DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Mail Center - WO66-G609
Silver Spring, MD 20993-0002

InSightec, Incorporation
% Nadir Alikacem, Ph.D.
Vice President, Regulatory Affairs and CRO
4851 LBJ Freeway, Suite 400
Dallas, Texas 75244

OCT 18 2012

Re: P110039
InSightec ExAblate® System, Model 2000/2100/2100 V1
Filed: December 5, 2011
Amended: December 13 and December 22, 2011; February 14, March 15, March 28, May 2, May 8, May 25, and July 19, 2012
Procode: NRZ

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) for the ExAblate System, Model 2000/2100/2100 V1. This device is indicated for pain palliation of Metastatic Bone Cancer in patients 18 years of age or older who are suffering from bone pain due to metastatic disease and who are failures of standard radiation therapy, or not candidates for, or refused radiation therapy. The bone tumor to be treated must be visible on non-contrast MR and device accessible. We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.

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 this 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. Two copies of 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 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 conduct two (2) Post-Approval Studies to evaluate device performance under actual conditions of use and to further evaluate device safety.

1. New Enrollment Study: You must perform a post-approval study (PAS) to evaluate the safety and effectiveness of the ExAblate system when the device is used in the intended patient population under actual conditions of use. This study will be a prospective, multi-site, single-arm cohort study with a total of 70 patients enrolled who meet the indications for use and are treated with the ExAblate system at7 to 10 sites. Office visits will occur at 1-week, 1-month, 2-months and 3-months post-treatment. Safety will be evaluated by collecting the incidence and severity of all device-related complications starting at the first treatment day visit through the 3-months post–treatment time point. The primary effectiveness endpoint will be the proportion of responders in terms of pain relief, which will be captured in a patient based pain assessment using a 0-10 pain Numerical Rating Scale (NRS) with anchored points in conjunction with a body diagram. "Pain relief" complete response will be defined as a pain score of zero (0) at the treated site without increase in analgesic consumption. "Pain relief" partial response will be defined as a reduction of 2 points on a 0–10 scale at the treated site without increase in the analgesic consumption. Response will be analyzed at 3 months compared to baseline. The proportion of responders is expected to be at least 30% greater than the proportion of subjects experiencing pain progression (i.e., 60% vs. 30%). Pain medication use and quality of life will be analyzed as secondary endpoints. Quality of life will be determined by the Brief Pain Inventory - Quality of Life (BPI-QoL) score. Additionally, at the 3-month visit, an analysis of both the safety and efficacy profiles will be compared to the original PMA pivotal study group. This comparison will be descriptive with no statistical hypothesis. The Agency expects that at least 85% follow-up will be achieved.

2. Enhanced Surveillance Registry Study: You must perform a two-year enhanced surveillance registry study ("ESRS") of the Exablate System to more fully characterize adverse events when the device is used in a broader patient population in a real world setting. The purpose of this ESS is to collect information regarding adverse events that are possibly related to the ExAblate System ("ExAblate") that are received by InSightec ("InSightec") following PMA approval. Information regarding the total number of subjects treated with the device at each participating site will be collected. All patients planned to undergo the ExAblate procedure in a commercial

setting will be asked to consent for participation in the ESRS. Information to be collected will include all adverse events possibly related to ExAblate device regardless of whether the event would qualify as an MDR. For patients having any adverse events, information collected will include patient characteristics, cancer characteristics, bone metastasis characteristics, treatment parameters (including number of lesions treated and re treatments), concomitant treatments, event onset, severity and resolution. A descriptive analysis of reported adverse event rates and 95% confidence intervals will be provided. There are no scheduled follow-up visits for the subjects in this Registry. Adverse events will be captured via web-based Registry system. Sites will be contacted quarterly for data.

Within 30 days of your receipt of this letter, you must submit two (2) PMA supplements that include the complete protocols of each of your post-approval studies. Your PMA supplements should be clearly labeled as a "Post-Approval Study Protocol" and submitted in triplicate 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.

Please be advised that the results from these studies 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.

FDA would like to remind you that you are required to submit separate PAS Progress Reports for each of the Post-approval studies listed above, every six (6) months during early stages of the study implementation up to two (2) years and annually thereafter. The reports should clearly be identified as Post-Approval Study Report. Two (2) 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).

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.

Before making any change affecting the safety or effectiveness of the 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" (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, 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 www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

In accordance with the recall requirements specified in 21 CFR 806.10, 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 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 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 copies of all approved labeling in final printed form. Final printed 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 printed labeling is identical to the labeling approved in draft form. If the final printed 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 in 6 copies, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing

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If you have any questions concerning this approval order, please contact Long Chen, Ph.D. at 301-796-6389.

Sincerely yours,

Christy Foreman

Christy Foreman
Director
Office of Device Evaluation
Center for Devices and Radiological Health