DE NOVO CLASSIFICATION REQUEST FOR LEICA FL400

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Diagnostic neurosurgical microscope filter. A diagnostic neurosurgical microscope filter is a device intended for use during neurosurgery to visualize fluorescence and enhance visualization of tissue associated with a specific disease or condition.

NEW REGULATION NUMBER: 21 CFR 882.4950

CLASSIFICATION: Class II

PRODUCT CODE: QFX

BACKGROUND

DEVICE NAME: Leica FL400

SUBMISSION NUMBER: DEN180024

DATE DE NOVO RECEIVED: May 8, 2018

CONTACT: Leica Microsystems (Schweiz) AG
Max Schmidheiny-Strasse 201
CH-9435 Heerbrugg, Switzerland

INDICATIONS FOR USE

The Leica FL400 is a surgical microscope accessory filter set for viewing fluorescence of fluorophores comprising an excitation filter for blue spectral range 380 nm – 430 nm and an observation filter comprising the long-wave blue, green, yellow and red spectrum in the spectral band greater than 444 nm.

The FL400 is a surgical microscope accessory used in fluorescent visualization of suspected grade III or IV gliomas during neurosurgery.

LIMITATIONS

For prescription use only.

Compatibility of the FL400 has only been demonstrated with Leica M525 and M530 surgical operating microscopes.

A pre-operational check of the FL400 device should be performed before surgery using

the FL400 Test Phantom.

The FL400 is not intended for diagnosis including the diagnosis of glioma.

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

DEVICE DESCRIPTION

The Leica FL400 is a fluorescence accessory that consists of an excitation (illumination) filter module and an emission (observation) filter module that are intended to be inserted into the optical beam path of compatible Leica surgical operating microscopes models M525 and M530. The excitation filter (380 nm – 430 nm), when placed into the light path, provides a fluorescence excitation light system for use in conjunction with an approved fluorophore selective for grade III or IV malignant gliomas.

The emission filter is a long pass filter allowing light wavelengths greater than 444 nm to pass. The fluorophore emits light at a longer wavelength than the excitation light. Once passed through the emission filter module, a camera adapted to the surgical microscope detects the fluorescence signal, allowing the user to visualize the fluorophore in the open neurosurgery field.

The Leica FL400 is supplied with a test phantom to confirm proper pre-operative fluorescence set-up. The Leica FL400 Test Phantom offers multiple levels of fluorescence intensity, which provides the clinician with a visual assessment of the FL400 pre-operative set-up. The clinician is advised to confirm the fluorescence spots are visible to confirm functionality prior to utilization.

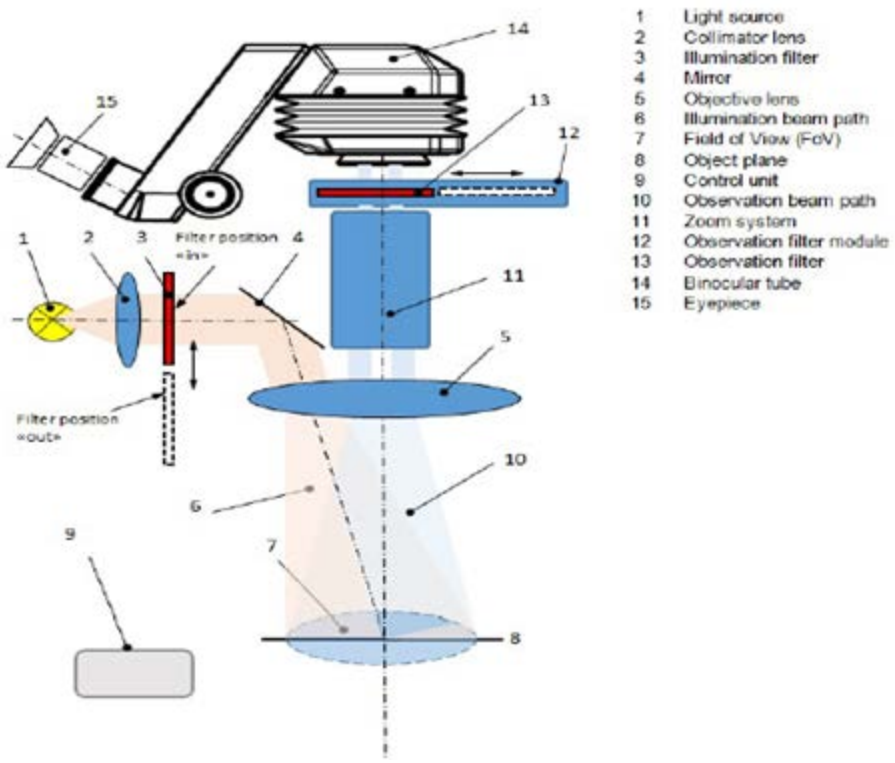

Figure 1: Leica FL400 Illumination Path

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The device does not have patient-contacting materials; therefore, a biocompatibility assessment is not needed for this device.

STERILITY

The device is provided non-sterile. Cleaning instructions are provided in the user manual that direct users to follow the cleaning procedures of the surgical operating microscope that the FL400 is installed in.

PERFORMANCE TESTING - BENCH

Testing was performed to verify device specifications for proper visualization of fluorescing agents, including the following:

- Spectrum of the Illumination Source: The irradiance spectrum (300 nm – 1100 nm, mW/cm^2) of the illumination source was measured and verified with a spectrometer. These measurements were assessed prior to application of the excitation filter module.

- Maximum Power and Irradiance of the Illumination Source: The maximum output power and irradiance of illumination sources were measured and verified with a power meter at the end of the microscope light guide. These measurements were assessed prior to application of the excitation filter module.

- Irradiance Spectrum of the Excitation Light and Spectral Response of the Excitation Filter: The irradiance spectrum (300 nm – 1100 nm) of the illumination light, following passage through the excitation filter module, was measured at a working distance of 30 cm for the M525 surgical operating microscope and 35 cm for the M530 with a spectrometer. This was divided by the irradiance spectrum of the illumination source without excitation filter module at the same working distance to provide the spectral response of the excitation filter.

- Maximum Excitation Power and Power Density: The maximum power (mW) and power density (mW/cm^2) of the excitation light was measured with a thermopile and a UV diode, calibrated set to 300 nm, at multiple different working distances and zoom settings, including the maximum and minimum zoom. These power density measurements were then compared to the excitation power densities observed in the clinical trials assessing the efficacy of the fluorophore.

- Optical Path Loss: To determine the overall detectable light output and the total losses in relation to device working distance and zoom setting, optical path loss was calculated by dividing the output signal measured at the microscope eyepiece (without emission filter) by the illumination signal measured at the microscope focal plane for the same zoom setting. A reflection standard (white silicon remission disc) was used at a working distance of 30 cm or 35 cm depending upon the model as described above.

- Spectrum of the Emission Filter: The spectrum (300 nm – 1100 nm) of the emission filter when integrated in the surgical operating microscope was measured to include all the coating and optics that affects the spectrum of the observation path. For this test the excitation filter was removed, and a reflection standard was used at the device focal plane with different zoom settings. Transmission of the emission filter was calculated from white light remission spectra at the oculars with emission filter in place versus without the filter.

- Homogeneity of the Excitation Light at the Focal Point: The reflected signal from a white sheet of paper positioned at 30 cm working distance was imaged by the surgical operating microscope camera and the intensity profile was calculated to demonstrate the homogeneity of the excitation light.

- System Sensitivity: A diffusely reflecting and fluorescent disc made of silicone was positioned at a microscope working distance of 30 cm. The device output spectrum was measured by a spectrometer at the microscope eyepiece for different zoom settings. The fluorescence/remission ratio was calculated by dividing the integral of intensities in the fluorescence bandwidth by the integral of intensities in remission bandwidth.

- Pre-Operative Phantom Test: This test was conducted to demonstrate that the Leica FL400 test phantom is suitable for the pre-operative checks of the Leica FL400 device. The optical phantom has 4 dots with different fluorophore concentrations and was imaged by the surgical operating microscope camera at different working distances and different magnification or zoom settings. The same tests were repeated by observation through the microscope eyepieces.

- Spectrum of Camera Filter: The spectrum of camera filter was measured to demonstrate that it can block near infrared and infrared leakage of excitation light to the camera.

SUMMARY OF CLINICAL INFORMATION

No clinical studies were evaluated assessing the safety or effectiveness of the Leica FL400 for the visualization of grade III or IV gliomas during neurosurgery in support of this De Novo request.

Pediatric Extrapolation

In this De Novo request, clinical data were not leveraged to support the use of the device in a pediatric patient population.

LABELING

User manual labeling was provided that:

- Describes the device specifications.
- States that the device should not be used in conjunction with an optical imaging agent that is not compatible with the device specifications.
- States that the device is not intended for diagnosis.
- States that medical decisions remain the responsibility of the clinician.
- Describes preparations to take prior to surgery including adjusting the surgical operating microscope, confirming appropriate settings, and providing operational instructions.
- Describes instructions for performing a pre-operational check utilizing the FL400 Test Phantom to ensure proper functionality prior to each use.
- Describes proper use with external light sources and compatible cameras for viewing.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of the diagnostic neurosurgical microscope filter and the measures necessary to mitigate these risks.

Table 1 – Identified Risks to Health and Mitigation Measures

Identified Risks to Health	Mitigation Measures
Incorrect or misinterpreted results, including: • False positive: visualization of fluorescence when in fact no target fluorophore is present • False negative: no visualization of fluorescence when in fact the target fluorophore is present	Non-clinical performance testing; and Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the diagnostic neurosurgical microscope filter is subject to the following special controls:

(1) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use, and verify and validate filter specifications and functional characteristics, including the following:
   (i) Spectrum and intensity of the illumination source;
   (ii) Spectrum of the excitation and emission filter modules when integrated in the surgical operating microscope;
   (iii) Excitation power and power density;
   (iv) Optical path loss from illumination source to objective lens or microscope camera;
   (v) Homogeneity of the excitation light at the focal plane;
   (vi) Fluorescence detection sensitivity;
   (vii) Verification of calibration or pre-operative procedures; and
   (viii) If camera-based, spectral sensitivity of the camera.

(2) Labeling must include:
   (i) Identification of the filter characteristics in conjunction with a compatible surgical operating microscope, to include the following:
      (A) Illumination spectrum and power density; and
      (B) Excitation and emission filter spectra.
   (ii) Instructions for calibration or pre-operative checks to ensure device functionality prior to each use;
   (iii) Instructions for use with compatible surgical operating microscopes, external light sources, and cameras;
   (iv) A warning that the device should only be used with fluorophores approved for use within the specified spectral ranges; and
   (v) A warning that the device is not a standalone diagnostic.

BENEFIT-RISK DETERMINATION

The Leica FL400 has significant clinical value as an adjunct to surgery for the fluorescent visualization of grade III or IV gliomas in patients that have been pre-operatively dosed with an FDA-approved tumor-selective substance (fluorophore). The performance capability of the device is dependent upon the ability of the fluorophore to accurately identify the pathological

tumor tissue, and upon compatibility of the technological characteristics of the device with the excitation and emission spectra of the fluorophore.

Prior clinical studies were conducted to demonstrate the efficacy of optical imaging agent aminolevulinic acid hydrochloride (ALA HCl). These studies utilized standard surgical operating microscopes with illumination sources with power density 40-80 mW/cm^2 adapted to visualize fluorescence excitation in the wavelength range from 400 nm to 410 nm and for observation from 620 nm to 710 nm. These clinical studies were reviewed by FDA's Center for Drug Evaluation and Research (CDER) under NDA 208630.[1]

The efficacy of ALA HCl as an adjunct for the visualization of grade III or IV gliomas during neurosurgery was demonstrated across three studies with consistent observed results: the PPV ranged from 96% to 98% and the NPV ranged from 19% to 24%. This demonstrates a high probability that fluorescence visualization corresponds to the presence of grade III or IV gliomas; however, this also demonstrates a high probability that grade III or IV gliomas are present where no fluorescence is visualized.

The risks of the device are based on the non-clinical testing described above, taken into consideration with the observed results in the drug trials briefly summarized previously. The risk of the Leica FL400 is failure to provide appropriate excitation and emission filter spectra when used with a compatible surgical operating microscope to effectively visualize an FDA-approved tumor-selective substance (fluorophore) for tissue characterization in the open neurosurgery field. This risk is mitigated by non-clinical testing demonstrating that the interactions between the illumination source, excitation filter module, and emission filter module are appropriately designed to visualize an approved fluorophore. This risk is further mitigated by labeling in the device's Instructions for Use that 1) allows for users to determine what fluorophores could be visualized by using the device, 2) ensures users properly calibrate or check to ensure functionality of the device prior to each use, and 3) explains the device is not intended for diagnosis. The ultimate responsibility in determining the acceptable degree of tumor resection resides with the neurosurgeon.

The probable benefits of the device are also based on the non-clinical testing described above, taken into consideration with the observed results in the drug trials briefly summarized previously. Although Leica M525 and M530 surgical operating microscopes adapted with the Leica FL400 filter set were not used in the clinical studies that were performed evaluating the efficacy of ALA HCl evaluated under NDA 208630, the non-clinical testing provided in this submission adequately demonstrates that the previously evaluated clinical data are representative of the expected benefits and risks when utilizing the subject device for visualization.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

[1] https://www.accessdata fda.gov/drugsatfda_docs/nda/2017/208630Orig1s000TOC.cfm

Benefit/Risk Conclusion

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

> The Leica FL400 is a surgical microscope accessory filter set for viewing fluorescence of fluorophores comprising an excitation filter for blue spectral range 380 nm – 430 nm and an observation filter comprising the long-wave blue, green, yellow and red spectrum in the spectral band greater than 444 nm.
>
> The FL400 is a surgical microscope accessory used in fluorescent visualization of suspected grade III or IV gliomas during neurosurgery.

The probable benefits outweigh the probable risks for the Leica FL400. The device provides benefits and the risks can be mitigated using general controls and the identified special controls.

CONCLUSION

The De Novo request for the Leica FL400 is granted and the device is classified as follows:

> Product Code: QFX
> Device Type: Diagnostic neurosurgical microscope filter
> Regulation Number: 21 CFR 882.4950
> Class: II