DE NOVO CLASSIFICATION REQUEST FOR TEARSCIENCE, INC. LIPIFLOW® THERMAL PULSATION SYSTEM

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Eyelid Thermal Pulsation System. An eyelid thermal pulsation system is an electrically-powered device intended for use in the application of localized heat and pressure therapy to the eyelids. The device is used in adult patients with chronic cystic conditions of the eyelids, including meibomian gland dysfunction (MGD), also known as evaporative dry eye or lipid deficiency dry eye. The system consists of a component that is inserted around the eyelids and a component to control the application of heat and pressure to the eyelids.

NEW REGULATION NUMBER: 886.5200

CLASSIFICATION: II

PRODUCT CODE: ORZ

BACKGROUND

DEVICE NAME: LIPIFLOW® THERMAL PULSATION SYSTEM

SUBMISSION NUMBER: K093937

DATE OF DE NOVO: AUGUST 6, 2010

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REQUESTER'S RECOMMENDED CLASSIFICATION: CLASS II

INDICATIONS FOR USE (IFU)

The LipiFlow® System is intended for the application of localized heat and pressure therapy in adult patients with chronic cystic conditions of the eyelids, including meibomian gland dysfunction (MGD), also known as evaporative dry eye or lipid deficiency dry eye.

LIMITATIONS

1. Caution: Federal Law restricts this device to sale by or on the order of a physician.

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

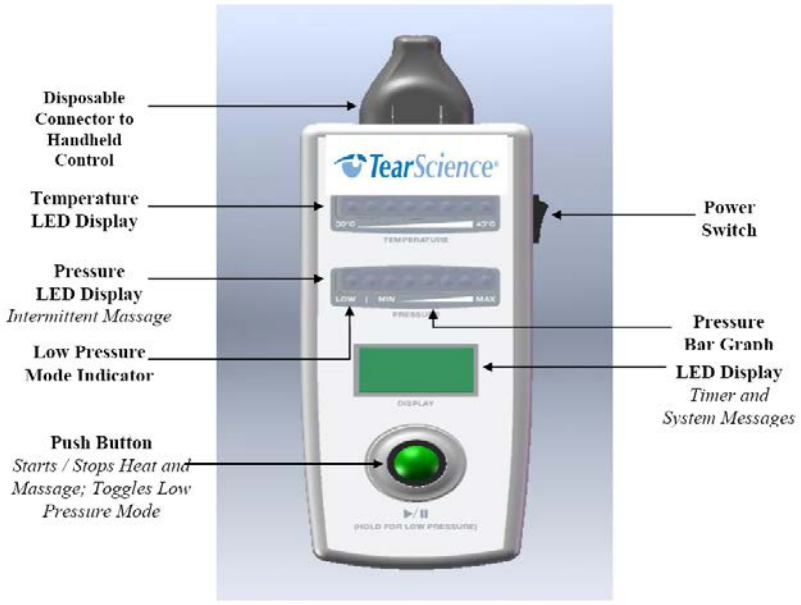
DEVICE DESCRIPTION

The physician uses the LipiFlow® System in an in-office procedure to control the application of warmth and massage to the eyelids. Two components comprise the LipiFlow® System, the Disposable unit and the Handheld Control System (HCS).

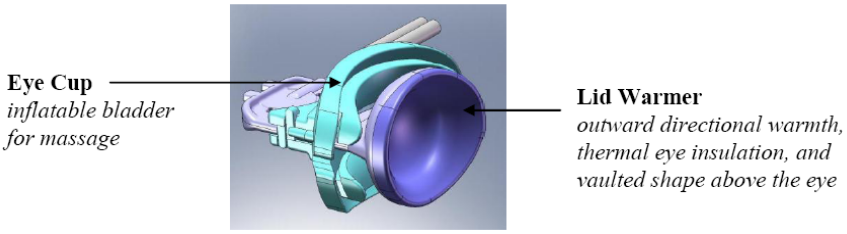
The Disposable unit is a sterile, single-use, biocompatible unit that is inserted around the patient's eyelids. The Disposable unit consists of a combined Eye Cup and Lid Warmer with attached tubing and wiring that connect to the Control unit with a connector. The Eye Cup contacts the outer eyelid and contains a soft, flexible bladder that intermittently inflates with air to provide controlled massage pressure to the eyelids. The Lid Warmer contacts the inner eyelid surface and provides controlled, outward directional (away from the eye and towards the eyelid) heat to the inner eyelid. The Lid Warmer has a smooth surface and edges, where the circumference rests lightly on the conjunctiva of the eye. The Lid Warmer shape vaults above the eye surface to prevent corneal contact. The Lid Warmer has an integrated insulator (also referred to as the Insulating Scleral Lens) to shield the eye from thermal transfer and redundant temperature sensors to ensure precise control of the temperature.

The HCS is a battery-operated, hardware interface that allows the physician to control the application of heat and pressure, which is delivered via a single, 12-minute treatment. The HCS regulates the level of heat and pressure that can be applied during treatment. The HCS consists of a visual Light Emitting Diode (LED) display, power switch, push button, electronic circuit board, pump, pressure regulator, pressure sensor, dump valve, connector and battery compartment. The HCS displays information to the physician including: the temperature at the Disposable; line air-pressure to the Disposable; treatment time; low pressure selection indicator; and system messages, such as low battery, a system error, or inadequate connection to the Disposable. By visualizing the temperature and pressure LED displays, the physician can determine when the therapeutic temperature is reached and the relative pressure being applied. The push button starts the application of heat and pressure and can be depressed again at any time to pause the treatment, which immediately stops the therapeutic application. In the event that the physician desires to reduce pressure for patient comfort, the pressure can be reduced by 30% (Low Pressure Mode) by pressing and holding the push button. The HCS uses three AA (1.5V) Lithium disposable batteries.

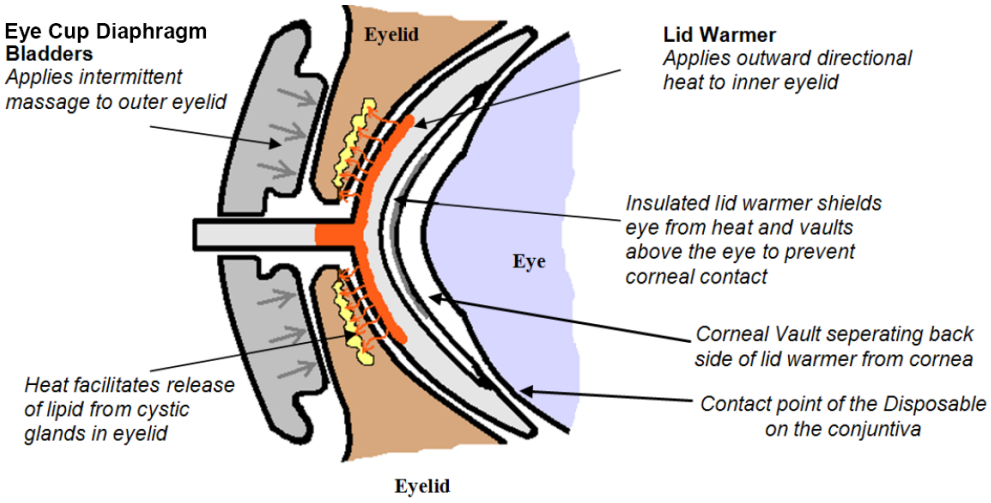
The HCS allows the physician to control the application of heat and pressure:



The Disposable consists of a combined Eye Cup and Lid Warmer, which connect to the HCS:



In this cross-sectional representation, the Disposable positions around the eyelids during device use:



SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The patient-contacting materials including the adhesive in the Disposable of the LipFlow System were evaluated for cytotoxicity (ISO 10993-5, Biological evaluation of medical devices-Part 5: Tests for in vitro cytotoxicity), irritation and sensitization (ISO 10993-10, Biological evaluation of medical devices-Part 10: Tests for irritation and delay-type hypersensitivity) in accordance with the recommendations in ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing, and in FDA 510(k) Memorandum 95-1 for materials with limited mucosal membrane contact. Additionally, the sponsor also provided a certificate of compliance from a test laboratory certifying that the adhesive passed the following tests; irritation (ISO 10993-10, Biological evaluation of medical devices-Part 10: Tests for irritation and delay-type hypersensitivity), acute systemic toxicity (ISO 10993-11, Biological evaluation of medical devices-Part 11: Tests for systemic toxicity), cytotoxicity (ISO 10993-5, Biological evaluation of medical devices-Part 5: Tests for in vitro cytotoxicity), hemocompatibility (ISO 10993-4, Biological evaluation of medical devices-Part 4: Selection of tests for interactions with blood), implantation (ISO 10993-6, Biological evaluation of medical devices-Part 6: Tests for local effects after implantation) as well as the USP physiochemical test. Material Safety Data Sheets (MSDSs) on the materials were also provided and they do not raise any concerns that have not been addressed by the testing performed by the sponsor.

The materials used in the Disposable are, therefore, believed to be biocompatible when the Disposable is used as intended.

SHELF LIFE AND STERILITY

The Disposable for the LipiFlow System is packaged in an 8 x 9 heat-sealed Tyvek® film pouch and is terminally sterilized by gamma radiation using a radiation dose of (b)(4) kGy. The validation of this sterilization process complies with ISO 11137-2:2006, "Sterilization of health care products - Radiation - Establishing the sterilization dose - Method VD-Max (b)(4)." The sterilization method achieves a sterility assurance level (SAL) of 10-6.

The proposed shelf life of 6 months has been validated using accelerated aging. The accelerated aging tests include:

- Tensile strength testing - ASTM F88:2007, “Standard test method for seal strength of flexible barrier materials”
- Burst /creep pressure testing - ASTM F1140:2007, “Standard test methods for internal pressurization failure resistance of unrestrained packages”
- Dye penetration testing – ASTMF 1929-98:2004, “Detecting seal leaks in porous medical packaging by dye penetration”
- Bubble test - ASTM F2096:2004, “Standard test method for detecting fross leaks in medical packaging by internal pressurization”

ANIMAL STUDY

The Electromechanical Engineering reviewer reviewed a study in which the maximum temperature at the cornea was studied using an excised porcine eye model. The enucleated porcine eyes were mounted in an aluminum fixture that is surrounded by temperature-controlled fluid to simulate body temperature. The device was positioned on the conjunctiva/sclera and covered with silicone sheets to mimic the thermal insulation provided by human eyelids. A temperature probe was inserted through the back of the porcine eye to sense the back surface of the cornea. A full (b)(4) device treatment was then initiated resulting in a measured average peak corneal temperature (b)(4)° C +/- (b)(4)° C across thirty tested eyes.

ELECTRICAL, MECHANICAL AND THERMAL SAFETY

During the Electrical Engineering/ Hermeticity review of K093937, an Engineering Analysis was conducted of the hermetic sealing of the device with regard to device performance and safety. The chief concern was that if the device exhibited a leak, fluids could enter the device and alter the thermal sensing and thermal transfer characteristics. The reviewer requested validation studies of the integrity of the glue joint forming the hermetic barrier, as well data on the potential harmful effects that could arise if moisture were to penetrate this barrier. The company responded to these requests and demonstrated that the proposed testing would detect a device with a compromised seal. The company further demonstrated that in the event that a seal was compromised, the safety of the device would not be affected. Deficiencies which were subsequently addressed to the satisfaction of the reviewer related to the integrity of the hermetic seals, validation testing for the vacuum testing of the glue joint, information on the effect of saline-filled tears on the electrical performance of the heating element, and changes in the heat transfer properties if fluid fills the air gap between the heater and the insulator shell.

A previous Electromechanical Engineering review of this device indicated deficiencies relating to the Electrical Inspection Criteria, the Insulator Assembly Inspection Criteria, the Quality Control Procedure, and the Protocol Verification results including verification of an applied pressure < (b)(4) mm Hg. In addition, no test results had been provided for the Controller Board Incoming Inspection Criteria or the Final Inspection Procedure. The reviewer notes that the sponsor has satisfactorily addressed each of the concerns. The device is considered to adhere to the following electrical safety standards:

a. IEC 60601-1: 1995, Medical Electrical Equipment – Part 1: General Requirements for Safety: 1988+ A1; 1991+A2; 1995
b. IEC 60601-1-2: 2001; Medical Electrical Equipment – Part 1-2: General Requirements for Safety; Collateral Standard: Electro Magnetic Compatibility
c. IEC 60601-1-2: 2007, Medical Electrical Equipment – Part 1-2: General Requirements for Safety; Collateral Standard: Electro Magnetic Compatibility.

The thermal safeguards of the device ensure control of the heating element to (b)(4)° C with an accuracy of (b)(4)° C. This temperature of the heating element when placed outside the eyelid was selected to obtain the design criteria for corneal temperature not to exceed (b)(4)° C when accounting for heat insulation of the eyelid and cooling by local blood flow. The

maximum corneal temperature measured immediately after device treatment using a thermal camera during performance testing with human eyes *in vivo* reached (b)(4)° C. Finite Element Analysis modeling device usage in worst case conditions of no blood flow, and thin eyelids resulted in a maximum predicted corneal temperature of (b)(4)° C. The safeguards include a current limiting switch, redundant temperature regulators, and temperature shutoff circuitry monitoring redundant temperature sensors.

SOFTWARE

Not Applicable

SUMMARY OF CLINICAL INFORMATION

A summary of the clinical study which was conducted follows:

The study objective was to evaluate the clinical utility, safety and effectiveness of the LipiFlow® System compared to warm compress therapy using a commercially available chemical heat device (iHeat™ Portable Warm Compress System) for application of localized heat therapy in adult patients with chronic cystic conditions of the eyelids, including meibomian gland deficiency (MGD), also known as evaporative dry eye or lipid deficiency dry eye.

A total of 139 subjects (278 eyes) were enrolled at nine sites with randomization of 69 subjects (138 eyes) to the LipiFlow® group and 70 subjects (140 eyes) to the Warm Compress Control group. LipiFlow® subjects received a single, 12-minute in-office treatment with the LipiFlow® System at the Treatment visit. LipiFlow® subjects were followed at 1 day, 2 weeks and 4 weeks after treatment. Control subjects received the initial 5-minute iHeat™ System therapy per the device labeling at the Treatment visit. Control subjects were instructed to use the warm compress therapy for 5 minutes daily at home until the 2-week visit. After 2 weeks the Control group crossed over to receiving a single LipiFlow® treatment.

Effectiveness parameters were Meibomian Gland Assessment, Tear Break-up Time and Standard Patient Evaluation of Eye Dryness (SPEED) and Ocular Surface Disease Index (OSDI) Dry Eye Questionnaires.

Safety parameters were Discomfort/Pain Evaluation, Ocular Surface Staining, Intraocular Pressure (IOP) by Goldmann tonometry, Slit Lamp and Dilated Retinal Exam, and Best Spectacle Corrected Visual Acuity (BSCVA). Safety parameters were used to assess for Adverse Events.

The LipiFlow® System met the primary study effectiveness endpoint with a statistically significant ($p<0.0001$) greater improvement at 2 weeks from baseline in the average number of meibomian glands yielding clear liquid secretion as compared to the Warm Compress Control. The LipiFlow® group showed a mean improvement in tear break-up time and a mean reduction in dry eye symptoms at 2 weeks from baseline with an effect greater than the Warm Compress Control. A single 12-minute treatment with the

LipiFlow® System provided sustained effectiveness, on average, over the 4-week study duration, as shown by the mean change in meibomian gland assessment, tear break-up time and dry eye symptoms at 4 weeks from baseline.

No device-related serious adverse events or unanticipated adverse device effects were reported in the study. Four eyes (2.9%) in the LipiFlow® group had device-related non-serious adverse events, including three eyes with moderate eyelid pain and one eye with moderate conjunctival vascular injection (redness). All of these adverse events resolved during the 4-week study without sequelae or medical treatment.

In conclusion, the study results demonstrate that the benefit of the LipiFlow® System in providing heat and pressure therapy for patients with meibomian gland dysfunction and dry eye symptoms outweighs the risk.

A previous Clinical review of this device indicated deficiencies relating to the standard of care for meibomian gland deficiency, as well as the lack of data to support two of the Indications for Use originally sought by the sponsor. Subsequently, each of the deficiencies has been satisfactorily addressed, as acceptable clarification was provided regarding the standard of care, and the unsupported Indications were removed. The clinical data, combined with the sponsor responses to the deficiencies, support the conclusion that the test device/ treatment is both safe and effective, compared to the control device/ treatment.

As part of the analysis for the primary safety endpoint, the significance of the observed device-related adverse events rates was determined. The clinician concluded the observed difference in device-related adverse events was not clinically significant between the two groups.

LABELING

The labeling for the LipiFlow® Thermal Pulsation System is consistent with the clinical data and covers all the hazards and other clinically relevant information that may impact safe and effective use of the device. The labeling is sufficient and satisfies the requirements of 21 CFR Part 801.109 Prescription devices.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of eyelid thermal pulsation systems and the measures recommended to mitigate these risks.

Identified Risks	Recommended Mitigation Measures
Infection	Sterility and Shelf Life Testing
Adverse tissue reaction	Biocompatibility
Electrical shock	Electrical Safety Testing
Electromagnetic interference	Electromagnetic Compatibility (EMC) Testing Labeling
Thermal damage	Temperature Performance Testing
Mechanical damage	Pressure Performance Testing
Malfunction	Non-clinical and Clinical Performance Testing
User error	Labeling

SPECIAL CONTROLS

In addition to the general controls of the Act, the LipiFlow® Thermal Pulsation System is subject to the following special controls:

(1) Appropriate analysis/ testing should validate electromagnetic compatibility (EMC) and safety of exposure to non-ionizing radiation;

(2) Design, description, and performance data should validate safeguards related to the temperature and pressure aspects of the device, including during fault conditions;

(3) Performance data should demonstrate the sterility of patient-contacting components and the shelf-life of these components;

(4) The device should be demonstrated to be biocompatible; and

(5) Performance data should demonstrate device safety and effectiveness.

CONCLUSION

The *de novo* for the LipiFlow® System is granted and the device is classified under the following:

Product Code: ORZ
Device Type: Eyelid Thermal Pulsation System
Class: II
Regulation: 21 CFR 886.5200