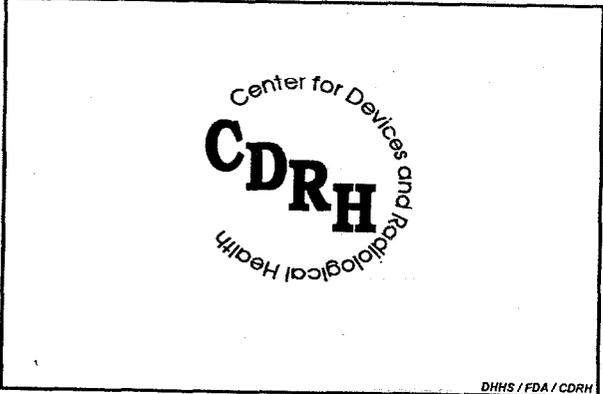


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**Medtronic Model 7250
Jewel® AF Implantable
Cardioverter Defibrillator
System**

PMA Application P980050/S1
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PDLB / DCRD / ODE / FDA
December 5, 2000 Gaithersburg, MD

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FDA Review Team

Lead Reviewer Doris Terry
Model 6937A Lead Lynette Gabriel
Clinical Data Stuart Portnoy
Statistical Data George Koustenis
Patient Labeling Walter Scott
Bioresearch Monitoring Kevin Hopson

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Function of the Device

- Model 7250 Jewel® AF detects and treats episodes of atrial and ventricular tachyarrhythmias and bradycardia by delivering defibrillation, cardioversion, ATP or bradycardia pacing.
- Atrial arrhythmias are detected by the Model 7250 as either AF or AT by monitoring the cycle lengths and regularity of the atrial intervals.

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System Components

- Pulse generator Model 7250
- Model 9465 Patient Assistant
- Model 6937A CS/SVC Lead
- Other commercially available leads and accessories

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Indications for Use Model 7250 Jewel® AF Only

- provide pacing, cardioversion and defibrillation for treatment of patients with:
 - symptomatic, drug-refractory atrial tachyarrhythmias and/or
 - ventricular tachyarrhythmias.

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Study Design

- Multi-center IDE study
- Prospective study for safety and effectiveness
- Randomized crossover study for evaluating prevention therapies
- Primary objectives
- Secondary objectives

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Patient Population

- 146 patients /144 implants
- Mean follow-up - 12.7 +/- 6.1 months
- Primary Indication - AT/AF only 97.0%
- NYHA Class I (53.4%) Class II (34.2%)
- Mean ejection fraction - 51.1%

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Data Analysis

- Time to first system-related complication
 - Cox Regression Model ≤ 3
- Results compared to the Model 7219D
- Episode treatment effectiveness
 - Generalized Estimating Equation (GEE)

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Adverse Events

Type	Definition
Implant	Prior to skin closure
System-related complications	Post implant with invasive intervention
System-related observations	Post implant without invasive intervention
Non system-related	Not device-related

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Summary of Adverse Events

Type	Number of Patients	Number of Events
Implant	11	11
System-related complications	23	26
System-related observations	97	221
Non system-related	95	322

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Complication-Free Survival Kaplan-Meier Estimates

Group	Number of Patients	Follow-up Time	K-M Estimates	95% Confidence Intervals
AF only	124	3 months	89.6	(83.4, 93.6)
Control	312	3 months	93.4	(91.1, 95.1)
AF only	108	6 months	86.6	(79.8, 91.3)
Control	173	6 months	91.6	(88.9, 93.8)

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Summary of Mortality Data

Death Category	Number of Patients
Sudden cardiac	0
Non-sudden cardiac	7
Non-cardiac	0
Unknown	1

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Survival Data Kaplan-Meier Estimates

Group	Number of Patients	Follow-up Time	K-M Estimates	95% Confidence Intervals
AF only	137	3 months	98.6	(94.5, 99.6)
Control	362	3 months	98.1	(96.6, 99.0)
AF only	122	6 months	98.6	(94.5, 99.6)
Control	192	6 months	96.4	(93.7, 98.0)

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Episode Treatment Effectiveness Atrial Tachyarrhythmias

- Requirement = lower 95% confidence bound is >75%.
- Atrial Therapies with atrial shock
 - 107 patients - 1200 atrial episodes
 - 91.0% terminated
- Atrial Therapies Effectiveness
 - 85.9% adjusted
 - 81.7% = lower 95% confidence

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Episode Treatment Effectiveness Atrial Tachyarrhythmias

- AT Episodes - ATP
 - 1049/2720 (38.6%, 32.1% adj.)
- AF Episodes - Burst
 - 286/1570 (18.2%, 14.1% adj.)
- AT episodes - Burst
 - 163/1394 (11.7%, 10.6% adj.)
- PPV 98.6% adj. (96.0, 99.5)

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Effect of Prevention Therapies on Frequency of Atrial Tachyarrhythmias

- Randomized cross-over assignment
 - 75 patients completed assignment
 - The median difference in reduction in frequency
 - ON/OFF- 0.0 episodes per 3 months
 - OFF/ON 1.0 episodes per 3 months
 - No statistically significant difference

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Model 9464 Patient Activator

- Model 9464 Patient Activator data used to support Model 9465 Patient Assistant
- 71% patients programmed with self-activated shocks
- Effectiveness - self-activated shocks 89.1% adj (lower 95% bound 84.6%)

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Adverse Events Patient Activator

Type	Number of Patients(n=71)	Number of Events
Device-related events	12	13
Non-device related events	14	14

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Model 6937A SVC/CS Lead

- 114 patients implanted
- Mean Atrial DFT 6.2+/- 4.6J
- Lead parameters stable through 3 months

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Summary of Model 6937A Lead Adverse Events

Type	Number of Patients	Number of Events
Implant	0	0
Lead-related complications	3	3
Lead-related observations	1	1

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Panel Questions

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Safety Results

1. In evaluating device safety, Medtronic's reported 3 and 6-month complication-free survival results were lower when compared to adverse event results from previous ICD studies (See Table 1, Panel Questions).

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Safety Results

1. (continued)

In addition, 4 patients had a stroke during the course of the study. The risk of stroke, possibly as a result of frequent cardioversions, raises an important issue when evaluating safety of atrial shock therapy. Please discuss the clinical significance of the complication-free survival results and the occurrence of stroke in assessing the safety of the Jewel AF for the new indication of treating patients with atrial tachyarrhythmias.

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Safety Results

2. In their investigational plan, Medtronic prospectively specified the Model 7219D as the safety control. It appears from the demographic co-morbidity data that the Model 7219D population was sicker than the Jewel AF only population. To address this, Medtronic performed a risk factor analysis intended to take into account baseline differences in cardiac

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Safety Results

2. (continued)

health. Given the choice of controls, do the clinical results of the Jewel AF only study demonstrate device safety for the intended patient population?

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Effectiveness Results

3. As reported in the clinical study, Medtronic met their specified effectiveness hypothesis for atrial shock. Additional effectiveness results were also reported (See Table 2, Panel Questions).

a. The study also examined the effectiveness of atrial prevention therapies on frequency of atrial tachyarrhythmias using a crossover study. Medtronic reported that the reduction in AT/AF frequency when atrial

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Effectiveness Results

3. a.(continued)

prevention therapies were programmed ON vs OFF was not statistically significantly different from zero. Based on these effectiveness results, please discuss whether you believe the potential benefits of atrial tachyarrhythmia termination and prevention therapies outweigh the risks of implanting the Jewel AF in the intended patient population.

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Model 9464 Patient Activator

4. The clinical experience from the Model 9464 Patient Activator is being used to support approval of the downsized Model 9465 Patient Assistant. Given the experience, do you have comments or concerns regarding the clinical use and labeling of the Model 9465?

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Risk/Benefit Assessment

5. Given the proposed new Indications for Use for the Jewel AF and the likelihood that the patients will be healthier than the ICD patient population, please discuss whether you believe that the potential benefits of implanting the Jewel AF in patients with atrial tachyarrhythmias outweigh the possible risk associated with the implantation and therapies of the device.

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Product Labeling

6. Of the 2 enrolled patients who did not receive the device, one patient had no atrial capture during the implant procedure. Also of the 10 reported device explantations, 6 of the reported reasons suggest that the device

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Product Labeling

6. (continued)
therapy in these patients was either ineffective or poorly tolerated. Medtronic reported that 13 patients had an ablation procedure (an alternative therapy) after being implanted with the Jewel AF.

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Product Labeling

6. (continued)
Please comment on whether you believe the Jewel AF provides adequate AF prevention and/or treatment therapy for this patient population, and whether you believe that the therapies (particularly atrial shock therapy) may be poorly tolerated in some patients.

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Product Labeling

6. (continued) Please provide your clinical impression of these potential intention-to-treat failures and discuss how this clinical information should be presented in the Jewel AF's Instructions for Use labeling.

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Indications for Use

7. The Jewel AF System is intended to provide pacing, cardioversion and defibrillation for treatment of patients with:

- symptomatic, drug-refractory atrial tachyarrhythmias and/or
- life threatening ventricular tachyarrhythmias

Please provide your clinical impression of Medtronic's proposed Indications for Usage and comment on whether they are clinically appropriate for the Jewel AF's indicated population.

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Panel Questions

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Safety Results

1. Please discuss the clinical significance of the complication-free survival results and the occurrence of stroke in assessing the safety of the Jewel AF for the new indication of treating patients with atrial tachyarrhythmias.

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Safety Results

2. Given the choice of controls, do the clinical results of the Jewel AF only study demonstrate device safety for the intended patient population?

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Effectiveness Results

3. Based on the effectiveness results, please discuss whether you believe the potential benefits of atrial tachyarrhythmia termination and prevention therapies outweigh the risks of implanting the Jewel AF in the intended patient population.

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Model 9464 Patient Activator

4. The clinical experience from the Model 9464 Patient Activator is being used to support approval of the downsized Model 9465 Patient Assistant. Given this experience, do you have comments or concerns regarding the clinical use and labeling of the Model 9465?

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Risk/Benefit Assessment

5. Given the proposed new Indications for Use for the Jewel AF and the likelihood that the patients will be healthier than the ICD patient population, please discuss whether you believe that the potential benefits of implanting the Jewel AF in patients with atrial tachyarrhythmias outweigh the possible risk associated with the implantation and therapies of the device.

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Product Labeling

6. a. Please comment on whether you believe the Jewel AF provides adequate AF prevention and/or treatment therapy for this patient population, and whether you believe that the therapies (particularly atrial shock therapy) may be poorly tolerated in some patients.

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Product Labeling

6. b. Please provide your clinical impression of these potential intention-to-treat failures and discuss how this clinical information should be presented in the Jewel AF's Instructions for Use labeling.

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7. The Jewel AF System is intended to provide pacing, cardioversion and defibrillation for treatment of patients with:

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Please provide your clinical impression of Medtronic's proposed Indications for Usage and comment on whether they are clinically appropriate for the Jewel AF's indicated population.

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