DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

MEMORANDUM

DATE: November 14, 2011

TO: The Record

FROM: [redacted], Lead Reviewer
CDRH/ODE/DCD/PDLB

SUBJECT: P050023/S047
Lumax 500/540 Thoracic Impedance
Biotronik

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RECOMMENDATION: APPROVAL

Signature	*Date*	*Signature*	*Date*
[redacted]		Mitchell Shein	
Lead Reviewer, PDLB		Branch Chief, PDLB	

BACKGROUND

BIOTRONIK first requested approval of the Thoracic Impedence (TI) feature as part of the PMA Supplement introducing the Lumax 500/540 devices, but this feature was withdrawn after the FDA reviewer of this file indicated that clinical data would be required to support approval of such a feature (P050023/S04/A01).

Data collection for the TI feature was approved as part of the EchoCRT Clinical Study (G080067/S07, dated August 26, 2009), this approval allowed optional, voluntary collection of data from study patients and sites. In the US, the feature is locked out of the currently marketed 1004.U programmer software (P950037/S92, dated February 11, 2011), and can be activated only through a protected release code. In addition, all EchoCRT investigators are fully blinded to the TI results (only available to BIOTRONIK via Home Monitoring) to avoid bias in patient treatment.

BIOTRONIK briefly discussed requirements for obtaining market approval for this feature in the US during a teleconference with FDA in July 2009, as part of adding this feature to the

EchoCRT Study. At that time, [redacted] indicated that BIOTRONIK would need to present a reasonable basis relating the device data to "real physiologic phenomena," and FDA recommended submitting plans to support market approval as a pre-IDE.

As a result of this suggestion, a pre-IDE [redacted] (b) (4)) was submitted on April 22, 2011 which presented the currently available preclinical and clinical data for this feature. The pre-IDE was limited to displaying trending information of TI data to the physician on the programmer and via BIOTRONIK's Home Monitoring® Service Center.

The following information was included in the pre-IDE:

- Bench data
- Animal Study Data from [redacted] (b) (4) studies
- Clinical Data: HomeCAREII Interim Report

As requested by FDA during the pre-IDE meeting, BIOTRONIK has revised their proposed labeling to remove any claims of [redacted] (b) (4) and added a statement regarding the limited data available.

With this PMA Supplement to P050023, BIOTRONIK provided the following information:

- Additional analysis of HomeCARE II data in patients without HF events
- Additional analysis of SAE data from HomeCARE II and EchoCRT studies. SAEs for patients with painless shock impedance will be compared to SAEs for patients with painless shock impedance and TI enabled.

BIOTRONIK revised the labeling with the following statement to indicate that clinical value of this feature has not been established:

> *"The TI trend does not replace assessments that are part of standard of care for the clinical practice. The clinical value of this feature has not been established for the management of patients.*
>
> *Note: Pocket and or lead revisions may affect the TI trend data. Therefore, the TI trend data should be interpreted cautiously within 6-10 weeks of a revision."*

During development the TI measurement parameter was also referred to as "LES." As a result, some of the documentation in the submission uses this term.

REVIEW TEAM

The following CDRH individuals contributed to the review of this submission:

[redacted]

ODE/DCD/PDLB - lead reviewer
OSEL/DP – animal study consult
ODE/DCD/CEMB - clinical consult
OC/PAPS – compliance analysis

INDICATIONS FOR USE

The Indications for Use and Contraindications for the Lumax Family of Implantable Cardioverter Defibrillators (ICDs) and Cardiac Resynchronization Defibrillators (CRT-Ds) are unchanged with this PMA Supplement.

ICDs:
Indications for Use: The Lumax Family of Implantable Cardioverter Defibrillators (ICDs) is intended to provide ventricular antitachycardia pacing and ventricular defibrillation, for automated treatment of lifethreatening ventricular arrhythmias.

CRT-Ds:
Indications for Use: The Lumax CRT-Ds are indicated for use in patients with all of the following conditions:

- *Indicated for ICD therapy*
- *Receiving optimized and stable Congestive Heart Failure (CHF) drug therapy*
- *Symptomatic CHF (NYHA Class III/IV and LVEF □ 35%)*
- *Intraventricular conduction delay (QRS duration □ 130 ms)*

DEVICE DESCRIPTION

The functional description of Thoracic Impedance (TI) Measurement from the submission:

The thoracic impedance (TI) measurement of Lumax 500/540 devices is based on the painless shock impedance feature of BIOTRONIK's currently marketed ICDs. It is carried out in 24 measurement windows evenly distributed over the course of each day (24 hour period) with 1024 impedance measurements per hour. The impedance is measured between the RV distal shock coil and the ICD housing with an excitation current. The device calculates and stores the mean hourly impedance values. All hourly values obtained within one Home Monitoring interval are transmitted to the Home Monitoring Service Center along with the daily Home Monitoring message.

Upon device interrogation, the programmer calculates and displays an intrathoracic impedance trend of the mean daily impedance values, similar to other trends such as mean heart rate, etc.; however BIOTRONIK is not providing any specific directions or data claims to the physicians on the interpretation of these impedance values.

CHANGES

In the US, the TI measurement is currently only used for research purposes and can only be unlocked using a specific release code. The ICS 3000 / Renamic programming software allows programming of the TI measurement in the Lumax 500/540 devices after entering a release code. This release code is a software key that allows the user to turn the TI measurement ON or OFF and select the TI measurement current gain setting. A comparison of the TI measurement to the BIOTRONIK's Painless Shock Impedance (approved through P050023/S01, December 7, 2006) is presented below with the differences in italics and red font:

Parameter	Painless Shock Impedance	TI
Hardware	DCAC IC	DCAC IC (identical circuitry)
Current Path	[redacted]	(b) (4)
Measurement		
# Pulses per Cycle		
Pulse Amplitude		
Pulse Interval		
Measurement Trigger		
# Measurement		
Home Monitoring Data Transmission		
Programmability		

The differences were reviewed by [redacted] during the course of her clinical review. In her review memo dated October 3, 2011, she found no concerns about the differences.

BENCH TESTING

Software

This PMA Supplement is not introducing a new programmer software to support the TI feature, it is simply requesting approval to use the feature that is already implemented in the currently marketed 1004.U programmer software (P950037/S92, dated February 11, 2011), and is activated through a release code.

(b) (4) . This feature was subsequently removed from the PMA Supplement at FDA's request because there was limited clinical data to support its approval. These test reports are designed to validate the full functionality of the TI feature.

The test reports were reviewed and found to be acceptable. From the information contained, it appears that the TI measurement function is functioning appropriately.

Current Consumption

The sponsor performed bench testing to assess the impact of activating the TI measurement on device longevity. The sponsor claims the results show that this measurement increases power consumption by no more than (b) (4) which corresponds to an estimated longevity loss of less than one month during the products expected lifetime. The test report included in the submission as Appendix 6 was reviewed. During the review, additional information was deemed necessary to make an appropriate determination if the information provided was sufficient. This process was handled interactively. The request was sent to Biotronik in the form of email questions. The company responded to the list of questions. The responses were reviewed and found to be acceptable.

There are no further questions regarding current consumption.

ANIMAL TESTING

Preclinical data have been obtained in the course of (b) (4) animal studies. The sponsor claims that both these studies show significant positive correlation between extravascular lung fluid levels and thoracic impedance. [redacted] reviewed the (b) (4) animal studies. In his review memo dated October 3, 2011, he found the two studies show a correlation of a decrease in thoracic impedance as measured from an intracardiac lead and the can in an acute swine model of pulmonary edema. In a further discussion with [redacted], it was also agreed that the sponsor is measuring thoracic impedance accurately.

The (b) (4) animal studies were also reviewed by [redacted] in the course of her clinical review. In her review memo dated October 3, 2011, she found the data demonstrate that the intrathoracic impedance is correlated to both classical measures of pulmonary edema.

There are no further questions regarding animal testing.

CLINICAL

Within the April 22, 2011 pre-IDE (b) (4) BIOTRONIK provided interim data from the HomeCARE II study which was described in submission Section 7.1.

On May 31, 2011, FDA provided comments and questions on the pre-IDE materials. On June 6, 2011 a teleconference was held with FDA to discuss and clarify these comments and questions. Additional data analysis of available TI data was performed to further answer FDA's comments and questions and is included in submission Section 7.2.

[redacted] reviewed the clinical data from the HomeCARE II study. She also reviewed the additional information provided by the sponsor in response to FDA's comments and questions from pre-IDE (b) (4). In her review memo dated October 3, 2011, she finds that the labeling accurately reflects the function of this feature as a "tool" that may contribute to standard management for HF patients and recommends approval of the Thoracic Impedance feature.

There are no further questions regarding the clinical data.

LABELING

As discussed during the June 6, 2011 pre-IDE meeting, BIOTRONIK agreed to provide updated labeling to address FDA's concerns. This was submitted to FDA with the final meeting minutes on June 6, 2011 and is also provided in submission Appendix 12. Division level concurrence at the FDA was received regarding the proposed labeling approach agreed to during the meeting.

All applicable changes described in this submission were applied and the Technical Manual can be found in submission Appendix 13. A version of the technical manual showing all revisions made the Lumax 500/540 technical manual was provided in submission Appendix 14.

The proposed labeling was reviewed by [redacted]. In [redacted] review memo dated October 3, 2011, she found that these caveats adequately address the issue that this feature is merely a tool that is used in conjunction with the normal management of patients with a history of heart failure and not a replacement for in-person assessments or other parts of standard HF care.

I also reviewed the proposed labeling and have no issues. The labeling does agree with the results of the pre-IDE meeting and addresses FDA's concerns.

MARKETING

During the pre-IDE discussion Biotronik was informed to follow up on their OUS TI press release and their US/OUS distinction on their company website. Biotronik TI press release for OUS dated October 14, 2010 and posted on their website is not consistent with the proposed US TI labeling.

[redacted] of OC's Promotion and Advertising Policy Staff reviewed the company website and OUS TI press release. In her review memo dated October 5, 2011, she found that Biotronik has clearly separated US and OUS products. She found that no further action is warranted at this time.

There are no further questions regarding Marketing.

OTHER REVIEW ELEMENTS

The following areas are not relevant for the subject review:

- Risk Analysis
- EMC/EMI
- Biocompatibility
- Manufacturing
- Human Factors
- Packaging, sterilization, shelf-life
- Post-market issues

SUMMARY OF INTERACTIONS

Sep 28, 2011: Email request for clarification of HF definition
Oct 3, 2011: Email response from Biotronik for HF definition
Oct 17, 2011: Email request for Current Consumption questions
Oct 28, 2011: Email response from Biotronik for Current Consumption questions

CONCLUSION/RECOMMENDATION

The results of the bench testing, the animal studies, and the clinical data confirm that Biotronik is able to measure Thoracic Impedance accurately. Biotronik has not claimed any clinical utility for the Thoracic Impedance measurement feature. The labeling accurately reflects the function of this feature as a "tool" that may contribute to standard management for heart failure patients. I believe that Biotronik has shown that the Thoracic Impedance measurement feature is safe and can effectively measure and display Thoracic Impedance.

I recommend that the sponsor receive an **APPROVAL** letter.