical benefit of the device. Importantly, the therapeutic gain is statistically significant in each one of the chronic and episodic sub-groups with gains of -3.04 (95% CI: -4.88, -1.21) and -2.26 (95% CI: -3.74, -0.78) migraine days in the chronic and episodic participants, respectively, indicating that Nerivio is effective for migraine preventive treatment of both chronic and episodic migraine.

Nerivio was statistically significant more effective than sham in the mean change in number of moderate/severe headache days per month in the last month of double-blind treatment phase: mean change of -3.82±0.40 days Vs. -2.23±0.39 in the Active and Sham groups, respectively (mean±SEM, p=0.005), with a therapeutic gain of -1.59 (95% C.I. -2.70, -0.48) moderate/severe headache days.

Nerivio was statistically significant more effective than sham in the mean change in number of total headache days per month in the last month of double-blind treatment phase: mean change of -4.46±0.42 Vs. -1.77±0.50 in the Active and Sham groups, respectively (mean±SEM. p<0.0001], with a therapeutic gain of -2.69 (95% C.I. -3.87, -1.51) headache days.

Nerivio was more effective than sham in the percentage of participants with at least a 50% reduction in the mean number of headache days per month in the last month of double-blind treatment phase. In the Active group, 26.3% of the participants (25 out of 95) demonstrated reduction of at least 50% in their number of headache days, compared to 11.9% of the participants in the Sham group (10 out of 84), resulted in 2.21 folds in favour of the Active group (p=0.015).

Nerivio was statistically-significantly more effective than sham in the mean change in number of acute headache/migraine medication days per month from weeks 1-4 to weeks 9-12, with a reduction of 3.5±0.42 in Active group Vs. 1.4±0.47 in the Sham group (mean±SEM, p=0.001), with a therapeutic gain of -2.08±0.63 (95% C.I [-3.33, -0.83]) acute headache/migraine medications days.

There were two serious adverse events (SAEs) during the study (suicidal attempt and a case of Appendicitis), which were deemed to be non-related to the study device or study procedures.

There was only one device-related adverse event, in the sham group (0.83%, [1/120]).

The study demonstrates the effectiveness and safety of the Nerivio as a therapy for prevention of migraine. The results are clinically meaningful and demonstrates that peripheral neurostimulation aiming can invoke conditioned pain modulation that induces a reduction in the number of monthly migraine days. No statistically significant differences were found between the Active and Sham groups in either the type or rate of adverse events during the treatment phase

During the data analysis it was found that 4 participants (2 from the active group and 2 from the sham group) did not complete 12 treatments during days 29-56 of the treatment phase and therefore were not included in the mITT dataset.

Nevertheless, analysis was performed including these 4 patients with similar results to the original mITT analysis.

For the primary endpoint, the original mITT analysis demonstrated a reduction of 3.97±0.41 Vs. 1.28±0.43 of migraine days in the active and sham groups, respectively (mean±SEM, p<0.001), with

a therapeutic gain of -2.69 (95% C.I. -3.87, -1.51) migraine days. The revised mITT analysis demonstrated a reduction of 3.96±0.42 Vs. 1.24±0.42 of migraine days in the active and sham groups, respectively (mean±SEM, $p<0.001$), with a therapeutic gain of -2.72 (95% C.I. -3.90, -1.53) migraine days.

In order to demonstrate the balance between the two groups, an analysis of the demographic and migraine history data was performed for both active and sham groups for both mITT and ITT datasets. No statistically significant differences were found between the active and the sham groups

These data, in conjunction with prior studies of the Nerivio device, support the use of the device for the listed indications.

Nerivio relies on the same, well-established mechanism in adults and adolescents (conditioned pain modulation, CPM) and previous studies (K203181) demonstrate a comparable safety and effectiveness profile for treatment of migraine in adolescents and adults. The company further analyzed the real-world data generated from adolescents using the device (for acute) in high frequency usage, which is equivalent to the suggested preventive use modality (10 times per month or higher).

Data was collected from all adolescent patients who used Nerivio on at least 10 days in their first 28-day month of using Nerivio (after being prescribed the device for acute treatment of migraine, by licensed providers in the US), and further used the device on at least 3 days in each one of the two subsequent 28-day months. Given that Nerivio is typically used as the only acute therapy (Ailani et al., Frontiers in Pain Research, 2022), especially by adolescents, the purpose of the analysis was to assess the mean reduction in migraine headache days in this group of young patients in their second and third months of using Nerivio.

61 patients (Age 15.7 ± 1.3 years, 87% female) were found eligible for this analysis. The analysis consists of prospective data, collected through the Nerivio App between January 2, 2021, and November 26, 2022. The results demonstrate a substantial month-to-month reduction in migraine headache days from 15.0 days (SE=0.6) in the 1st month, to 10.6 days (SE=0.8) in the 2nd month of consecutive use ($p<<0.0001$, paired t-test), and further down to 8.7 days (SE=0.7) in the 3rd month of consecutive use ($p<<0.0001$, paired t-test).

The data shows that in adolescent patients who treated themselves for migraine at least 10 times per month, there was a substantial reduction in headache days from the first month of use to the third month.

Conclusions

The Nerivio has similar intended use, as demonstrated by the clinical data to support the safety and effectiveness for the new indications (with the addition of preventive treatment), and identical technological characteristics and principles of operation as its predicate device. The clinical study results demonstrated that Nerivio is a safe and effective therapy for migraine prevention. The requested indication expansion does not alter the targeted disease, nor the administration of a treatment, and does not affect its safety when used as labeled. In addition, the minor software differences between the Nerivio and its predicate device raise no additional questions of safety or usability. Performance data demonstrate that the Nerivio is as safe and effective as the predicate device. Thus, the Nerivio is substantially equivalent to its predicate device.

Extrapolating data from adult patient, following the FDA guidance, ("Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices", June 21, 2016), and given that Nerivio mechanism of action (triggering CPM) is the same for adults and adolescents suggested that the device is effective for prevention of migraine also in adolescents. This was further supported by real-world evidence data from adolescents who used Nerivio (for acute treatment) at a high frequency, similar to the frequency required for preventive treatment (every other day). The combination of the real-world evidence data and the extrapolation of data from adult users led to the conclusion that using the using Nerivio every other day is effective for migraine prevention also for adolescents.