DE NOVO CLASSIFICATION REQUEST FOR OCUCOOL

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Ophthalmic cooling anesthesia device. An ophthalmic cooling anesthesia device is a device that performs rapid, controlled cooling of the conjunctiva and sclera to provide temporary pain relief during ophthalmic procedures.

NEW REGULATION NUMBER: 21 CFR 886.4190

CLASSIFICATION: Class II

PRODUCT CODE: QZQ

BACKGROUND

DEVICE NAME: OcuCool

SUBMISSION NUMBER: DEN230011

DATE DE NOVO RECEIVED: February 16, 2023

SPONSOR INFORMATION:

RecensMedical, Inc.
1820 Medical Arts Building
Minneapolis, Minnesota 55402

INDICATIONS FOR USE

The OcuCool is indicated as follows:

OcuCool is a cooling anesthesia device intended for topical application to the conjunctiva and sclera. OcuCool is intended for the temporary reduction of pain associated with intravitreal injections.

OcuCool is indicated for patients who are allergic to deep penetrating pharmaceutical based anesthetics used for temporarily reducing pain during and following intravitreal injections.

LIMITATIONS

The sale, distribution, and use of OcuCool are restricted to prescription use in accordance with 21 CFR 801.109.

The following contraindications, warnings, and precautions apply to the OcuCool device:

- Contraindications: patients who are younger than 22 years old; patients who have a history or presence of scleromalacia; patients who have preexisting conjunctival, episcleral or scleral defects.

- The OcuCool device was not studied in the population of patients who are allergic to deep penetrating pharmaceutical based anesthetics. Therefore, the safety and effectiveness of OcuCool in this patient population is unknown.

- The effectiveness of the OcuCool in patients who are allergic to deep penetrating pharmaceutical based anesthetics has not been demonstrated. Therefore, pain may not be adequately controlled with use of OcuCool, which may lead to patient non-compliance with intravitreal treatment and worsening of the underlying eye condition for which the intravitreal treatment is being given. Inadequately controlled pain may also lead to inadvertent patient movement or eye movement during the injection, which may lead to traumatic injuries to other ocular structures such as the lens.

- The long-term safety and effectiveness of OcuCool use (i.e., regular, repeated use over time) has not been established. There is limited clinical data on repeated OcuCool use.

- Always perform intravitreal injections (IVT) within 30 seconds of completing the cooling anesthesia process. The anesthetic effect decreases over 30 seconds and injections performed beyond that time could lead to patient discomfort or injury. If the IVT is not performed within 30 seconds, apply cooling anesthesia by shifting from the previous injection site. Do not repeat cooling anesthesia on the same injection site.

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

DEVICE DESCRIPTION

The OcuCool is a hand-held, cooling anesthesia device that provides rapid and controlled cooling to the conjunctiva and sclera. It is intended to provide an anesthetic effect via a controlled cooling treatment. The main device performs controlled thermoelectric cooling of a single-use sterile OcuCool Tip. The hand-held device has a rechargeable battery, an LCD display screen to show device status, and two LED indicators to show cooling status and battery charging status. Other features of the hand-held device include the Priming Button, which activates the cooling process in preparation for device use and the Cooling Trigger, which activates the cooling anesthesia process. The device has a built-in 30 second timer and alarm to indicate the effective duration of the anesthetic effect after device use.

The device is intended to be used on patients by a healthcare provider trained and qualified to diagnose and treat ophthalmic disease and perform intravitreal injections. After inserting a single-use OcuCool Tip into the main, hand-held device, the OcuCool Tip is cooled to -13ºC, or primed, prior to making contact with the eye. The OcuCool device detects the heat flow between the Tip and ocular surface and determines if a proper contact is made. When proper contact has been made with the eye, the device signals that the Cooling Trigger is ready to be pressed with audible beep notification. The device then delivers 10 seconds of cooling, resulting in the conjunctiva reaching a temperature of -15ºC. Once cooling of the conjunctiva is complete, the device increases the Tip temperature to -3ºC and notifies a user that the OcuCool is ready to detach from ocular surface.

SUMMARY OF NONCLINICAL/BENCH STUDIES

Non-clinical testing for the OcuCool included a biological safety evaluation, sterilization, packaging, and shelf-life testing, software and cybersecurity testing, electromagnetic compatibility (EMC) testing, performance testing and human factors validation testing.

BIOCOMPATIBILITY/MATERIALS

Biocompatibility testing was performed on the OcuCool patient contacting OcuCool Tips. The biocompatibility assessment was performed in accordance with International Standard Organization (ISO) 10993-1: Biological evaluation of medical devices-Part 1: Evaluation and testing within a risk management process, Part 5: Tests for in vitro cytotoxicity, - Part 10: Tests for skin sensitization. All tests were performed in accordance with Good Laboratory Practices (GLP). The information provided is in alignment with FDA's Biocompatibility Guidance "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process". This evaluation was found to be acceptable.

SHELF LIFE/STERILITY

The OcuCool Hand-Held Device, OcuCool Battery Charger, OcuCool Cradle, OcuCool Protective Cover, and OcuCool Test-Tip are reusable, non-sterile components. The use-life of the battery has been shown to withstand 500 charging cycles. The labeling provides instructions for cleaning the external surfaces of the reusable components.

The OcuCool Tips are single-use components provided sterile with a Sterility Assurance Level (SAL) of 1 x 10^{-6}. The sterilization process for gamma irradiation was validated based on the VDMAX25 method as recommended in ANSI/AAMI/ISO 11137: Sterilization of health care products: requirements for validation and routine control – Radiation Sterilization. The packaging was validated to maintain sterility for a 3-year shelf-life based on sealing strength testing in accordance with ASTM F88/F88M: *Test Method for Seal Strength of Flexible Barrier Materials* (ASTM F88) and dye penetration testing in accordance with ASTM F1929: *Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye penetration* (ASTM F1929)

Performance testing following conditioning of samples for environmental and shipping conditions and aging. Environmental and shipping conditioning was performed according to ASTM D4169 (Standard Practice for Performance Testing of Shipping Containers and Systems). Testing demonstrates consistent device performance following shipping and over the labeled shelf-life of the device. These evaluations for shelf life and sterility were found to be acceptable.

ELECTROMAGNETIC COMPATIBILITY & ELECTRICAL SAFETY

Testing was provided to address electrical safety and electromagnetic compatibility (EMC) of the OcuCool device as per the following recognized consensus standards:

- IEC 60601-1 Medical electrical equipment – Part 1: General requirements for basic safety and essential performance
- IEC 60601-1-6 Medical electrical equipment – Part 1-6: General requirements for basic safety and essential performance – Collateral standard: Usability
- IEC 60601-1-2 Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances

This evaluation was found to be acceptable. The results support electrical safety and EMC.

Additionally, the OcuCool has a rechargeable battery in which certification of battery testing demonstrates compliance with:

- IEC 62133 Secondary cells and batteries containing alkaline or other non-acid electrolytes - Safety requirements for portable sealed secondary cells, and for batteries made from them, for use in portable applications.

SOFTWARE & CYBERSECURITY

RecensMedical, Inc. has classified their documentation to be of "Enhanced Documentation Level" for the OcuCool device as a failure or flaw of any device software function(s) could present a hazardous situation with a probable risk of death or serious injury, either to a patient, user of the device, or others in the environment of use.. The software was developed and tested according to the recommendations in accordance with FDA Guidance document: "Content of Premarket Submissions for Device Software Functions: Guidance for Industry and Food and Drug Administration Staff," issued June 14, 2023. FDA reviewed the software documentation provided in support of the OcuCool Software v1.04 and found it acceptable.

Software controls have been implemented in the OcuCool to facilitate the proper timing of device usage and the administration of intravitreal injection (IVT). The user will be presented with on-screen instructions, countdown timer, and alarm sounds to inform the users when to employ the proper procedures for:

1) When the OcuCool tip has reached –13ºC and is ready, contact should be made with the ocular surface within 20 seconds, notification will be given when the right pressure between the OcuCool tip and ocular surface is achieved.
2) Depression of the cooling trigger to start the cooling anesthesia within 5 seconds, follow by a 10 second timer for the application of the cooling anesthesia and to limit any excessive cooling
3) When the OcuCool tip has finished applying cooling anesthesia, it is warmed up to -3º C and notification is given to inform that it is safe to detach the tip from the ocular surface without ice adhesion
4) After detachment, a 30-seconds count down timer is given to inform the user to administer IVT within these 30 seconds.

The software evaluation was found to be acceptable.

The cybersecurity of the OcuCool was developed according to the recommendations in accordance with FDA Guidance document: "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices," issued October 2, 2014. FDA reviewed the cybersecurity documentation provided to support the security of the OcuCool and found it acceptable.

PERFORMANCE TESTING - BENCH

The following tests were provided and found to be acceptable in support of the performance of the OcuCool:

- Verification and validation testing verified the performance of the cooling trigger, the priming button and the tip insertion.

- Device functionality for producing the required temperature profile was confirmed via validation testing in "Test Mode".
- Safety features for cooling deactivation when the temperature is exceeded and for time error code for prolonged use were validated with bench testing.
- Testing was performed to verify the battery charging and battery life within acceptable limits.

PERFORMANCE TESTING - ANIMAL

The OcuCool device was tested in an animal study to demonstrate the safety of the treatment. A total of 16 eyes of New Zealand white rabbits were treated at -5° and -20°C with the cooling anesthesia device once a week for 10 or 24 weeks showed no signs of hemorrhage, inflammation, or necrosis. The animals' second eyes were used as an untreated control group.

HUMAN FACTORS VALIDATION

The OcuCool device was tested in a human factors validation study in a simulated-use format to demonstrate that end users were capable of using the OcuCool device as intended. Participants were provided with the device, the instructions for use, and any relevant accessories. Participants were observed by human factors specialists as they performed the various tasks, and difficulties and use errors were documented. The results of the study were analyzed to identify root causes of difficulties or use errors observed during testing. The human factors validation results, analyses, and conclusions for the OcuCool device established that the device is found to be safe and effective for the intended users, its intended uses, and use environments.

SUMMARY OF CLINICAL PERFORMANCE TESTING

Clinical performance data were collected from a pivotal clinical study (the "COOL-3" study).

Overview of "COOL-3"

"COOL-3" was a prospective, multi-center, randomized, controlled, double-masked trial to determine whether the OcuCool device is non-inferior to lidocaine gel with regard to pain scores as measured by a numeric rating scale by adults age 22 years or older who are undergoing intravitreal injections (IVT) of either Lucentis® or Eylea®. Key exclusion criteria included the following: participants with prior experience with OcuCool; history of scleromalacia; preexisting conjunctival, episcleral, or scleral defects; history of using any topical ophthalmic eyedrops three times a day or more in the prior 30 days; history of endophthalmitis with IVT; history of uveitis, retinal detachment, or vitrectomy; history of previous use of anesthetic gel for IVT in either eye. Participants were randomized in a 1:1 ratio to pre-IVT anesthesia with either OcuCool with application of a sham gel or lidocaine 3.5% ophthalmic gel with sham cooling procedure. Participants in both groups received topical proparacaine 0.5% eyedrops prior to preparation of the ocular surface for IVT. Three treatments were scheduled to be delivered across three study visits, including the initial visit. The primary effectiveness endpoint was mean pain score as

measured on the numeric rating scale 5 minutes after IVT at the first treatment visit. The pre-specified hypothesis for the primary effectiveness endpoint was that the mean numeric rating scale score of the OcuCool group is non-inferior to that of the control group, based on the per-protocol (PP) cohort. The non-inferiority threshold was defined as the lower boundary of the 2-sided 95% confidence interval (CI) being greater than -1.3, at an alpha level of 0.05 for statistical significance. Safety outcomes of interest included adverse event (AE) reporting, visual acuity assessment, findings on slit-lamp biomicroscopy and indirect ophthalmoscopy, changes in intraocular pressure (IOP), and signs and symptoms of dry eye.

Summary of results

90 participants were enrolled across eight sites in the United States. 44 were assigned to the OcuCool group and 46 to the control group. A significant proportion (21.7%, 10/46) of the OcuCool participants did not complete the study. Of the 10 participants in the OcuCool who did not complete the study, 40% (4/10) withdrew consent and 40% (4/10) cited pain or irritation. Participant accountability across all study visits was not provided. There is uncertainty as to how many participants completed all three scheduled study visits. The PP cohort was comprised of 39 participants in the OcuCool group and 41 in the control group. Major protocol deviations were reported in 77.3% (33/44) of the OcuCool group and 76.1% (35/46) of the control group. Minor protocol deviations were reported in 45.4% (20/44) of the OcuCool group and 50.0% (23/46) of the control group. The summary of the protocol deviations reported in the study is provided in the table below.

The numeric rating scale used to collect pain scores was overlaid with a qualitative descriptor scale intended to collect participants' reports of their pain severity (i.e., mild, moderate, and severe). Information on the qualitative descriptor scale was not included in the verbal instructions given to the participants who could not see the scale. It is unclear how many participants could not see the scale, which may have affected their responses. Therefore, there is uncertainty around the effectiveness results and the qualitative descriptors scale's results cannot be interpreted.

Major Protocol Deviations[1]

Category	Lidocaine Gel Topical Anesthesia n/N (%)		Cooled at -15°C for 10 seconds n/N (%)	
Consent	2/35	(5.7%)	6/34	(17.6%)
Eligibility	1/35	(2.9%)	2/34	(5.9%)
Good Clinical Practices (GCP)	6/35	(17.1%)	4/34	(11.8%)
Non-Compliance/Un-Blinding	2/35	(5.7%)	2/34	(5.9%)
Out of Window Procedure/Missed Procedure	20/35	(57.1%)	16/34	(47.1%)
Safety	1/35	(2.9%)	3/34	(8.8%)
Stratification	2/35	(5.7%)	1/34	(2.9%)
Other	1/35	(2.9%)	0/34	

Note: Unit of analysis is the is the protocol deviation.

Minor Protocol Deviations[2]

Category	Lidocaine Gel Topical Anesthesia n/N (%)		Cooled at -15°C for 10 seconds n/N (%)	
Consent	2/23	(8.7%)	0/20	
Good Clinical Practices (GCP)	0/23		1/20	(5.0%)
Out of Window Procedure/Missed Procedure	16/23	(69.6%)	14/20	(70.0%)
Out of Window Visit/Missed Visit	5/23	(21.7%)	3/20	(15.0%)
Other	0/23		2/20	(10.0%)

Note: Unit of analysis is the is the protocol deviation.

[1] Major Protocol Deviation Details:
"Eligibility" deviations included: 1 test subject was inadvertently included in the study with a history of vitrectomy in the study eye.; 1 control subject was inadvertently included in the study with myopic degeneration and did not have nAMD, DR, or RVO.; 1 test subject was inadvertently included in the study although the participant was using eye drops more than 3 times/week for Glaucoma. "Good Clinical Practices" deviations included: The study site discarded source documentation for all assessments not part of SOC (those captured in the clinic EMR) in error for 6 control and 4 test subjects. "Non-compliance/un-blinding" deviations included: An unmasked investigator did not correctly perform device operation for 1 test subject during study treatment.; 1 test subject inadvertently received Fellow Eye Treatment by Masked PI 7 minutes after Study Eye Treatment (i.e., early Fellow Eye Treatment was performed).; An unmasked investigator did not review training video prior to performing procedure for 1 control subject.; 1 subject was unmasked by unmasked investigator during study procedure in a second follow up. "Out-of-window procedure/missed" deviations included: Site did not adhere to the 6 min ±1 min from gel application to device/sham application for 25 subjects (14 control and 11 test subjects). 2 subjects received device application early (1min) and 22 subjects received device application late (ranging from 8-36 min).; Time between Device application and IVT Injection for 3 control subjects and 1 test subject was >30 sec (88 sec-19 min).; Time between Device/Sham Application and Time of injection was greater than 10 seconds for 1 control subject (42 sec).; 2 control subjects and 1 test subject had the 5 minute (-/+ 2 minutes) NRS Assessment completed 2 minutes after treatment, which is 1 minute out of window.; 1 control and 1 test subject had the 30 minute (+/- 15 minutes) NRS Assessment completed 12-13 minutes after treatment, which was 2-3 minutes out of window.; Time of Fellow Eye treatment was 2 minutes after Study Eye treatment for 1 test subject. Per protocol, fellow eye should be treated after all study eye assessments.; Time from 2 beeps of device to administration of IVT is >20 seconds for 1 control subject. "Safety" deviations included: SAE not reported within 24 hours of site awareness for 3 test subjects.; 1 test subject post injection IOP was 27 mmHg. Per protocol, post injection IOP needs to be less than 25 mmHG or within 5 mmHg of pre injection IOP before completing study visit. Site failed to recheck IOP to ensure IOP lowered to below 25mmHg and/or was within 5 mmHg of pre injection. "Stratification" deviations included: Site incorrectly checked off "treatment naive subject" for 1 test subject when this subject was not treatment naïve.; 1 control subject was registered as treatment naive, however, subject had received treatment in the past.; 1 control subject was registered as not treatment naïve, however, subject was treatment naïve. "Other" deviations included: 1 control subject did not complete the entire SPEED Questionnaire worksheet.
[2] Minor Protocol Deviation Details:
"Good Clinical Practices" deviations included: 1 test subject had a Vision and Pre Injection IOP performed by non-study staff. "Out-of-window Procedure/Missed Procedure" deviations included: Site did not adhere to the 6 min ±1 min from gel application to device/sham application for 20 subjects (12 control and 8 test subjects). 19 subjects received device application early (2-4 min) and 1 subject received device application late (9 min).; Site did not adhere to the 6 min ±1 min from gel application to device application for 1 control subject where gel was applied then reapplied 8 minutes later before device application 2 minutes after gel reapplication.; 2 test subjects had Post Injection IOP checked outside of the 30 +/- 15 min window (checked within 8-10 min).; Time from device to IVT was >30 seconds for 4 control subjects and 2 test subjects (IVT was performed after 33-120 seconds).; 2 test subjects 30 minute (+/- 15 minutes) Fluorescein Staining was completed at least 2 minutes out of window. "Out-of-window Visit/Missed Visit" deviations included: 1 test subject and 2 control subjects could not be reached for the post-injection follow up call.; Site was unable to reach 1 test subject for follow up call #1 and 1 test subject for follow up call #2.; The time for administration for the Participate Survey was not completed after all study assessments for 1 control subject. The same survey was completed prior to all other study assessments being complete for the last study visit for 2 control subjects. "Other" deviations included: Site changed IOP instrument from Goldman (pre) to Tonopen (post) for 2 test subjects.

For the PP cohort, the mean age was 70.4±14.5 and 68.7±12.4 years (OcuCool vs. control, respectively). 56.1% (23/41) of the OcuCool group and 46.2% (18/39) of the control group were women. The majority were Caucasian/white (97.6% OcuCool, 87.2% control). 2.4% of the OcuCool and 10.3% of the control group were Black/African American. There were no Asians in the OcuCool group while 2.6% of the control group were Asian. 13 (14.0%) were Black/African American, and 15 (16.1%) were Asian. Most participants (82.9% OcuCool, 87.2% control) reported Ethnicity of not Hispanic/not Latino. Participants had diagnoses of diabetic macular edema (17.1% OcuCool, 17.9% control), non-proliferative diabetic retinopathy (4.9% OcuCool, 10.3% control), proliferative diabetic retinopathy (9.8% OcuCool, 5.1% control), retinal vein occlusion (9.8% OcuCool, 17.9% control), and neovascular age-related macular degeneration (58.5% OcuCool, 48.7% control). Mean baseline (pre-IVT) numeric rating scale score was 0.3±1.00 (range 0 – 5) in the OcuCool group and 0.1±0.3 (range 0 – 2) in the control group.

For the first visit, mean numeric rating scale scores 5 minutes after IVT were 2.1±2.1 (median 2.0; range 0 – 8) in the OcuCool group and 1.4±2.0 (median 1.0; range 0 – 10) in the control group. Mean numeric rating scale scores 30 minutes after IVT were 1.1±1.6 (range 0 – 5) in the OcuCool group and 0.5±1.0 (range 0 – 5) in the control group. The between-group difference was -0.739 (95% CI -1.6329 – 0.1557), indicating that pain was lower for the control treatment. Non-inferiority of OcuCool to the control treatment was not established based on the lower 95%

CI bound exceeding the pre-specified non-inferiority threshold. Numeric rating scale scores across visits were not reported.

In the safety cohort (N=90), ocular treatment-emergent adverse events (TEAEs) were reported in 70.5% of the OcuCool group (31/44) and 54.3% of the control group (25/46). The most frequently reported ocular TEAEs were punctate keratitis (38.6% OcuCool, 28.3% control) and conjunctival hemorrhage (9.1% OcuCool, 2.2% control). Eye pain, injection site pain, medical device site pain, and procedure pain were reported in 13.6% of the OcuCool group and 15.25% of the control group. Blurry vision and vitreous hemorrhage were reported in the OcuCool group (2.3% each; none in the control group). No ocular TEAEs were reported as serious. Device-related TEAEs were reported in 22.7% (10/46) of the OcuCool group and 21.7% (10/46) of the control group. The most frequently reported device-related TEAE was punctate keratitis. IOP increase of ≥10 mm Hg from baseline was reported in 18.2% of the OcuCool group and 11.1% of the control group at Visit 1. Increased IOP as an AE was reported in 13.6% of the OcuCool group and 8.7% of the control group. Moderate or severe fluorescein staining after IVT (at the first visit) of the ocular surface was reported in 40.9% of the OcuCool group and 24.5% of the control group. Totality of dry symptoms (frequency and severity) as measured by the Standard Patient Evaluation of Eye Dryness Questionnaire (SPEED) was moderate or severe in 52.3% of the OcuCool group and 41.3% of the control group at the first visit. It should be noted that although post-injection slit lamp examinations were pre-specified, there is uncertainty regarding this safety assessment as data was inconsistently documented and not provided.

No analyses were performed for any specific demographic subgroups.

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.

POSTMARKET EVALUATION

A postmarket study will be conducted to evaluate the performance of the device under the anticipated conditions of use in the intended patient population. Assessments will include pain assessments to characterize the pain experience associated with intravitreal injection following use of the OcuCool device and the tolerability of the pain intensity, using valid patient-reported outcome (PRO) instruments that are fit-for-purpose. Safety will also be evaluated through collection of all observed ocular adverse events.

LABELING

The labeling is sufficient and satisfies the requirements of 21 CFR 801.109 for prescription devices.

The labeling describes how the prescribing user is to use the device, including turning on the device, inserting the Tip, preparing the device and patient for treatment, applying the device to the eye, safe removal of the device from the surface of the eye after treatment, and appropriate

cleaning and storage. It describes the treatment procedure, which is uniform for all patients. It describes all components of the user interface, including the buttons, display, and timer.

The labeling provides a description of the intended patient population that may be treated with the device and includes a summary of the clinical study performed to support the device's safety and effectiveness in this population, including a summary of the demographic and racial distributions of the study cohort.

The labeling includes contraindications, warnings, and precautions to ensure safe use of the device in the intended patient population.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of an ophthalmic cooling anesthesia device:

Risks to Health	**Mitigation Measures**
Infection	Sterilization validation
Adverse tissue reaction	Biocompatibility evaluation
Failure of software or system components resulting in inadequate pain relief or patient harm, including pain and tissue damage	Software verification, validation, and hazard analysis Non-clinical performance testing Shelf life testing
Equipment malfunction leading to user or patient injury (e.g., shock, burn, interference)	Electromagnetic compatibility (EMC) testing Electrical safety testing Labeling
User error leading to adverse patient events including pain and tissue damage or inadequate pain relief	Human factors validation testing Labeling
Damage to the eye from treatment	Animal performance testing Clinical performance testing Postmarket surveillance Labeling
Ineffective treatment leading to patient discomfort	Clinical performance testing Postmarket surveillance Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the ophthalmic cooling anesthesia device is subject to the following special controls:

(1) Data obtained from premarket clinical performance testing, and from postmarket surveillance conducted per a protocol approved by FDA and acquired under the anticipated conditions of use, must demonstrate that the device performs as intended in the real-world population defined by the indications for use and per the instructions for

use, unless FDA determines based on the totality of the information provided for premarket review that data from postmarket surveillance is not required. All premarket and postmarket clinical performance testing must evaluate the following:
(i) Pain intensity and tolerability associated with the ocular procedure of interest as assessed by instruments that are fit-for-purpose; and
(ii) Ocular adverse events.

(2) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. Testing must include:
(i) Validation of the intended temperature profile; and
(ii) Validation of all safety features to prevent use outside the intended temperature range and intended treatment duration.

(3) Animal performance testing must evaluate the safety profile of the device over the intended cooling temperature and treatment duration, including a detailed evaluation of all ocular adverse events.

(4) Software verification, validation and hazard analysis must be performed. Software documentation must include the following:
(i) A description of cooling temperature, contact verification to ocular surface, and contact timing alerts to limit any excessive cooling of the ocular surface; and
(ii) A description of all timing alerts to inform the user of safe detachment from ocular surface at a safe detachment temperature and appropriate time duration of anesthetic effect.

(5) The patient-contacting components of the device must be demonstrated to be biocompatible.

(6) Performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the identified shelf life.

(7) Performance testing must demonstrate the sterility of the patient contacting components of the device.

(8) Performance testing must demonstrate the electrical safety and electromagnetic compatibility (EMC) of the device in the intended use environment.

(9) Human factors validation testing must demonstrate that the intended users can correctly use the device, based solely on the instructions for use.

(10) Labeling must include:
(i) Summaries of treatment parameters;
(ii) A summary of clinical performance testing with the device, including a description of the patient population studied; and

(iii) A detailed summary of all postmarket surveillance data collected, including updated labeling to accurately reflect outcomes observed in postmarket surveillance.

BENEFIT-RISK DETERMINATION

The probable risks of the device are based on data collected in the "COOL-3" study as described above. They include ocular adverse events (AEs) such as conjunctival hemorrhage, punctate keratitis, signs and symptoms of dry eye, acute increase in intraocular pressure (IOP) after injection, eye pain, and injection site pain.

The probable benefits of the device are also based on data collected in the "COOL-3" study as described above. They include temporary lowering of pain during an intravitreal injection and serving as a non-pharmacologic alternative to subconjunctivally-injected or gel-formulation anesthetic drugs. While the OcuCool device did not perform as well as the comparator (lidocaine), the OcuCool device was shown to provide an anesthetic effect. The FDA recognizes that, though small, there is a population of patients who may have allergies to deep penetrating pharmaceutical-based anesthetics. Thus, in this subpopulation of patients, the probable benefits of the OcuCool may outweigh the probable risks, but considering the significant uncertainty around the probable benefits, a postmarket surveillance study was determined to be necessary to reduce this uncertainty(please see Special Control #1). There are major sources of uncertainty around the probable benefits of the device. Furthermore, the benefits have not been evaluated in the population of patients who are allergic to deep-penetrating anesthetic drugs. In addition, the durability of these benefits across multiple device uses over time has not been evaluated. Other sources of uncertainty include missing data for the key effectiveness endpoint across scheduled study visits, unclear reliability of the pain scores on the single-item pain scale, high proportions of protocol deviations, and lack of information on long-term AE rates.

Additional factors were considered in determining probable risks and benefits for the OcuCool including uncertainty, risk mitigation, the novelty of the technology, and the lack of non-pharmacologic anesthetic options for patients who are allergic to deep-penetrating anesthetic drugs.

Patient Perspectives

See the discussion of the pain patient-reported outcomes in the SUMMARY OF CLINICAL INFORMATION section.

Benefit/Risk Conclusion

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

> OcuCool is a cooling anesthesia device intended for topical application to the conjunctiva and sclera. OcuCool is intended for the temporary reduction of pain associated with intravitreal injections.

OcuCool is indicated for patients who are allergic to deep penetrating pharmaceutical based anesthetics used for temporarily reducing pain during and following intravitreal injections.

The probable benefits outweigh the probable risks for OcuCool. 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 OcuCool is granted and the device is classified as follows:

Product Code: QZQ
Device Type: Ophthalmic cooling anesthesia device
Regulation Number: 21 CFR 886.4190
Class: II