DE NOVO CLASSIFICATION REQUEST FOR
INTRANASAL TEAR NEUROSTIMULATOR

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Tear Electrostimulation Device. A tear electrostimulation device is a non-implantable device intended to increase tear production.

NEW REGULATION NUMBER: 21 CFR 886.5300

CLASSIFICATION: Class II

PRODUCT CODE: PQJ

BACKGROUND

DEVICE NAME: Intranasal Tear Neurostimulator

SUBMISSION NUMBER: DEN160030

DATE OF DE NOVO: July 5, 2016

CONTACT: Oculeve, Inc.
395 Oyster Point Blvd, Suite 501
South San Francisco, CA 94080

INDICATIONS FOR USE

The Intranasal Tear Neurostimulator provides a temporary increase in tear production during neurostimulation in adult patients.

LIMITATIONS

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

The safety and effectiveness of the Intranasal Tear Neurostimulator for the treatment of aqueous deficient dry eye disease has not been established.

The device increases tear production during neurostimulation, i.e., tearing was assessed only during stimulation.

The clinical study was not designed to evaluate any changes in nerve sensitivity.

Clinical study results demonstrate a trend of decreased effectiveness (tear production) over time. The mechanism for this decrease has not been identified and was not analyzed as part of the study.

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

DEVICE DESCRIPTION

The Intranasal Tear Neurostimulator is a non-surgical, non-implantable device intended for the application of low level electrical stimulation to sensory neurons of the nasal cavities to acutely increase tear production in adult patients.

The device consists of four distinct non-sterile subassemblies, as listed below:

1. **Disposable Tips** that insert up to 28mm into the nasal cavity and stimulate the target tissue of the intranasal skin and mucosa.
2. A reusable **Base** which produces the electrical stimulation waveform.
3. A reusable **Charging Station** which recharges the sealed battery inside the Base.
4. A reusable **Cover** to protect the Disposable Tips.

Figure 1 provides a photograph of the device assembly; additional details for each component are discussed below.

FIGURE 1. THE OCULEVE INTRANASAL TEAR NEUROSTIMULATOR COMPONENTS

The device (Base) automatically turns off after one minute of stimulation. Alternatively, the device may also be turned off by holding down the "–" button for 2 seconds. The device will vibrate and the LEDs will turn off to indicate that the power has been switched off.

Additionally, the device (Base) has a "Daily device usage limit" of thirty (30) minutes. If an orange LED flashes 2 times, the daily use limit (30 minutes) has been reached, and the device will no longer deliver stimulation.

Figure 2 is a schematic showing correct use of the device.

FIGURE 2. USE OF THE INTRANASAL TEAR NEUROSTIMULATOR. (L) STARTING POSITION AND (R) CORRECT TREATMENT POSITION

DISPOSABLE TIPS
The Disposable Tips connect to the Base and incorporates a silicone hydrogel that touches the inside of the nose, at a depth of up to 28 mm from the nasal columella (the skin separating the two nostrils), to provide stimulation. The Disposable Tips are removed and replaced daily; a separate Cover can be used to protect the Disposable Tips between uses.

BASE
The hand-held, battery-powered Base is the portion of the device which produces the required electrical output for stimulation. The Base produces a train of charge-balanced pulses that is patterned by modulating pulse amplitude, pulse width and pulse shape. The intensity of the stimulation is adjustable by using the (+) or (-) control buttons, which cycle the Base through six different levels (including zero, a non-stimulation level). The Base is held in the palm of the hand, allowing the patient to press one of two buttons to increase or decrease the intensity of stimulation. A series of LEDs on the Base illuminate to indicate powering the device on/off, the intensity level during use, and the charging of the Base's battery when connected to the Charging Station.

CHARGING STATION
The Charging Station provides a dock for recharging the battery located inside the Base. With the Disposable Tips removed, the Base can be inverted and placed onto the Charging Station.

COVER
The Cover is made of polycarbonate material and fits over the tips. The Cover can be used to protect the Disposable Tips between uses.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The Disposable Tips of the Intranasal Tear Neurostimulator were tested for cytotoxicity, sensitization, irritation, acute systemic toxicity per ISO 10993-1 "Biological evaluation of medical devices -- Part 1: Evaluation and testing within a risk management process." All results demonstrated acceptable performance.

SHELF LIFE/STERILITY

The Intranasal Tear Neurostimulator is non-sterile. The Disposable Tips are disposable and are meant to be replaced daily. The Cover is reusable. Cleaning and maintenance instructions of the stimulator components of the device are included in the labeling.

ELECTRICAL SAFETY

The Intranasal Tear Neurostimulator was tested per the requirements of AAMI/ANSI ES60601-1:2012 and IEC 60601-1:2006 "Medical Electrical Equipment Part 1: General Requirements for Basic Safety and Essential Performance." The Base and Charging Station are compliant to these standards.

The device was also tested per the requirements of IEC 60601-1-11:2015 "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 is in conformance with this standard.

The Intranasal Tear Neurostimulator was tested specifically per the requirements of IEC 60601-2-10, Edition 2.0 Issue: 2012/06 "Medical Electrical Equipment Part 2-10: Particular Requirements for the Safety of Nerve and Muscle Stimulators - Includes Amendment A1: 2001." The device is in conformance with this standard.

ELECTROMAGNETIC COMPATIBILITY

The Intranasal Tear Neurostimulator was tested according to the IEC 60601-1-2, Issue: 2007/03/01 Ed:3.0 (Equivalent to AAMI/ANSI/IEC 60601-1-2:2007/(R)2012) "Medical Electrical Equipment - Part 1-2:General Requirements for Basic Safety and Essential Performance – Collateral Standard: Electromagnetic Compatibility - Requirements and Tests." Results demonstrated that the Base and Charging Station are compliant to this standard.

SOFTWARE

The following device functions of the Intranasal Tear Neurostimulator are controlled by the software:

- The allowance of multiple stimulation sessions of various intensity levels.
- The control of stimulation intensity levels.
- The notification to the user when the charging is complete.
- The connection to mobile applications to download or clear historical stimulation data.

The software will mitigate safety risks as follows:

- The software limits the output current to a maximum of 5 mA.
- The software disables stimulation if the tip expiration time is exceeded, if the stimulation mode exceeds the maximum usage time, or exceeds the maximum usage time within the rolling usage time window.

A failure or latent flaw in the software for the Intranasal Tear Neurostimulator could indirectly result in patient injury; therefore, the software of this device is considered to have a "Moderate" level of concern. The submission contained all of the elements of software documentation corresponding to the "Moderate" level of concern, as outlined in the "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices." Adequate documentation describing the software/firmware, software specifications, architecture design, software development environment, traceability, revision level history, unresolved anomalies provide the foundation that the software will operate in a manner as described in the specifications. 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 results.

SUMMARY OF CLINICAL INFORMATION

The applicant conducted two pivotal clinical trials, OCUN-009 and OCUN-010, and a human factors usability study, OCUN-012, described below, which demonstrated that patients can use the Intranasal Tear Neurostimulator properly. The safety and effectiveness of the device was evaluated based upon the outcomes of studies OCUN-009 and OCUN-010. The two pivotal studies were found to be appropriate to support the action of the device effect (increased tear production during neurostimulation); however, therapeutic benefit, e.g., symptomatic relief from dry eye, was not assessed in the clinical studies.

OCUN-009

Pivotal clinical trial OCUN-009 was conducted to evaluate the safety and acute tear production during neurostimulation. The results of this trial provide reasonable assurance of safety and effectiveness of the device to increase tear production during stimulation. This two-day trial was a randomized, controlled, double-masked, study conducted at 2 sites in the United States. Forty-eight subjects (≥22 years of age) received one active and two control treatments. On Day 1, participant eligibility was assessed. On Day 2, each study participant was subjected to three applications (1 active and 2 control) of the device in random order. Active treatment was performed using the Intranasal Tear Neurostimulator as intended. One control treatment used an active device that was "off-target" (i.e., extra-nasal). The other control treatment used a sham device. Tear production was assessed using the Schirmer test, which uses a paper strip that is

inserted into the eye for several minutes to provide a direct measurement of tear production in subjects due to the naso-lacrimal reflex. Schirmer scores and assessment of oxygen saturation (SpO2), heart rate (HR) and blood pressure (BP) were performed simultaneously during each application. Following completion of the 3 applications, subjects were assessed for visual acuity changes and underwent slit lamp and nasal examinations.

The primary effectiveness endpoint was the difference between unstimulated and stimulated tear production quantified by Schirmer scores. Based on measurements using the Schirmer test, there was an increase in tear production during electrostimulation. The average Schirmer score was reported for the active and two control applications. An average Schirmer score of 25.3 mm ± 10.7 was observed during active electrostimulation, compared with 9.2 mm ± 7.3 for the Sham control application ($p < 0.0001$), and 9.5 mm ± 8.2 for the extranasal control application ($p < 0.0001$). The primary effectiveness endpoint was met with increased tear production relative to each of the two control applications.

The primary safety measure was the proportion of subjects reporting one or more adverse events (AEs) in addition to the proportion of subjects reporting device-related AEs. No significant clinical changes or findings were observed on Day 2 in intranasal speculum examination, slit lamp biomicroscopy, corneal integrity, or best-corrected spectacle visual acuity. The primary safety endpoint was met with no device-related serious adverse events (AEs) or AEs that led to discontinuation of the study. A total of 4 subjects reported 4 AEs (1 corneal abrasion not related to the subject device). The 3 remaining non ocular AEs were "nasal itching" (related), "transient lightheadedness" (possibly related), and "exacerbation of hypertension" (not related to the device). All AEs resolved without sequelae. Heart rate and BP were slightly increased during stimulation with the Oculeve device applied Intra-nasally and returned to pre-stimulation levels approximately two minutes following stimulation. Minimal change was observed in SpO2 between the pre-stimulation, stimulated and post-stimulated values for the investigational device or controls.

OCUN-010

Pivotal clinical trial OCUN-010 was conducted to evaluate the tear production during neurostimulation over time. The results of this trial provide reasonable assurance of safety and effectiveness of the device to increase tear production upon multiple stimulations over 6 months.

This trial was a single-arm, multicenter, open-label study conducted at 3 sites in the United States. Ninety-seven subjects with aqueous tear deficient dry eye were evaluated for safety and effectiveness after 180 days of use with the subject device. Subjects were given the device for home use and instructed to perform neurostimulation at least 2-10 times per day. Subjects were seen at days 7, 30, 90, and 180. Schirmer tests were performed at each visit.

The primary effectiveness endpoint was the increase in tear production in the study eye during use of the Intranasal Tear Neurostimulator compared to the unstimulated tear production as assessed by the Schirmer test at Day 180. Secondary endpoints were Schirmer values at days 0, 7, 30, and 90. On Day 0, as well as at each follow-up visit, the Schirmer test was performed, followed by a subsequent Schirmer test with device stimulation. The unstimulated vs stimulated data was compared on the same eye, which was previously designated as the Study eye. The

difference in mean Schirmer scores between active stimulation and no stimulation at those time points was statistically significant. The outcomes were also stratified by age, sex, race, and baseline Schirmer score, and were statistically significant for all age strata except those subjects over age 70, which was comprised of only 6 subjects. The results were also statistically significant for both males and females as well as white and non-white races. The results were also statistically significant for patients with baseline Schirmer score in the range of 0 – 5 mm and in the range of 6 – 10 mm.

The study met its primary effectiveness endpoint and each of its secondary effectiveness endpoints, as statistically significant increases in stimulated tear production were seen in the study eye at all study visits. The mean difference between stimulated and unstimulated tear production was 18.0 mm on Day 0, 13.1 mm on Day 7, 8.1 mm on Day 30, 8.3 mm on Day 90, and 9.4 mm on Day 180. However, the results indicate that in comparing stimulated vs. unstimulated tear production over the 180 days, there was a trend toward decreased tear production over time with device usage; this trend appeared to plateau toward the end of the study. Device effectiveness beyond 180 days is unknown. Therapeutic benefit (e.g., symptomatic relief from dry eye) was not assessed in the clinical studies.

The primary safety endpoint was the proportion of subjects who experienced one or more device-related AEs. Safety results for this study reported NO device related SAEs. The most frequently related AEs were all nasal: nasal pain/discomfort (aching, burning, soreness, etc. in 10 subjects), transient intra-nasal discomfort (sharp tingle in 5 subjects), nosebleed (mild nose bleed in 5 subjects), nasal congestion in 3 subjects), headaches (in 2 subjects), blood in nostril in 2 subjects, facial pain in 2 subjects, and 1 each for sore eye, sinus pain, periorbital pain, runny nose, nasal ulcers, lightheadedness.

OCUN-012

The human factors study, OCUN-012, was performed to ensure the subject device is not vulnerable to harmful use-errors that could lead to injury. Sixteen laypeople were tested; subjects served as their own control. Each test session lasted up to 75 minutes consisting of a test orientation, background interview and six tasks. The tasks consisted of four hands-on and two IFU comprehension tasks. No safety related use-errors were reported. Also, none of the participants required test administrator assistance, encountered safety-related close calls, or experienced patterns of safety-related difficulties when performing the tasks (e.g., set up and first treatment, charge battery, replace tip & deliver treatment, and IFU comprehension).

A post-test interview focused on task performance and the participants' perception of the device's safety. All participants were able to use the device correctly and understood the labeling. All participants considered the device to be safe based on a questionnaire.

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 (Professional Information Guide and Patient Information Guide) is sufficient and meets the requirements of 21 CFR 801.109. Both guides contain the Indications for Use, contraindications, device description, warnings, precautions, potential complications, instructions for use, recommended stimulation schedule, instructions for device maintenance/cleaning, summary of clinical trials, information related to electromagnetic compatibility, expected service life, disposal & replacement, environmental operating conditions, electrical specifications, and symbols & markings. The patient labeling also includes additional information such as a glossary, quick start guides, "facts about dry eye," and potential benefits.

RISKS TO HEALTH

Table 1 identifies the risks to health that may be associated with use of the Tear Electrostimulation Devices and the measures necessary to mitigate these risks.

Table 1 – Identified Risks to Health and Mitigation Measures

Identified Risk	**Mitigation Measures**
Tissue damage due to over-stimulation/under-stimulation or mechanical injury (ex: tips too long), device breakage	• Non-clinical performance testing • Software verification, validation and hazard analysis • Electrical, thermal, and mechanical safety testing • Labeling
Pain, headache, or discomfort	• Non-clinical performance testing • Electrical, thermal, and mechanical safety testing • Labeling
Adverse tissue reaction	• Biocompatibility • Labeling
Infection	• Labeling
Electrical shock or burn	• Electrical, thermal, and mechanical safety testing • Software verification, validation and hazard analysis • Labeling
Interference with other devices	• Electromagnetic compatibility (EMC) testing • Software verification, validation and hazard analysis • Labeling

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the Tear Electrostimulation Device is subject to the following special controls:

1. Non-clinical performance testing must assess the following electrical output specifications: waveforms, output modes, maximum output voltage, maximum output current, pulse duration, frequency, net charge per pulse, maximum phase charge at 500 ohms, maximum current density, maximum average current, and maximum average power density.

2. Patient-contacting components of the device must be demonstrated to be biocompatible.

3. Performance testing must demonstrate the electrical, thermal, and mechanical safety along with electromagnetic compatibility (EMC) of the device in the intended use environment.

4. Software verification, validation and hazard analysis must be performed.

5. Physician and patient labeling must include:

    a. Summaries of electrical stimulation parameters.
    b. Instructions on how to correctly use and maintain the device.
    c. Instructions and explanations of all user-interface components.
    d. Information related to electromagnetic compatibility classification.
    e. Instructions on how to clean the device.

BENEFIT/RISK DETERMINATION

The risks of the device are based on non-clinical laboratory data, as well as data collected in a clinical studies described above. The device exhibited an acceptable safety profile in the clinical studies which were conducted. No device-related serious adverse events were observed. Non-serious device-related adverse events were few in number, all self-limited, predominantly nasal in nature and decreased in incidence over the course of the study. The human usability study showed that participants used the device without safety-related use errors, requiring test administrator assistance, encountering safety-related close calls, or experiencing patterns of safety-related difficulties when performing the tasks.

The probable benefits of the device are also based on nonclinical laboratory data, as well as data collected in clinical studies. The device has been shown to increase tear production during single and numerous stimulations based on the Schirmer test, an accepted test to quantify tear production. The measured increase in tear production was evaluated both per single device-application and after numerous device applications. During a single application compared to two control applications, the mean difference between Schirmer score with active stimulation versus Sham control application and extranasal control application was 16.1 mm and 15.8 mm, respectively (25.3 mm ± 10.7 active and 9.2 mm ± 7.3 for the Sham control and 9.5 mm ± 8.2 for the extranasal control). During multiple applications over a six month period, the mean difference between stimulated and unstimulated tear production was 18.0 mm on Day 0, 13.1 mm on Day 7, 8.1 mm on Day 30, 8.3 mm on Day 90, and 9.4 mm on Day 180. While there was a trend toward decreased tear production with time, this trend appeared to plateau and still demonstrates an increase in tear production during electrostimulation compared to baseline measurements without electrostimulation. In multiple neurostimulation, mean stimulated tear production was statistically significantly better than the mean unstimulated tear production at all study visits through Day 180. Based on the two studies, this device shows that during stimulation, there is an increase in tear production. While the effect appears to diminish over time compared with initial application (based on study results from Study OCUN-010), there is a clear increase compared to baseline, or no device use.

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, the data support for the temporary increase in tear production during neurostimulation in adult patients, the probable benefits outweigh the probable risks for the Intranasal Tear Neurostimulator. The device provides benefits and the risks can be mitigated by the use of general and the identified special controls.

CONCLUSION

The De Novo request for the Intranasal Tear Neurostimulator is granted and the device is classified under the following:

Product Code: PQJ
Device Type: Tear Electrostimulation Device
Class: II
Regulation: 21 CFR 886.5300