

**FDA Executive Summary Memo**  
**Cardima REVELATION Tx Microcatheter and NavAblator System, P020039**

Atrial fibrillation (AF) is an important public health problem in the United States affecting millions of Americans. Currently, no devices have been approved for the treatment of this disorder. A priority of the Food and Drug Administration (FDA) is to facilitate the introduction of safe and effective treatment for atrial fibrillation.

FDA has carefully reviewed Cardima's trial execution, original results, and subsequent analyses and data. The Agency has concluded that important problems exist with the trial execution and results. Accordingly, FDA has concluded that Cardima has not provided reasonable assurance of safety and effectiveness of the Cardima REVELATION TX Microcatheter and NavAblator System for the treatment of patients with paroxysmal atrial fibrillation (PAF).

FDA has attempted to summarize key findings in the Executive Summary that follows. More detailed reviews of the trial and results can be found in the clinical and statistical reviews. Important information such as official FDA correspondence, summaries of critical meetings between FDA and Cardima, the May 29, 2003 Advisory Panel transcript, and information provided in the Cardima's amendment in response to the FDA's first not approvable letter is provided in the FDA Panel Pack.

Thank you for taking time out of your busy schedules to review this information.

## ***Device Description***

The Revelation Tx Microcatheter and NavAblator System consists of the Revelation Tx Ablation Microcatheter (3.7 F), the NavAblator Ablation Catheter (8F), and the Naviport Guiding Catheter. The Revelation Tx Microcatheter is a single use, steerable, non-deflectable, multi-electrode microcatheter with a flexible, non-electrically active tip. It has eight electrodes and eight thermocouple temperature sensors on the distal end of the catheter in a linear array. Radiofrequency (RF) energy is applied to each electrode individually. This catheter is designed for the treatment of PAF by creating linear lesions. The NavAblator Ablation Catheter is a single use, deflectable catheter with an electrically active tip. This catheter is designed for ablation of the cavo-tricuspid isthmus and is intended for the creation of spot lesions from its tip. The Naviport Guiding Catheter is a legally marketed device (previously cleared under K974683) and is a deflectable guiding catheter used to aid in the positioning of the Revelation Tx.

## ***Cardima's Proposed Indications for Use***

The Cardima Inc., Revelation Tx Microcatheter with NavAblator RF Ablation System is indicated for treatment of patients with drug refractory paroxysmal atrial fibrillation, by mapping, pacing and ablating with a compatible radiofrequency generator, creating a set of continuous linear lesions along the lateral and septal walls and along the isthmus in the right atrium.



Figure 1. NavAblator catheter



Figure 2. Revelation Tx catheter

## ***Background***

September 30, 2002.....Original PMA submission  
May 29, 2003.....Circulatory System Devices Advisory Panel Meeting  
June 26, 2003.....First FDA Not-Approvable letter  
May 21, 2004.....Second FDA Not-Approvable letter  
August 5, 2004.....Meeting with ODE management regarding next steps  
June 10, 2005.....Meeting with ODE review team regarding next steps  
June 9, 2006.....Cardima's request for Dispute Resolution  
February 27, 2007.....Meeting with CDRH regarding options to avoid dispute resolution

The original PMA (P020039) was submitted to FDA on September 30, 2002. The primary clinical data provided in support of the device consisted of the results of a multi-center, non-blinded, single arm trial. The number of episodes of PAF recorded during the one month baseline monitoring was compared to the number of episodes of PAF that were recorded during the 6<sup>th</sup> month post ablation procedure. PAF episodes were self reported by the patient with a transtelephonic monitor (TTM).

The submission was presented to the Circulatory System Devices Advisory Panel on May 29, 2003. This panel voted unanimously (7-0) that the application be found not approvable. After considering the data that had been provided by Cardima, and the recommendation of the Advisory Panel, FDA determined that the application did not provide sufficient valid scientific evidence to demonstrate reasonable assurance of safety and effectiveness of the Revelation Tx and NavAblator System for its intended use. Therefore, on June 26, 2003, FDA issued a Not Approvable letter. In response to FDA's June 26, 2003 letter, Cardima submitted an amendment to the PMA (Amendment 6). This amendment included data on an additional 36 patients enrolled into the pivotal portion of the trial. After reviewing this additional information, FDA concluded that the amended PMA did not resolve the safety and efficacy issues raised in FDA's June 26, 2003 letter and by the Advisory Panel. Therefore, FDA issued a second Not Approvable letter on May 21, 2004.

After issuance of the two Not Approvable letters, Cardima submitted appeals to the division, office, and center levels. In addition, FDA and Cardima have met on several occasions to discuss next steps for the Revelation Tx Microcatheter and NavAblator System. As no agreement could be reached between Cardima and FDA, Cardima has requested review of their system by the Medical Devices Dispute Resolution Panel.

## ***Clinical Protocol Summary***

The study was a single arm unblinded trial with the patient as their own control and was completed in three different phases: Phase IIa (Feasibility), Phase IIb (Expanded Feasibility), and Phase III (Pivotal). All patients had a standard ablation procedure using the two catheters in the right atrium.

Procedural success was defined in the protocol as “The procedural effectiveness of the Revelation Tx will be established based on achieving the following outcome: demonstration of at least one of the following conditions at the line(s) of ablation during sinus rhythm; (a) reduction in the amplitude, fragmentation or widening of local electrograms; (b) appearance of split potentials; or (c) increase in pacing threshold.”

The primary effectiveness endpoint was reduction in number of symptomatic episodes during the sixth month of follow-up compared to the baseline frequency while “either maintained on the same anti-arrhythmic drug regimen or a reduced dosage.” For subjects with  $\geq 5$  episodes in the 30 day screening period, the target level reduction was 50% of baseline episodes as compared to sixth month follow-up to be considered a success. For subjects with 3-4 episodes during the baseline period, the target level reduction of 75% was to be considered a success.

## ***Clinical Data Summary (Original and Amendment 6 Submissions)***

The original PMA submission contained data on all 38 subjects in Phase IIb and 78 of the 98 subjects in Phase III. (Phase III was ongoing when the original PMA was submitted.) After receiving the Not Approvable letter, Cardima submitted Amendment 6 which contained the collected acute data on all the Phase III patients and six month data on 83 patients. Amendment 6 also included additional analyses to respond to the FDA’s concerns regarding compliance with TTM transmissions, determination whether reported symptomatic episodes were discrete, investigator adherence to the protocol regarding lesion sets and use of non-investigational catheters, and changes to the patient’s anti-arrhythmic medications.

### ***Acute Effectiveness:***

Adequate data to assess acute procedural effectiveness was not collected during the study. Specifically, atrial electrogram amplitudes pre- and post-ablation for each electrode for each lesion are missing in 100% of the patients. The percent of missing measurements for these patients is 83% for the lateral lesion and 85.8% for the septal lesion. Cardima concludes on page 120 of the PMA submission

“The data reported in Section 7.5.3, pages 72 through 74 [Procedural Success Endpoint], are not sufficient to demonstrate either success or failure for the procedure...”

Without this information it is not possible to correlate acute procedural success with ultimate patient outcome or to determine if any patient had a procedurally successfully ablation.

Effectiveness for the NavAblator ablation catheter was determined by the number of patients that successfully achieved bidirectional conduction block at the cavo-tricuspid isthmus. The catheter produced this endpoint in 48/77 or **62.3%** (50.6%, 73.1%) of the study subjects. The objective performance criterion for this lesion set is **90%** with a lower bound of 80%. The study results fail to demonstrate that the NavAblator was effective in creating bidirectional conduction block at the cavo-tricuspid isthmus.

*Chronic Effectiveness:*

Of the 84 patients with six month data, only 30 had the target level decrease in telephone transmissions without increase or change in antiarrhythmic medications, AV node ablation and pacemaker implantation prior to six months and who had reasonable compliance with event recording. This is a rate of 35.7% (25.6%, 46.9%). However, as the rate of compliance with the TTM recordings is unknown, it is likely that this success rate of 35.7% is optimistic.

*Safety:*

Combining both Phase IIb and Phase III, 131 patients received the ablation procedure. Five patients had major adverse events according to the protocol definition. In addition there were 4 patients that required implantation of permanent pacemaker within one week after the procedure. If these 4 occurrences are considered to be adverse events, the adverse event rate would be 9/131 or 6.9%.

In considering the safety of the system, it is also important to note that there were a total of 27 (20.6%) patients who had a pacemaker implanted during the course of the study, 14 of whom also had an AV node ablation.

*Episode Assessment and Compliance with Event Recording:*

Episodes of symptomatic atrial fibrillation were captured during the baseline and follow-up period using a transtelephonic monitor (TTM). The protocol required the patients to record whenever they had symptoms they believed were atrial fibrillation. Transmissions were evaluated to determine if they were indeed AF. It is important to note that the protocol did not include a method to determine if each transmission was a discrete instance of AF. FDA is concerned that some patients may have transmitted a single AF episode more than once.

During the baseline evaluation period, potential study subjects were aware that a minimum number of episodes were required for enrollment into the study. The percentage of transmissions that were actual AF episodes ranged from 12.9 to 100% per patient.

During the post-ablation period, the protocol required patients to transmit symptomatic episodes as they occurred as well as mandatory weekly transmissions in the sixth month regardless of the presence of symptoms. Therefore, each study subject should have had a minimum of 4 transmissions during the sixth month for the determination of the primary effectiveness endpoint. However, in the original PMA dataset, only 36% of study

subjects complied with this protocol requirement. Of the 83 patients where detailed sixth month post-procedure transmission data was provided, 22 patients or 26.5 % provided no transmissions and an additional 31 patients or 37.3% provided less than the minimum required transmissions.

In Amendment 6, Cardima reanalyzed the transtelephonic transmission data. In this reanalysis, Cardima elected to use “a computer-based algorithm to identify the 30-day period closest to the midpoint of the sixth month after ablation in which episode monitoring was maximal.” The new analysis of the TTM transmissions at six months resulted in an improved calculated compliance rate of 60/84 (71.4%); however, this also resulted in a lower treatment success rate.

## ***Safety and Effectiveness Analysis***

### ***Acute Effectiveness was not Demonstrated***

**Cardima did not collect the data needed to demonstrate the acute procedural success of the Revelation Tx catheter.** Cardima did not collect data on the atrial electrogram amplitude as required by the protocol, as well as other procedural data required in the case report forms (CRFs). These data include numbers of ablation burns completed per lesion line, temperature set point used, actual temperature achieved, power used, etc. Therefore, it is not possible to determine if any study subject had a successful ablation procedure with the Revelation Tx as defined in the investigational protocol. Without these data, it is not possible to characterize how each investigator used the Revelation Tx catheter or supplemental catheters during the procedure. Consequently, FDA is not able to write adequate instructions for use to allow future users of the system to duplicate the results of the study.

Additionally, **due to the lack of recorded procedural data, FDA is not able to determine the true safety of the catheter.** For example, if all the investigators had used the Revelation Tx catheter aggressively to achieve the  $\geq 50\%$  decrease in atrial electrogram amplitude, it is possible that there may have been a higher adverse event rate.

Finally, **the NavAblator catheter was not effective in producing bidirectional conduction block at the cavo-tricuspid isthmus.** The bidirectional conduction block rate of 62.3% as achieved with the NavAblator is significantly less than the objective performance criteria of 90% that is used routinely by the FDA to evaluate catheters used to create bidirectional conduction block. These results do not support approval of the NavAblator catheter for creation of the isthmus lesion.

### ***Chronic Effectiveness was not Demonstrated***

**FDA cannot determine if any measured chronic clinical success or failure was due to patients being ablated with the system.** This is because FDA cannot determine if any patient had a successful procedural use of the ablation system.

**However, if FDA accepts that the investigators used the catheter in an effective fashion during the procedure, the number of patients who reached the required decrease in self-reported episodes at the sixth month would only be 35.7% (25.6%, 46.9%). This is not a clinically meaningful benefit.**

Moreover, the number of patients reaching this endpoint with only the use of the Cardima system is likely to be smaller than 35.7% as the patients who required treatment with a non-protocol catheter were not identified. Additionally, FDA does not agree with Cardima's classification of certain subjects as study successes. For example, some patients that were non-compliant with TTM transmission during the sixth month follow-up (as determined by not transmitting the minimum mandatory number of transmissions) were counted as successes. Further, contrary to the protocol, several patients who received new and increased medications, AV node ablation, or pacemaker implants were reported as successes. Therefore FDA believes that Cardima may have significantly over-estimated the chronic success of the device system.

**Over-reporting at baseline and under-reporting at follow-up may have occurred.**

The chronic effectiveness endpoint of the trial was subjective. Patients had to recognize that they were having symptoms possibly due to AF and record the rhythm with the event recorder at that time. FDA is concerned that there may have been a significant bias toward recording symptomatic episodes at baseline compared to the sixth month. Because patients knew that a minimum number of events was required for entry into the study, they had a strong incentive to record events during the baseline period. This incentive to accurately capture events was not present during the follow-up period. The investigational procedure had been completed and there would be no change in patient treatment regimen as a result of the number of transmission.

*Safety was not Demonstrated*

**The safety profile of the device system cannot be characterized because the acute use of the device remains unclear due to the lack of recorded acute procedural data.**

Although no major safety issues were apparent from the data submitted, FDA cannot be sure that the device is in fact safe for the proposed intended use because it is unclear to what extent the device was used during the study ablation procedures. If all investigators had used the catheter aggressively to try to produce a complete line of block at both the lateral and septal wall of the right atrium, a different number of adverse events may possibly have occurred.

**The ablation procedure to be completed with the Cardima system is an invasive procedure similar to other catheter procedures and has inherent risks.** All invasive procedures carry certain risks, such as those associated with anesthesia, femoral access, ablation, etc. Therefore, the rate of risks associated with this procedure and the Cardima system is not negligible.

**The 20.6% rate of pacemaker implants is higher than expected.** In assessing the overall safety of the system, it is important to consider the number of patients who end up needing pacemaker implants. Given the relatively healthy condition of patients upon entry into the study, FDA is concerned that a rate of 20.9% for pacemaker implants is excessively high. For reference, the literature reported rate of pacemaker implantation in similar patient populations ranges from 4% to 8.6% (please refer to clinical review memo for details).

## ***Conclusions***

Approval of a PMA occurs when FDA determines a sponsor has provided sufficient valid scientific evidence to demonstrate a reasonable assurance of safety and effectiveness for the proposed intended use.

FDA cannot adequately characterize the safety and effectiveness of the device system. Therefore, FDA is unable to recommend approval of the Revelation Tx Microcatheter and NavAblator System.