DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

Division of Cardiovascular Devices
Pacing, Defibrillator & Leads Branch

Date: 31 March 2011

From: (b) (6), Mechanical Engineer, FDA/CDRH/ODE/DCD/PDLB

Subject: P080006/S004 (19 Oct 2009)
Medtronic, Inc.
Attain Ability Straight Model 4396 Left Ventricular Lead
Submitted: 19 Oct 2009
Amended: 20 Oct 2009; 15 Sep 2010, 1 Mar 2011

Contact: Lisa Stahl

To: The Record

Recommendation: Deficiency Letter

Background/ Reason for Supplement

This PMA supplement was submitted to gain approval of the Medtronic Attain Ability Straight Model 4396 left ventricular lead. The lead is based upon the approved Model 4196 lead (P080006, approved April 7, 2009) but with a straight distal tip and tine fixation. The firm states that the design is intended to meet physician requests for a lead that provides selectable electrodes and improved tracking through tortuous anatomies by eliminating the bias created by pre-shaped leads. The firm supports the approval of the Model 4396 lead with bench testing, animal study, and human clinical study data. The approval is also supported by the previous approval of the Model 4196 lead which has the identical lead body and proximal connector.

Review Team

Lead Reviewer:	(b) (6) FDA/CDRH/ODE/DCD/PDLB
Clinical:	(b) (6)., FDA/CDRH/ODE/DCD/PLDB
Engineering:	(b) (6) FDA/CDRH/ODE/DCD/PDLB
Chemistry:	(b) (6) FDA/CDER/OPS/ONDQA/DPA I
Biopharmaceutics:	(b) (6). FDACDER/OPS/ONDQA
Epidemiology:	(b) (6), OSB/DEPI/EERB1

Indications For Use

The Model 4396 lead has a similar indication to the approved Model 4196 lead as follows:

> *The Attain Ability Straight 4396 steroid eluting, dual electrode, IS-1 transvenous lead with tined fixation has application for chronic pacing and sensing in the left ventricle via the cardiac vein, when used in conjunction with a compatible Medtronic Cardiac*

Resynchronization Therapy (CRT) system. Extended bipolar pacing is available using this lead in combination with a compatible CRT-D system and RV defibrillation lead or with a compatible CRT-P system and RV pacing lead.

Device Description

The Medtronic Attain Ability Straight Model 4396 is a 4 Fr, transvenous, steroid eluting, dual electrode, polyurethane insulated, single coil, cardiac vein lead with an IS-1 BI connector. The Model 4396 lead has a straight distal end with tines for fixation. The lead can be implanted using either a guide wire or stylet in conjunction with a Medtronic 5.7 Fr guide catheter. The lead has application for chronic pacing and sensing in the left ventricle via the cardiac vein, when used in conjunction with a compatible Medtronic Cardiac Resynchronization Therapy (CRT) system and RV defibrillation lead or with a compatible CRT-P system and RV pacing lead. The Model 4396 lead is based on the Model 4196 lead (P080006, approved April 7, 2009). Detailed characteristics of the Model 4396 lead and standard accessories are provided in the engineering review consultation memo dated 12 March 2010.

The description of the lead, accessories, and packaging was found complete and acceptable.

Preclinical/Bench

The firm supports the approval of the Model 4396 lead with bench testing and animal study data as summarized below.

Animal Studies

The firm provided a summary of a canine study for the Model 4396 lead originally submitted under the IDE. The (b) (4) Good Laboratory Practice (GLP) canine study was conducted to demonstrate the in-vivo performance of the Model 4396 lead. The purpose of the study was to evaluate the electrical and stability performance of the Model 4396 lead. The handling, electrical performance and histology were found acceptable.

The same GLP study data were previously reviewed for IDE study approval of the Model 4396 lead clinical study. Under the study, the 4396 lead demonstrated acceptable electrical and stability performance compared with historical controls (Model 4194 and Model 4196). No new review of the animal study data was considered necessary under this PMA supplement.

Engineering / Mechanical

The engineering review was performed by CDRH/ODE reviewer (b) (4) and is documented in review memos dated 12 March 2010 and 30 March 2011. A (b) (4) of bench testing was performed by Medtronic, consistent with the test program accepted for the similar Model 4196 lead. The mechanical testing was performed on (b) (4) Model 4195 lead samples stored in (b) (4) conditions for (b) (4) prior to testing according to the test plan included in the submission. Lead samples were final production, packaged, sterilized, and preconditioned samples. Testing of aged devices included mechanical testing, functional testing, electrical testing, and accessory compatibility testing as documented in the submission. Additional information was provided in A003 regarding tip and tine tensile strength.

The engineering review presented the following analyses, conclusions and recommendations. The sample sizes, preconditioning, and test sequence were previously approved as part of the original IDE and are still appropriate and acceptable. The pre-agreed storage conditions were presented in the submission and are still appropriate and acceptable. Testing was completed and documented in the test reports. The data provided a 90% confidence and 90% reliability based on the sample size as prespecified in the protocol. Tensile testing for the lead tip and histology of the tissue surrounding the lead tip was provided to address concerns in the 15 March 2010 major deficiency letter. All engineering issues were resolved upon review of A003.

Biocompatibility, Sterilization & Shelf Life

The review of biocompatibility, sterilization, packaging and shelf life was performed by CDRH/ODE reviewer (b) (6) and is documented in the engineering review memo dated 12 March 2010. The Model 4396 lead uses identical materials as the approved 4196 lead and the firm provided a biocompatibility certification to document that there are new materials, processes, additives or other differences affecting biocompatibility. The firm documented that the 4396 lead will be packaged using an identical container as the approved 4196 lead. The firm provided an assessment of the sterilization requirements for the Model 4396 lead and verified that the lead could be properly sterilized under the validated sterilization cycle used for 4196. The firm requested a shelf life matching the approved shelf life for Model 4196 at the time of approval.

The current status is the device can be approved for a shelf life of 2 years based on real-time testing. The approved shelf life of the drug is currently 6 months for 4196. CDER agreed that the drug component of 4396 could be set to match the 4196 model. By agreement under review of a shelf life extension supplement for Model 4196, a condition of approval will be assigned to the 4396 lead for elution specifications and future age testing. The approved shelf life for Model 4396 will be 12 months which is the current shelf life for the approved Model 4196 lead which has the identical drug component.

Drug Component

The drug component review for chemistry, manufacturing and controls (CMC) was performed by CDER/OPS reviewer (b) (6) l in a memo dated 1 February 2010 and by email dated 21 Sep 2010. The drug component review for pharmacology and elution was performed by CDER/OPS/ONDQA reviewer (b) (6) in a memo provided by email on 16 Feb 2010 and by emails on 20 Sep 2010 and 15 Jan 2011. The Model 4396 lead utilizes two drug monolithic controlled release devices (MCRDs) which are identical to those approved for the Model 4196 lead. The label's total dose of dexamethasone acetate (DXA) is 232 µg. Documentation for the Model 4396 lead drug components was presented in Volume 5 including chemistry manufacturing and controls, drug substance, drug product, elution development and methods, drug stability, and annual stability testing. The firm provided updates in A003 to four minor CMC deficiencies in the 15 Mar 2010 letter including COA format, specification table format, and minor word substitutions. The firm provided updates in A003 to two biopharmaceutic deficiencies regarding elution method paddle speed and elution specifications.

The chemistry manufacturing and controls (CMC) review states that the CMC information has been previously reviewed and is acceptable. The finished product specification is acceptable. The COA for 4396 batch analysis is acceptable. The drug stability (shelf life) for 4396 can be approved at 1 year based on the results for 4196 by similarity. Alternating the 4396 in the existing annual stability plan for 4196 is acceptable. There were 4 minor deficiencies identified in the original CMC review. The responses to these minor issues provided in A003 were found acceptable by the CMC reviewer.

The biopharmaceutics consultant reviewed the in vitro elution information provided in the supplement. The information was largely acceptable due to the 4396 similarity with 4196. There were 2 deficiencies identified in the biopharmaceutics review that were included in the 15 Mar 2010 letter. The firm's response in A003 to the paddle speed deficiency was acceptable. The response to the elution specification deficiency was discussed interactively and an agreement for a condition of approval was generated and approved by the biopharmaceutics reviewer.

Clinical Data

The clinical review was performed but ODE/DCD/PDLB reviewer (b) (6) M.D. and is documented in a review memos dated 15 Mar 2010 and 6 Mar 2011. The clinical report was provided in Volume 3 of the submission. The clinical study on the Model 4396 lead is being conducted under

IDE (b) (6) (approved 16 Dec 2008). The firm provided a complete description of the study design, enrollment, results and deviations. The Model 4396 LV lead study was a prospective,multi-center, non-randomized study designed to include up to (b) subjects at up to (b centers in the U.S., (centers in Canada, and (centers in EMEA. There were (b) subjects enrolled in the study, (b) attempts, (b) Model 4396 attempts, and (b) subjects were implanted with the Model 4396 lead. The primary safety endpoint was Model 4396 lead related complications-free rate (b) (4) at (b) (b) (4). The primary efficacy endpoint was distal tip threshold at (b) (4) (b) UCB=(b)) and proximal ring electrode threshold at (b) (4) (b) UCB = (b)). The complication free rate for the study was documented as 94.4% with a 95% lower confidence bound of 88.8%. The mean threshold for LV tip to RV coil voltage threshold at (b) (4) was (b) (n=(b)). The mean threshold for LV ring to RV coil voltage threshold at (b) (4) was (b) (n=(b) . A secondary objective was to measure bipolar performance of the dual cathode configuration with mean voltage threshold at (b) (4) measured at (b) (n=(b). The firm concluded that Model 4396 implant success, lead handling, and electrical performance were found acceptable.

> (b) (6) *reviewed the clinical study data and labeling. The study was of a familiar design and there were no concerns with its conduct or adverse events. Upon review of the study electrical data,* (b) (6) *found that while the mean LV lead capture thresholds and upper confidence bounds had met the study endpoint, the threshold values were significantly higher than those of the approved Model 4196 lead. High pacing thresholds for the tip or ring could lead to loss of pacing, phrenic nerve stimulation, and premature battery depletion.* (b) (6) *included three deficiencies in his memo that were considered efficacy issues potentially affecting approvability of the supplement. These major deficiencies were included in a letter dated 15 Mar 2010. Interactive review between FDA and Medtronic identified updates to the package label, technical manual, and summary of clinical studies documents that addressed the concerns for potentially lesser performance than the 4196 lead.* (b) (6) *reviewed the updated labeling and found that the changes had addressed the major deficiency concerns in the 15 Mar 2010 letter. I participated in the interactive review of this issue and agree with* (b) (6) *' recommendation.*

Manufacturing

The manufacturing and assembly process used for the Model 4396 are the same as those used in manufacture of the approved Model 4196 lead. The firm provided an overview of the manufacturing facility, manufacturing equipment, and a manufacturing flowchart. The firm presented pending annual report and 30-day notice manufacturing changes under P080006 that would potentially apply to the 4396 lead model.

> *The manufacturing section was reviewed under the engineering review and found acceptable. A deficiency was included in the 15 Mar 2010 letter asking the firm to provide an update on the status of pending manufacturing changes under P080006. The firm provided an update in A003 documenting that the annual reported changes had been found acceptable by FDA and that the submitted 30-day notices had been approved by FDA. The firm justified that the changes would not be affected by the lead model. The review team agreed with the assessment. The manufacturing facility associated with PMA P080006 was initially on the FDA's OAI (Official Action Indicated) list but the firm addressed the issues and there are no manufacturing concerns.*

Labeling

The firm provided copies of labeling for the Model 4396 lead including a user manual, specification sheet, and package labels. These documents were based upon the approved labeling for the Model 4196 lead.

The proposed package label, technical manual, and summary of clinical studies labeling for the Model 4396 lead were found generally acceptable upon initial review as they were nearly identical to what is approved for the 4196 lead. However all three forms of labeling were updated to address deficiencies in the letter dated 15 Mar 2010. Interactive review between Medtronic and FDA generated the updated labeling submitted in A003. The labeling was reviewed and found acceptable by (b) (6) *and I concur with his recommendation that the updates address the major deficiencies in the 15 Mar 2010 major deficiency letter.*

Postmarket Study

The firm provided a post-market study proposal in the original submission. Medtronic proposed using its Common Platform Protocol (CPP) as the main study protocol with a separate addendum for the Model 4396-specific content. This same post-approval study structure was approved for the 4296 lead model under S002. FDA and Medtronic engaged in extensive interactive discussions regarding the 4396 post-approval study addendum, analysis plan, and case report forms. A final post-approval study plan dated 18 Feb 2011 was submitted in A003.

The use of the Product Performance Platform (PPP) base protocol was approved for the 4296 lead model while S004 has been under review. The addendum and analysis plan presented for the 4396 lead is similar to what was approved for the 4296 lead with a requirement for 1016 enrollments and 600 subjects followed to 5 years. (b) (6) *provided the epidemiological review for this submission in a memo dated 25 Mar 2011.* (b) (6) *found that Medtronic's protocol dated 28 Feb 2011 met the requirements for a chronic performance post-approval study for the 4396 lead. I participated in the interactive review of the post-approval study for the 4396 lead and agree with* (b) (6) *that the protocol and case report forms in A003 are acceptable. The post-approval study condition of approval text provided by OSB/Epi on 30 Mar 2011 will be used in the approval letter.*

Conclusion

Through a long and interactive review process with FDA, Medtronic has addressed all deficiencies in the 15 Mar 2010 major deficiency letter. The Model 4396 lead is similar to the approved 4196 lead and leverages much of the same design and validation documentation for the device and drug. However, the clinical data from the IDE study had unacceptably high LV capture thresholds for some subjects though the mean value met the primary effectiveness endpoint. Medtronic and FDA worked interactively to address this concern with an "Attention" statement on the package label and with additional and comparative performance content in the technical manual and summary of clinical studies documents. Medtronic has agreed to conduct a 5 year chronic performance post-approval study for the 4396 lead as a condition of approval.

Recommendation

At this time all deficiencies from the 15 Mar 2010 major deficiency have been addressed. The supplement is recommended for approval with conditions of approval included for future drug elution specification testing and conduct of a post-approval study.

(b) (4) Lead Reviewer, PDLB Date

(b) (6), Chief, PDLB Date