December 16, 2018

InSightec, Inc.
Nadir Alikacem, PhD
VP Global Regulatory Affairs and Chief Regulatory Officer (CRO)
4851 LBJ Freeway, Suite 400
Dallas, Texas 75244

Re: P150038/S006
Trade/Device Name: Exablate Model 4000 Types 1.0 and 1.1 System (Exablate Neuro)
Filed: June 19, 2018
Product Code: POH

Dear Dr. Alikacem:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) supplement for the Exablate Model 4000 Type 1.0 and 1.1 Systems (Exblate Neuro). This device is indicated for a Unilateral Thalamotomy (ventralis intermedius) treatment of Tremor-dominant Parkinson's Disease with medication-refractory tremor. Patients must be at least 30 years of age. The Exablate was previously approved in 2015 for use in the unilateral Thalamotomy treatment of idiopathic Essential Tremor patients with medication-refractory tremor (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P150038).
We are pleased to inform you that the PMA supplement is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below. Although this letter refers to your product as a device, please be aware that some approved products may instead be combination products. The Premarket Approval Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm identifies combination product submissions.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the labeling must specify the specific training or experience practitioners need in order to use the device. FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Continued approval of the PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. This report, identified as "Annual Report" and bearing the applicable PMA reference number, should

be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the PMA device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

In addition to the Annual Report requirements, you must provide the following data in a post-approval study (PAS) report for the PAS listed below. A PAS Progress Report must be submitted for this study every six (6) months during the first two (2) years of the study and annually thereafter, unless otherwise specified by FDA. Two (2) copies of the report, identified as an "ODE Lead PMA Post-Approval Study Report" in accordance with how the study is identified below and bearing the applicable PMA reference number, should be submitted to the address below.

1. *ODE Lead PMA Post-Approval Study – "Post Approval Registry Study for Exablate 4000 ("Exablate Neuro") Type 1.0 and 1.1 for Unilateral Thalamotomy in the Treatment of Medication -Refractory Tremor Dominant Parkinson's Disease (TDPD)"*. The Office of Device Evaluation (ODE) will have the lead for the study initiated after its approval. On December 5, 2018, you agreed to conduct a study as follows:

   You will conduct a prospective, multi-center, new enrollment, long-term safety and effectiveness study, in which the postoperative outcomes of the subjects are compared to their preoperative baselines. The study is designed to evaluate the long-term safety of the Exablate device when used to treat patients who have failed medication for Dominant Parkinson's- related tremors. A total of 50 subjects are to be enrolled. A t-test graph demonstrated that the power will be sufficient to determine any significant differences in long-term effectiveness at α=0.05. The graph showed that at 25 subjects, the number of subjects needed had plateaued. With an approximate average of an 8 % dropout per year through Year 5, the remaining population is estimated to be approximately 30 subjects still at year 5, which shows full power. Eligible subjects will be followed for five years post-operatively with the following frequency of assessments: baseline/screening/medical history will be collected prior to treatment. The Clinical Rating Scale for Tremors (CRST) will be captured at baseline, at 1, 3, and 6 months, 1-5 years post-treatment visits, and annually, as per standard clinical practice.

   The study will evaluate the primary safety outcomes through the descriptive analysis of the number and severity of adverse events. This study profile will also be comparable to the safety profiles of the TDPD study and the ET study, since it is the same device treatment at the same target, without large significant deviations. Further analyses will descriptively compare the adverse events to those occurring in comparable patient populations with Parkinson's Disease treated with Deep Brain Stimulation (DBS).

   Effectiveness will be evaluated by descriptive analysis of the score values compared to baseline and the percent change from baseline.

   - Tremor/Motor scores components of the CRST
   - Posture-Rest Part A components of CRST

- Part C of the CRST.

Within 30 days of your receipt of this letter, you must submit a PMA supplement that includes a complete protocol for your post-approval study. Your PMA supplement should be clearly labeled as a "Post Approval Registry Study for Exablate 4000 ("Neuro") Type-1.0 & 1.1 for Unilateral Thalamotomy for the Treatment of Medication-Refractory Tremor Dominant Idiopathic Parkinson's Disease" and submitted in triplicate to the address below. Please reference the PMA number above to facilitate processing.

FDA would like to remind you that you are asked to submit separate PAS Progress Reports every six months during the first two years of the study and annually thereafter. The reports should clearly be identified as Post-Approval Study Report. Two copies for each study, identified as "PMA Post-Approval Study Report" and bearing the applicable PMA reference number, should be submitted to the address below. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order" (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm#2).

This is a reminder that as of September 24, 2014, class III devices are subject to certain provisions of the final UDI rule. These provisions include the requirement to provide a UDI on the device label and packages (21 CFR 801.20), format dates on the device label in accordance with 21 CFR 801.18, and submit data to the Global Unique Device Identification Database (GUDID) (21 CFR 830 Subpart E). Additionally, 21 CFR 814.84 (b)(4) requires PMA annual reports submitted after September 24, 2014, to identify each device identifier currently in use for the subject device, and the device identifiers for devices that have been discontinued since the previous periodic report. It is not necessary to identify any device identifier discontinued prior to December 23, 2013. Combination Products may also be subject to UDI requirements (see 21 CFR 801.30). For more information on these requirements, please see the UDI website, http://www.fda.gov/udi.

Before making any change affecting the safety or effectiveness of the PMA device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm.

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52 for devices or post marketing safety reporting (21 CFR 4, Subpart B) for combination products, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm and on combination product postmarketing safety reporting is available at (see https://www.fda.gov/CombinationProducts/GuidanceRegulatoryInformation/ucm597488.htm).

In accordance with the recall requirements specified in 21 CFR 806.10 for devices or the postmarketing safety reporting requirements (21 CFR 4, Subpart B) for combination products, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at http://www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm.

CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm. Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with a copy of all final labeling. Final labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final labeling is identical to the labeling approved in draft form. If the final labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing:

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact Daryl Kaufman at 301-796-6467 or Daryl.Kaufman@fda.hhs.gov.

Sincerely,

Carlos L. Pena -S Digitally signed by Carlos L. Pena -S
Date: 2018.12.16 08:56:57 -05'00'

Carlos L. Peña, PhD, MS
Director
Division of Neurological
and Physical Medicine Devices
Office of Device Evaluation
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