
**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: 22 December 2010

From: Erin Cutts, Biomedical Engineer, FDA/CDRH/ODE/DCD/PDLB

Subject: P070008/S015
Biotronik, Inc.
Corox OTW-L BP Left Ventricular Pacing Lead

Consultants: Engineering- Erin Cutts, Biomedical Engineer, FDA/CDRH/ODE/DCD/PDLB
Clinical- Kim Selzman, MD, FDA/CDRH/ODE/DCD/PDLB
Epidemiology- Naomi Herz, FDA/CDRH/OSB/DPS
Epidemiology- Daniel Canos, FDA/CDRH/OSB/DPS

Contact: Jon Brumbaugh, Vice President, Regulatory Affairs and Compliance

To: The Record

Recommendation: **Approval**

Erin Cutts, Lead Reviewer, PDLB Date

Mitchell Shein, Chief, PDLB Date

Background/ Reason for Supplement

This PMA supplement was submitted to gain approval for an additional left ventricular pacing lead in Biotronik's Corox OTW BP family of leads. The firm states on page 3 of the submission that the lead is identical to legally-marketed Corox OTW BP leads with the following exceptions that are intended to provide the physician with another option of shape and fixation method for different vessel anatomies:

1. Modification to the shape of the distal end of the lead
2. Extension of the polyurethane tubing by 3 mm
3. (b) (4) silicone molded parts of the fixation tip

Boston Scientific, St Jude Medical, and Medtronic each have a double curve left ventricular lead of similar design to the proposed Corox OTW-L BP lead. Those leads were approved as follows:

1. Medtronic Attain Model 4194 (P010015/S012)- 20 August 2004

2. St Jude Medical QuickSite 1056T/1058T LV lead (P030054/S004)- 11 April 2005
3. Boston Scientific Acuity Steerable LV lead (P050046, original submission)- 13 April 2007

Review Team

Clinical: Kim Selzman, MD, FDA/CDRH/ODE/DCD/PDLB
Engineering: Erin Cutts, FDA/CDRH/ODE/DCD/PDLB
Epidemiology: Naomi Herz, FDA/CDRH/OSB/DPS and Daniel Canos, FDA/CDRH/OSB/DPS

Indications For Use

The Corox OTW-L BP left ventricular pacing lead is a bipolar steroid-eluting lead intended for permanent implantation in the left ventricle via the coronary veins to provide pacing and/or sensing when used in conjunction with a compatible IS-1 pulse generator.

The sponsor indicates that these indications for use are identical to those of the other Corox OTW BP left ventricular leads (P070008, approved 12 May 2008). The changes described in this submission would not affect the indications for use, and, therefore, I have no concerns about this section of the review.

Device Description

The Corox OTW-L BP left ventricular lead is a device/drug combination product made up of two regulated components: (1) a device (the lead) and (2) a drug component (1 mg total dexamethasone acetate (DXAC) per lead located in equal portions at the tip and ring electrodes). The lead is designed to be used with a 7Fr introducer and can be inserted using the standard stylet method or an "over-the-wire" method. Molded silicone parts have been added to create a pre-shaped double curve at the lead tip when no stylet or guide wire is inserted.

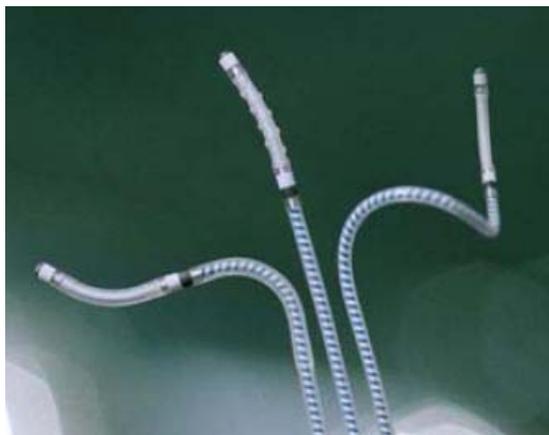


Figure 1. The Corox OTW BP family of LV leads (from left to right): the proposed Corox OTW-L BP, the market-approved Corox OTW-S BP, and the market-approved Corox OTW BP leads.

The new lead is offered in two sizes: 77 and 87 cm. The lead body is insulated with polyurethane and (b) (4), a silicone elastomer. The lead body is isodiametric in geometry and has a diameter of 5.4 Fr. The electrodes are made of (b) (4) and have surface areas of 5.0 mm² and 8.0 mm² for the tip and ring respectively.

Preclinical/Bench

The firm supports the approval of the new dual-curve lead with documentation of verification and validation testing, an accelerated aging shelf life study, OUS clinical data, and Post Approval Study modifications.

Verification and Validation Testing

The engineering review was performed by CDRH/ODE reviewer Erin Cutts and documented in a review memo dated 21 May 2010. Mechanical testing was performed on specimen subjected to sterilization cycle(s) identical to that of normal manufacturing process as well as environmental or in vitro conditions as specified in each test procedure. A report for each test (tensile testing, bending fatigue, fixation force, leakage, tip stiffness, accessory-compatibility, insulation integrity, and anchoring sleeve performance) is provided in separate appendices of the original submission.

ENGINEERING REVIEWER COMMENTS: The engineering review presented the following analyses, conclusions and recommendations. The sponsor provides information on the mechanical testing performed in the indicated appendices. This information was not initially detailed enough in many cases to understand the testing conducted and, therefore, evaluate the appropriateness of both the test method and results. Deficiencies were sent formally to the sponsor on June 11, 2010 (and informally via email on October 12, 2010) requesting additional information on the test set up and rationale. The firm provided detailed drawings and pictures of the test set up in addition to detailed rationale for the absence of a (b) (4) cycle fatigue test. The firm's responses are adequate and demonstrate appropriate bench evaluation of the changes described. The information provided in this submission and its amendment support approval of the subject lead.

Steroid Component

The sponsor indicates on page 23 of the submission the subject modifications do not expose the steroid collar to any new materials, processes, residues, vapors, or other manufacturing changes that could potentially affect drug stability and/or performance. The steroid collars used are identical to those of the other Corox OTW BP left ventricular leads.

LEAD REVIEWER COMMENTS: The firm states that the steroid collars are not only identical, but are also not exposed to any new materials or processes. Based on this understanding, I believe steroid testing should not be required for the subject lead- the safety and performance of the drug has been adequately studied during the review of the predecessor leads. I have no concerns with the steroid component of the Corox OTW-L BP left ventricular lead.

Sterilization

As indicated on page 43 of the submission, the Corox OTW-L BP lead will be sterilized with Ethylene Oxide (EtO) gas to achieve a sterility assurance level (SAL) of 10⁻⁶ in facilities and with equipment already used for other market-released Biotronik endocardial leads and accessories. The environmental controls, sterilization process, and sterility assurance procedures for the proposed Corox OTW-L BP leads are also identical to those used for other Biotronik market released leads. In addition, the firm conducted Bioburden testing according to ISO 11737-1, Pyrogen testing according to FDA Guideline 1987 and sterilization validation according to ISO 11135-1 and EN 556-1. All tested specimen met acceptance criteria.

LEAD REVIEWER COMMENTS: The changes to the proposed lead relative to its market released predecessors (namely the modification of the geometry of the distal end, the

extension of polyurethane tubing by (b) (4) mm, and the incorporation of (b) (4) silicone molded parts at the fixation tip), would not increase the device's sterilization burden. Therefore, I have no concerns about the sterility of the Corox OTW-L BP pacing lead.

Packaging

On page 44 of the submission, the firm indicates that the packaging of the proposed Corox lead will be identical to that approved for the other Biotronik leads including the proposed lead's predecessor Corox OTW-L BP left ventricular leads. This package consists of a double sterile blister package made of PETG (b) (4) and sealed with a Tyvek covering. The inner blister contains a silicone component and a Polyethylene ring to secure, respectively, the distal end of the lead and the accessory stylets during transportation. Stylets are also available separately and provided within a sterile bag. This method of packaging has been used effectively since 1991 for Biotronik's US-distributed medical devices. In addition, the firm conducted environmental preconditioning testing (including temperature cycling, moisture changes, and transport and drop testing) and evaluated the completeness of the sales unit and initial inspection.

ENGINEERING REVIEWER COMMENTS: The proposed packaging is identical to that of the market-released predecessor; this packaging has already been shown to effectively maintain a sterile barrier and protect its contents from mechanical or environmental damage. The differences between the predecessor and proposed lead would not affect the ability of the already-approved packaging to perform acceptably for the Corox OTW-L BP lead; therefore, I have no concerns about the packaging of the proposed lead.

Shelf Life

The firm requests a 24 month shelf life for the Corox OTW-L BP lead. This shelf life has been approved for the predecessor lead (P070008) in addition to all other Biotronik pacing leads. Shelf life testing including accelerated storage equivalent to 2 years was conducted with successful results.

ENGINEERING REVIEWER COMMENTS: The differences between the proposed lead and its market-released predecessor would not affect the 24 month shelf life. However, real time aging was requested as a follow up to the accelerated aging results during review of the predecessor lead, so were also requested for the subject lead. The firm indicated real time aging was already underway in the response to deficiencies dated June 11, 2010. No further concerns remain with the shelf life of the subject lead.

Biocompatibility

The firm indicates on page 25 of the submission that all of the materials used in the construction of the Corox OTW-L BP lead are the same as those used in the market-approved predecessor leads (P070008, approved 12 May 2008). In addition, the firm conducted Cytotoxicity, Hemocompatibility, and Residual Gas Analysis on various samples of the subject lead. All specimens tested met acceptance criteria.

LEAD REVIEWER COMMENTS: Since no new materials or manufacturing processes are being introduced with the implementation of the described changes, I have no concerns about the biocompatibility of the subject device.

Clinical Data

The clinical review was performed by CDRH/ODE reviewer Kim Selzman, MD, and documented in a review memo dated 04 June 2010. No US clinical data was provided to support approval of this submission. However, the lead is legally marketed outside the US in Europe, so post market clinical data was available and provided in Section 9 of the submission. The data was collected at implant, at the pre-hospital discharge, and at a one month follow-up (+/- one week) as part of an observational registry without pre-defined endpoints or sample size calculations. The firm compared the pacing threshold, pacing impedance, and bipolar signal amplitude of the subject lead to that of the predecessor triple-curve LV lead, the Corox OTW BP. The study enrolled (b) (4) patients, of which (b) (4)

were successfully implanted with the subject lead. Of those implanted, lead measurements and observations were available only for a subgroup of (b) (4) patients. The sample size was narrowed further to (b) (4) patients due to the measurement of threshold at pulse widths other than 0.5 ms or incorrect/improper data collection.

CLINICAL REVIEWER COMMENTS: The data presented by the sponsor for (b) (4) implants does not appear to raise a safety concern. In addition, the handling survey indicates adequate performance of the new distal tip design (b) (4) (b) (4)). The changes to the subject lead relative to the other Corox LV leads appears fairly minimal, and the effectiveness appears satisfactory in the studied patients. Initially, the patient selection method was unclear, but the firm's response to a June 11 deficiency provided the necessary information to understand the study methodology. Although the (b) (4) patients were not randomly selected, the overall results are acceptable, so no selection concerns remain. An additional deficiency was provided regarding the relatively low implant success rate of (b) (4). The sponsor provided an Appendix listing reasons why the subject lead was not implanted in each relevant case. The reasons seem acceptable from a clinical perspective, and no concerns regarding approval remain.

Post Approval Study

The firm proposes to include the subject lead as part of the Post Approval Study (PAS) designed to evaluate the long term performance of the market-approved Corox LV leads. The study, CELESTIAL Post Approval Registry, will evaluate the performance of the Corox OTW BP leads in over 2000 patients in 100 sites for up to 5 years. An updated protocol for the study was included as Appendix 4 of the submission.

LEAD REVIEWER COMMENTS: The firm's proposal to include the subject lead in the ongoing CELESTIAL PAS appears appropriate in that the failure modes would be similar and should be studied in a post market environment. Additionally, the clinical reviewer noted that "it seems reasonable to include all 3 Corox leads in the PAS." Offline conversations with Mark Fellman and Brian Lewis, MD, of ODE/DCD/PDLB indicated they also believed inclusion of the new model appeared to be appropriate. However, the initial PAS protocol did not provide sufficient detail to understand how data from each lead model would be pooled and how sample sizes might be affected. A deficiency was sent on June 11, 2010 requesting additional information and a redlined copy of the protocol. A formal epidemiology review was requested for the responses to those deficiencies. The review is documented in an email sent September 30, 2010 and was followed up with several in person and telephone meetings with both the lead reviewer and the firm.

EPIDEMIOLOGY REVIEWER COMMENTS: The firm's responses to questions regarding poolability and sample size in the June 11 letter were inadequate. According to the engineering reviewer, the new lead has a different distal fixation tip and, therefore, will be placed in different loading configurations. Based on the potential for different chronic safety performance, a minimum sample size should be required for each model of the lead family. In addition, the new lead accounts for more than (b) (4) of the families sales OUS as indicated in an email from the firm. That being said, the original CELESTIAL PAS (approved in 2007) did not require a minimum sample size for each of the two approved leads and, arguably, those two models were more different from one another than either is from the new OTW-L lead. However, PAS expectations have been strengthened since the approval of the CELESTIAL study to require more rigorous poolability analyses. For example, Medtronic's ongoing PAS for the Attain family of LV leads (Models 4196, 4296, and 4396) requires a minimum of (b) (4) evaluable subjects for each model for poolability analyses. Biotronik needs to update their protocol to require at least (b) (4) evaluable subjects with the new lead for any adverse event analysis based on model number. Also, the (b) (4) allowable attrition should be strengthened to allow for only (b) (4) loss.

LEAD REVIEWER COMMENTS: FDA's concerns and expectations were communicated to the firm through a number of telephone and email conversations. The firm provided a number of revised protocols for FDA review, the final of which was sent 16 Nov 2010 and was acceptable to FDA Epidemiologists Naomi Herz and Daniel Canos as indicated in the attached emails.

Several discussions between Epidemiology and PMA Staff regarding the correct way to document review and acceptance of a PAS protocol sent via email resulted in FDA's request that the firm send an amendment with the final protocol. The firm sent P070008/S015/A002 on 14 Dec 2010 at which point it was reviewed by Naomi Herz and Daniel Canos as documented in the Epidemiology review memo dated 22 Dec 2010. The final protocol was deemed acceptable and the following description was provided by Epidemiology to include in the Approval Order.

You have also agreed to conduct the Post-approval study of BIOTRONIK's Corox BP LV pacing leads as used in conjunction with any BIOTRONIK CRT pulse generator CRT-P or CRT-D. This study is intended to be rolled into the requirements for the Corox OTW BP and Corox OTW-S BP LV pacing leads (P070008) approved on May 12, 2008. The existing study requirement for P070008 is a prospective study designed to characterize chronic lead performance following device implant, as well as a robust process to retrospectively collect implant data for each study subject with a post-approval study patient follow-up duration of at least 5 years. The first primary endpoint will evaluate if the serious adverse event-free rate for the Corox BP LV leads at 5-years post-enrollment is greater than (b) (4). In addition to the chronic lead related 5-year complication-free rate, individual adverse events contributing to the endpoint will also be examined. The individual adverse event rates and (b) (4) upper confidence bounds should be provided. Both endpoints should be evaluated separately for each Corox BP lead model. You have also agreed to increase the overall sample size to (b) (4). This would allow for estimation of a (b) (4) upper confidence bound of no more than (b) (4) for individual adverse event rates, assuming an expected rate of (b) (4), using the (b) (4). In order to incorporate the Corox BP LV pacing leads into the existing post-approval study, you have agreed to amend the P070008 requirement to include a minimum of (b) (4) evaluable subjects for the Corox OTW-L BP lead which assumes an equal (b) (4) distribution of each lead model (Corox OTW BP LV lead, Corox OTW-S BP LV lead, and Corox OTW-L BP LV lead).

No concerns remain regarding post market evaluation of the subject lead.

Labeling

All labeling for the proposed Corox OTW-L BP lead was provided in Appendix 28 of the submission. The technical manual (a redlined version) was located in Appendix 26 and the electronics manuals insert in Appendix 27.

LEAD REVIEWER COMMENTS: The labeling appears to be acceptable. A review of the technical manual found all changes were appropriate editorial changes made to include the new model number and describe the Corox OTW-L BP lead in addition to the predecessor leads in the comprehensive lead family manual. I have no concerns about the labeling of the new lead.

Manufacturing

All manufacturing and quality control procedures, including packaging sterilization of the Corox OTW-L BP leads will be performed at one of two facilities that are already used to manufacture all other Biotronik leads and accessories distributed in the US: (1) BIOTRONIK SE & Co. KG in Berlin, Germany and (2) BIOTRONIK AG in Bulach, Switzerland.

LEAD REVIEWER COMMENTS: The manufacturing sites listed are already being used for production of the market-released predecessors and other Biotronik leads and accessories. The differences between the predecessor leads and the proposed lead would not affect the ability of the cited facilities to manufacture the devices using approved protocols and in compliance with FDA Quality System Regulation 21 CFR 820; therefore, I have no concerns about the production of the Corox OTW-L BP lead.

Summary of interactive Review/correspondence

June 11, 2010: Major deficiency letter sent to firm
August 25, 2010: Deficiency responses received (P070008/S015/A001)
October 12, 2010: Additional engineering questions emailed to firm
October 21, 2010: Email question responses received
October 22, 2010: PAS concerns communicated over email
November 16, 2010: Final PAS protocol sent via email
December 14, 2010: Final PAS protocol received as an amendment to the file (P070008/S015/A002)
December 22, 2010: Epidemiology review memo received- PAS protocol deemed acceptable

Conclusion

The firm has provided documentation of verification and validation testing, shelf life testing, and OUS clinical data to support approval of an additional distal tip design to their Corox OTW BP family of left ventricular leads. The firm responded adequately to initial deficiencies concerning the bench testing conducted and methods and results of the OUS clinical study. Concerns were addressed interactively to reach resolution for updates to the ongoing CELESTIAL Post Approval Study protocol to incorporate the new model. No concerns remain, and I recommend approval of this submission.