DE NOVO CLASSIFICATION REQUEST FOR
TRUETEAR INTRANASAL TEAR NEUROSTIMULATOR

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Intranasal electrostimulation device for dry eye symptoms. An intranasal electrostimulation device for dry eye symptoms is a prescription non-implantable, electrostimulation device intended to increase tear production for improvement in dry eye symptoms

NEW REGULATION NUMBER: 21 CFR 886.5310

CLASSIFICATION: Class II

PRODUCT CODE: QBR

BACKGROUND

DEVICE NAME: TrueTear Intranasal Tear Neurostimulator

SUBMISSION NUMBER: DEN170086

DATE DE NOVO RECEIVED: October 23, 2017

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INDICATIONS FOR USE

The TrueTear Intranasal Tear Neurostimulator provides a temporary increase in tear production during neurostimulation to improve dry eye symptoms in adult patients with severe dry eye symptoms.

LIMITATIONS

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

Patient training is required on the proper use of the device before home use.

The TrueTear device is limited only to the improvement in dye eye symptoms as the safety and effectiveness in the treatment of 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 TrueTear 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 increase tear production to improve dry eye symptoms in adult patients with severe dry eye symptoms.

The design has not been significantly modified from the device granted under DEN160030. The following are the technical changes from DEN160030:

1) Enabling Bluetooth functionality within the device, to enable one-way (outbound only) wireless communication
2) Removal of (b) (4) from the (b) (4) material used in the disposable tip
3) Disabling of the tip detection feature in the Base Unit
4) Addition of an optional mobile application (TrueTear App) for reading and summarizing device usage data.

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

1) **Disposable Tips** that insert up to 28 mm into the nasal cavity and stimulate the target tissue of the intranasal skin and mucosa.
2) A reusable **Base Unit** 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 figures of the device components; additional details for each component are discussed below.

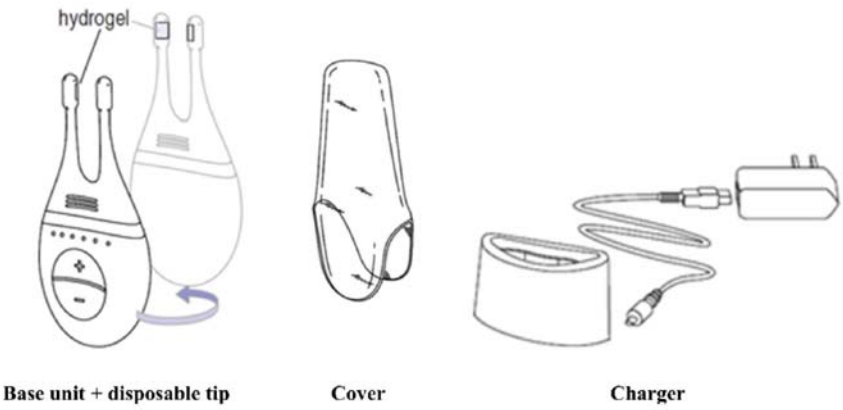

FIGURE 1. THE TRUETEAR INTRANASAL TEAR NEUROSTIMULATOR COMPONENTS

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 Light-Emitting Diodes (LED) 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 TRUETEAR 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. The base includes the wireless Bluetooth Low Energy communication channel for one-way (outbound) communication with the TrueTear mobile application. 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.

TrueTear App
The TrueTear application is intended to be used on a mobile device (e.g., a smart phone) and uses the phone's Bluetooth functionality to connect to the TrueTear device, downloading device usage data. The TrueTear application, when connected to the TrueTear device, displays usage statistics for the TrueTear device and a summary of the TrueTear device's Instructions for Use. The usage statistics consist of summaries of the user's stimulation duration and frequency tabulated and/or displayed on a periodic (e.g., daily) basis. The mobile application does not provide any diagnostic and treatment recommendations and does not control or modify the TrueTear device.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The Disposable Tips of the TrueTear 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 TrueTear 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.

ELECTROMAGNETIC CAPABILITY (EMC) AND ELECTRICAL SAFETY

The device conformed to the following electromagnetic compatibility, electrical, mechanical, and thermal safety standards:

- The TrueTear Intranasal Tear Neurostimulator was tested per the requirements of IEC 60601-1: 2005 + CORR. 1:2006 + CORR. 2:2007 + AM1:2012. "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 TrueTear 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.

- The TrueTear 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 TrueTear 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 TrueTear 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 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, measurement related errors and cybersecurity. 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, which demonstrated that patients can use the TrueTear Intranasal Tear Neurostimulator properly. The safety and effectiveness of the device was evaluated based upon the outcomes of trials OCUN-009 and OCUN-010. The two pivotal trials were found to be appropriate to support the action of the device effect of increased tear production during neurostimulation in DEN160030. Please see FDA's summary of the De Novo Classification Request for DEN160030 for summaries of OCUN-009, OCUN-010, and OCUN-012. The current De Novo request was submitted for the new indication of improving dry eye symptoms. New effectiveness information was submitted from OCUN-10 to support the new indication. A brief summary of the symptoms information is provided below.

Participants meeting the enrollment criteria at a Screening Visit were enrolled at day 0 (baseline), provided patient training on the correct use of the device, and provided with a TrueTear device for home use.

Patient training for each subject in OCUN-010 covered all content found in the proposed Instructions For Use (IFU) and Patient Quick Start Guide. A demonstration device was used with each subject as a visual aid. All training was provided by site personnel. This training took up to 30 minutes.

Participants were instructed to perform intranasal neurostimulation at least 2 times a day and as often as 10 times per day, as needed, and no more than 3 minutes per use. Participants were followed for 180 days and were seen for follow-up exams at days 7, 30, 90, and 180. Symptoms were assessed with the Ocular Surface Disease Index (OSDI) at the Screening Visit and days 0, 7 and 30. Dry eye symptom severity subgroups were determined by the Screening Visit OSDI total score where moderate dry eye was defined as an OSDI total score of 13 to 22 and a severe

dry eye was defined as an OSDI total score of 33 or more. Within participant change in OSDI from baseline was analyzed. The minimal clinically important difference (MCID) thresholds for the analyses were based on those characterized by Miller et al (Arch Ophthalmol. 2010;128(1):94-101).

The proportion of participants with a clinically important change in OSDI at follow-up days 7 and 30 for all available participants stratified by dry eye symptom severity subgroup and by the upper and lower limit of the MCID was analyzed. Of the 97 participants that were enrolled, 77 had severe dry eye symptoms at the Screening Visit and were seen following treatment. As shown in Table 4 below, of these participants seen at day 30, approximately 25-39% had a clinically meaningful improvement in their symptoms and approximately 7-12% had clinically meaningful worsening of their symptoms from baseline. The sample size of the moderate dry eye group was too small to make meaningful inferences regarding their results.

TABLE 1: PROPORTION OF SUBJECTS WITH SEVERE DRY EYE SYMPTOMS AT SCREENING WITH A CLINICALLY IMPORTANT CHANGE IN THE OSDI* FROM BASELINE AT DAYS 7 AND 30

Cohort	MCID**	Change	Day 7	Day 30
Severe Dry Eye Subgroup	7.3	Improved	42.86% (33/77)	38.67% (29/75)
		Worsened	12.99% (10/77)	12.00% (9/75)
	13.4	Improved	23.38% (18/77)	25.33% (19/75)
		Worsened	5.19% (4/77)	6.67% (5/75)

*OSDI – Ocular Surface Disease Index

**MCID – Minimal Clinically Important Difference

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 professional and patient labeling are adequate and meet the requirements of 21 CFR 801.109. Both guides contain requirements for use by prescription only and proper patient training, 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, “facts about dry eye,” and potential benefits.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of the intranasal electrostimulation device for dry eye symptoms and the measures necessary to mitigate these risks.

Table 2 – Identified Risks to Health and Mitigation Measures

Identified Risks	**Mitigation Measures**
Tissue damage due to overstimulation/understimulation 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
Adverse tissue reaction	Biocompatibility evaluation 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
Pain, headache, or discomfort	Clinical performance testing Non-clinical performance testing Electrical, thermal, and mechanical safety testing Labeling
Failure to mitigate dry eye symptoms	Clinical performance testing Training Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the intranasal electrostimulation device for dry eye symptoms is subject to the following special controls:

(1) Clinical performance testing must evaluate improvement of dry eye symptoms under anticipated conditions of use.

(2) 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.

(3) Patient-contacting components of the device must be demonstrated to be biocompatible.

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

(5) Software verification, validation and hazard analysis must be performed.

(6) Training for the proper use of the device must be provided.

(7) 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.
   f. Summaries of clinical performance testing demonstrating safety and effectiveness.

BENEFIT-RISK DETERMINATION

The risks of the device are based on non-clinical laboratory data, as well as data collected in clinical trials described above and in FDA's summary of the De Novo Classification Request for DEN160030. 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 probable benefits of the device are also based on nonclinical laboratory data, as well as data collected in clinical trials. There were more participants with severe dry eye symptoms that had a meaningful improvement in symptoms as measured with the Ocular Surface Disease Index (OSDI) than the number with clinically significant worsening of symptoms at day 7 and at day 30.

Patient Perspectives

Patient perspectives were considered for the TrueTear Intranasal Tear Neurostimulator during the review. Dry eye symptoms were assessed using the OSDI patient-reported outcome measure.

Benefit/Risk Conclusion

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

The TrueTear Intranasal Tear Neurostimulator provides a temporary increase in tear production during neurostimulation to improve dry eye symptoms in adult patients with severe dry eye symptoms.

The probable benefits outweigh the probable risks for the TrueTear Intranasal Tear Neurostimulator. 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 TrueTear Intranasal Tear Neurostimulator is granted and the device is classified as follows:

Product Code: QBR
Device Type: Intranasal electrostimulation device for dry eye symptoms
Class: II
Regulation Number: 21 CFR 886.5310