



October 29, 2021

INSIGHTEC, Inc.
Nadir Alikacem, Ph.D.
V.P. Global Regulated Clinical Affairs
4851 LBJ Freeway, Suite 400
Dallas, Texas 75244

Re: P150038/S014

Trade/Device Name: Exablate Model 4000 Type 1.0 and 1.1 System (“Exablate Neuro”)

Product Code: POH

Filed: May 3, 2021

Amended: August 11, 2021

Dear Dr. Nadir 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 System (“Exablate Neuro”) for expanding the indications to include the unilateral pallidotomy of patients with advanced, idiopathic Parkinson’s disease with medication-refractory moderate to severe motor complications as an adjunct to Parkinson’s disease medication treatment. Patients must be at least age 30. The designated area in the brain responsible for the movement disorder symptoms [globus pallidus (GPi)] must be identified and accessible for targeted thermal ablation by the Exablate device. This device is indicated for use:

1. In the unilateral thalamotomy treatment of idiopathic essential tremor patients with medication-refractory tremor. Patients must be at least age 22. The designated area in the brain responsible for the movement disorder symptoms (ventralis intermedius) must be identified and accessible for targeted thermal ablation by the Exablate device.
2. In the unilateral thalamotomy (ventralis intermedius) treatment of tremor-dominant Parkinson’s disease with medication-refractory tremor. Patients must be at least age 30.
3. In the unilateral pallidotomy of patients with advanced, idiopathic Parkinson’s disease with medication-refractory moderate to severe motor complications as an adjunct to Parkinson’s disease medication treatment. Patients must be at least age 30. The designated area in the brain responsible for the movement disorder symptoms [globus pallidus (GPi)] must be identified and accessible for targeted thermal ablation by the Exablate device.

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 post-approval study (PAS) reports for each PAS listed below.

You must obtain approval of your PAS protocol(s) within 60 days from the date of this order. Within 30 days of your receipt of this letter, you must submit a PMA supplement that includes a complete protocol of your post-approval study described below. Your PMA supplement should be clearly labeled as a "PMA Post-Approval Study Protocol" as noted below and submitted to the address below. Please reference the PMA number above to facilitate processing. If there are multiple protocols being finalized after PMA approval, please submit each protocol as a separate PMA supplement.

PMA Post-Approval Study (PAS): The purpose of the PAS is to provide follow-up on those patients in the "A Pivotal Clinical Trial of the Management of the Medically-Refractory Dyskinesia Symptoms or Motor Fluctuations of Advanced Idiopathic Parkinson's Disease with Unilateral Lesioning of the Globus Pallidum using the Exablate Neuro System (PD006)" study and enroll new patients to determine the durability of treatment and whether there are fewer serious adverse events in the newly enrolled patients than occurred in the pivotal study. The PAS will evaluate the safety and long-term effectiveness of the Exablate Neuro in the unilateral pallidotomy of patients with advanced, idiopathic Parkinson's disease with medication-refractory moderate to severe motor complications as an adjunct to Parkinson's disease medication treatment. The PAS should be a registry study that includes the patients in the PD006 pivotal trial and all eligible patients from multiple sites with a minimum of 60 newly enrolled and treated

patients. Newly enrolled patients should be followed at baseline, 6-months, 1-year, 2-years, 3-years, 4-years, and 5-years post-procedure with a missing data rate of 10% or less. The primary effectiveness outcome should be the same primary effectiveness outcome as the PD006 clinical study. The primary safety outcome is the assessment of all adverse events starting on or after the day of treatment through all study follow-up visits.

From the time of study protocol approval, you must meet the following timelines for the new enrollment cohort of the PAS:

- First subject enrolled within 6 months,
- 20% of subjects enrolled within 12 months,
- 50% of subjects enrolled within 18 months,
- 100% of subjects enrolled within 24 months,
- Submission of final study report: 3 months from study completion (i.e., last subject, last follow-up date).

In addition, you must submit separate periodic reports on the progress of the PAS as follows:

- PAS Progress Reports every six (6) months until subject enrollment has been completed, and annually thereafter.
- If any enrollment milestones are not met, you must begin submitting quarterly enrollment status reports (i.e., every 3 months), in addition to your periodic (6-months) PAS Progress Reports, until FDA notifies you otherwise.

For all other condition of approval studies, you must submit separate PAS Progress Reports for each study, every six (6) months for the first two (years) and annually thereafter, unless otherwise specified by FDA.

Each PAS report should be submitted to the address below identified as a "PMA Post-Approval Study Report" in accordance with how the study is identified above and bearing the applicable PMA reference number.

Be advised that failure to comply with any post-approval requirement, including the initiation, enrollment, and completion requirements outlined above for the PAS, constitutes grounds for FDA withdrawal of approval of the PMA in accordance with 21 CFR 814.82(c) and 814.46(a)(2).

Be advised that the failure to conduct any such study in compliance with the good clinical laboratory practices in 21 CFR part 58 (if a non-clinical study subject to part 58) or the institutional review board regulations in 21 CFR part 56 and the informed consent regulations in 21 CFR part 50 (if a clinical study involving human subjects) may be grounds for FDA withdrawal of approval of the PMA in accordance with 21 CFR 814.46(a)(3)-(4).

Be advised that protocol information, interim and final results will be published on the Post Approval Study Webpage https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm. In addition, the results from any post approval study should be included in the labeling as these data become available. Any updated labeling must be submitted to FDA in the form of a PMA supplement. For more

information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order" (<https://www.fda.gov/media/71327/download>).

This is a reminder that as of September 24, 2014, class III devices are subject to certain provisions of the final Unique Device Identification (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, <https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/unique-device-identification-udi-system>.

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" <https://www.fda.gov/media/81431/download>.

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 <https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems> and on combination product post-marketing safety reporting is available at (see <https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products>).

In accordance with the recall requirements specified in 21 CFR 806.10 for devices or the post-marketing 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

<https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/industry-guidance-recalls>.

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 Home Page located at

<https://www.fda.gov/medical-devices/device-approvals-denials-and-clearances/pma-approvals>. 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 Adam Pierce, Ph.D., at 240-402-6128 or Adam.Pierce@fda.hhs.gov.

Sincerely,

**Christopher
Loftus -S**

Digitally signed by
Christopher Loftus -S
Date: 2021.10.29 12:21:52
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Christopher Loftus, M.D.

Acting Director

OHT5: Office of Neurological

and Physical Medicine Devices

Office of Product Evaluation and Quality

Center for Devices and Radiological Health