DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

September 27, 2017

Medtronic, Inc.
% Janis Taranto
Principal Regulatory Affairs Specialist
HeartWare, Inc.
500 Old Connecticut Path
Framingham, Massachusetts 01701

Re: P100047/S090
Trade/Device Name: HeartWare™ HVAD™ System
Filed: February 2, 2017
Amended: May 3, 2017 and June 29, 2017
Product Code: DSQ

Dear Janis Taranto:

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 HeartWare™ HVAD™ System for expanding the indications to include destination therapy. This device is indicated for hemodynamic support in patients with advanced, refractory left ventricular heart failure; either as a bridge to cardiac transplantation (BTT), myocardial recovery, or as destination therapy (DT) in patients for whom subsequent transplantation is not planned. We are pleased to inform you that the PMA supplement is approved. You may begin commercial distribution of the device as modified 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 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. 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. 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. For more information on these requirements, please see the UDI website, http://www.fda.gov/udi.

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. Separate PAS Progress Reports must be submitted for each 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 each report, identified as an "ODE Lead PMA Post-Approval Study Report" or "OSB 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* – Continued Follow-up of HW004-A ENDURANCE Supplemental Study Cohort: The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval. The study will consist of all living subjects who are currently enrolled in the ENDURANCE Supplemental Study, including the continued access investigation, at participating institutions and who consent to be followed per protocol up to 5 years. The study objective is to compare the safety and effectiveness of a prospective blood pressure management strategy with particular focus on stroke rates in subjects receiving the HeartWare HVAD system, and to compare the safety and effectiveness of the HeartWare HVAD system for destination therapy to other FDA-approved LVADs approved for destination therapy in subjects with end-stage heart failure who are ineligible for heart transplantation. For continued follow-up of patients, the primary and secondary endpoints are listed in the protocol as follows: The primary endpoint is a non-inferiority test comparing HVAD to Control considering the incidence at 12 months on the originally implanted device of neurologic injury, defined as an ICVA or HCVA with an MRS > 0 at 24-weeks post-stroke, or a TIA, or as a spinal cord infarction. The first secondary endpoint is the reduction in stroke/TIA incidence at 12 months on the originally implanted HVAD. The second secondary endpoint is stroke-free success (Modified

Rankin Scale < 4 at 24weeks post-stroke) at 12 months comparing HVAD to Control. Additional endpoints include the primary endpoint excluding subjects with baseline MRS >0, overall survival, incidence of all serious adverse events, neurocognitive status and unanticipated adverse device effects, maintenance of mean arterial pressure per IBPM Guidelines, stroke incidences and rates, incidence of all device failures and device malfunctions, health status improvement, and functional status improvement.

2. *OSB Lead PMA Post-Approval Study*- ENDURANCE Supplemental PAS: The Office of Surveillance and Biometrics (OSB) will have the lead for studies initiated after device approval. On 9/19/2017 (email) you agreed to conduct a study as follows:

   A confirmatory study of the safety and effectiveness of the HeartWare Ventricular Assist Device (HVAD) for destination therapy (DT), with special attention paid to the occurrence, risk factors, and severity of stroke. This prospective, non-randomized, multi-center, observational study will be conducted through Medtronic's Product Surveillance Registry (PSR). A total of 300 subjects will be enrolled. Approximately 50 study sites will be enrolled, and no more than 20% of these sites will be located outside of the United States. Study subjects will be newly enrolled (using the HVAD system as DT). Subjects will be followed through five years post-implant. However, the FDA agrees to reevaluate the need for continued data collection to address study objectives once all eligible subjects have completed two years of follow-up. This evaluation will take into consideration primary and secondary endpoints/objectives from this PAS, as well as from the other required PAS (continued follow-up of the ENDURANCE Supplemental IDE cohort #G090243 and the Continued Access Protocol cohort), and other clinical data available at the time of evaluation.

   The primary endpoint/objective is survival free of disabling stroke or device malfunction requiring exchange, explant, or urgent transplant. There will be three secondary endpoints/objectives. The first secondary endpoint/objective is to determine the observed early stroke rate (stroke occurring ≤2 years post-implant), and stroke risk factors. The second secondary endpoint/objective is to determine the late stroke rate (stroke occurring >2 years post-implant) and to evaluate risk factors for late stroke. Stroke rate will be estimated using Kaplan-Meier methods, and Cox proportional hazards modeling will be used to determine factors that influence time to first stroke post-HVAD implant. The third secondary endpoint/objective is to evaluate stroke severity for all subjects who experience a stroke on device while in this study. Stroke severity will be assessed through modified Rankin Scale (mRS) scoring which will be conducted by trained individuals. The mRS scoring will be conducted at the time of stroke, 12 weeks post-stroke, and 24 weeks post-stroke. Rates and their corresponding 95% confidence intervals will be reported, where appropriate, for each endpoint/objective.

   Additionally, the following will be evaluated: the effectiveness of Invasive Blood Pressure Monitoring (IBPM), a summary of neurologic dysfunction events (ischemic cerebrovascular accidents, hemorrhagic cerebrovascular accidents, and transient ischemic attacks), overall survival on device, INTERMACS adverse event rates, quality of life measures (measured by EuroQol EQ-5D-DL and Kansas City Cardiomyopathy

Questionnaire), and functional status (measured by the 6-minute walk test). Patients will be followed at three months, six months, and every six months thereafter or as reportable adverse events prompt. PAS progress reports will be provided to the FDA biannually for the first two years following approval, and annually thereafter.

Please be advised that description of the Analysis Plan, interim (per agreed plan), and final results will be published on the Post Approval Study Webpage http://www.fda.gov/devicepostapproval.

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.

Be advised that protocol information, interim and final results will be published on the Post Approval Study Webpage http://www.fda.gov/devicepostapproval.

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" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm).

Within 30 days of your receipt of this letter, you must submit PMA supplements that include a complete protocol of your revised ODE-led Continued Access Protocol (CAP) specifying five (5) year follow-up and your OSB-led post-approval study described above. Your PMA supplements should be clearly labeled as an "ODE Lead PMA Post-Approval Study Protocol" or "OSB Lead PMA Post-Approval Study Protocol" as noted above 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.

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, 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.

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 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 copies 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 in 6 copies, 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
PMA 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 Claire Hambright at 301-796-7058 or Claire.Hambright@fda.hhs.gov.

Sincerely,

Nicole G. Ibrahim -S

for Bram D. Zuckerman, M.D.
Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and Radiological Health