



Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Mr. Todd A. Fonseca, RAC
Manager, PGP
Medtronic, Inc.
7000 Central Avenue, N.E., MS T275
Minneapolis, MN 55432

JAN 30 1998

Re: P970012
Medtronic.Kappa 400 Series Pacemakers
Filed: February 7, 1997
Amended: February 24, April 21, June 16, August 26, October 22, November 18,
December 1, 2, and 30, 1997, and January 26 and 28, 1998

Dear Mr. Fonseca:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the Medtronic.Kappa 400 Series Pacemakers, which includes; Medtronic.Kappa KDR 401/403 and KSR 401/403 Implantable Pulse Generators with Medtronic.Vision (Model 9952E) Software, and Medtronic Model 9462 Remote Assistant. These devices are indicated for the following:

- Rate adaptive pacing in patients who may benefit from increased pacing rates concurrent with increases in activity and/or minute ventilation.
- Accepted patient conditions warranting chronic cardiac pacing which include:
 - symptomatic paroxysmal or permanent second or third-degree AV block;
 - symptomatic bilateral bundle branch block;
 - symptomatic paroxysmal or transient sinus node dysfunctions with or without associated AV conduction disorders;
 - bradycardia-tachycardia syndrome to prevent symptomatic bradycardia or some forms of symptomatic tachyarrhythmias;
 - vasovagal syndromes or hypersensitive carotid sinus syndromes.
- Medtronic.Kappa 400 Series Pacemakers are also indicated for dual chamber and atrial tracking modes in patients who may benefit from maintenance of AV synchrony. Dual chamber modes are specifically indicated for treatment of conduction disorders that require restoration of both rate and AV synchrony, which include:
 - various degrees of AV block to maintain the atrial contribution to cardiac output;
 - VVI intolerance (e.g., pacemaker syndrome) in the presence of persistent sinus rhythm.

We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval for Cardiac Pacemakers and Programmers" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Expiration dating for this device has been established and approved at 1 year. This is to advise you that the protocol you used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(8).

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

In addition under section 522(a) of the act, manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under section 522(a)(1)(A) the above noted device as requiring postmarket surveillance.

Upon approval and within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you will be required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For

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your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

At that time you should submit five (5) copies to:

Postmarket Studies Document Center
1350 Piccard Drive (HFZ-544)
Rockville, Maryland 20850

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will be considered violations of section 522.

In accordance with the Medical Device Amendments of 1992, failure of a manufacturer to meet its obligations under section 522 is a prohibited act under section 301(q)(1)(C) of the act (21 U.S.C. 331(q)(1)(C)). Further, under section 502(t)(3) of the act (21 U.S.C. 352(t)(3)), a device is misbranded if there is a failure or refusal to comply with any requirement under section 522 of the act. Violations of sections 301 or 502 may lead to regulatory actions including seizure of your product, injunction, prosecution, or civil money penalties or other FDA enforcement actions including (but not limited to) withdrawal of your PMA.

If you have any questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch, at (301) 594-0639.

Under section 519(e) of the act (as amended by the Safe Medical Devices Act in 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of device user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. Under section 519(e), FDA believes that your device is a device that is subject to tracking because it is a permanent implant whose failure would be reasonably likely to have serious adverse consequences.

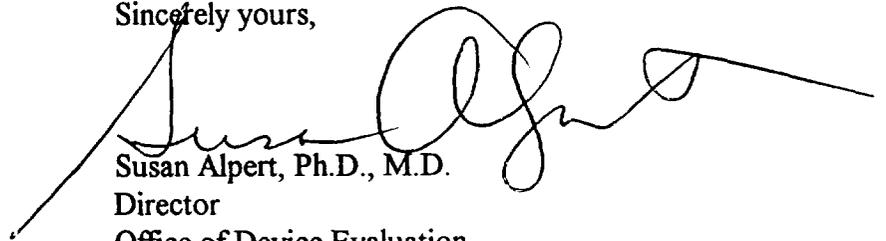
FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that

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FDA believes must be tracked at 21 CFR 821.20(b) and the devices that FDA has designated for tracking at 21 CFR 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705-10709 (March 27, 1991), 57 FR 22973-22975 (May 29, 1992), and 58 FR 43451-43455 (August 16, 1993)).

If you have any questions concerning this approval order, please contact Marian Kroen at (301) 443-8517.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Susan Alpert', with a long horizontal flourish extending to the right.

Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

SUMMARY OF SAFETY AND EFFECTIVENESS

General Information

| | |
|---|---|
| Device Generic Name: | Implantable Pacemaker Pulse Generator |
| Device Trade Name: | <ul style="list-style-type: none">• Medtronic.Kappa Models KDR401, KDR403 Pulse Generators• Medtronic.Kappa Models KSR401, KSR403 Pulse Generators• Medtronic.Vision (Model 9952E) Software• Medtronic Model 9462 Remote Assistant |
| Applicant's Name and Address | Medtronic, Inc. 7000 Central Avenue N.E. Minneapolis, MN 55432 |
| Pre-Market Approval (PMA) Application Number: | P970012 |
| Date of Notice of Approval to the Applicant: | January 30, 1998 |

Indications for use

Medtronic.Kappa 400 pacemakers are indicated for the following:

- Rate adaptive pacing in patients who may benefit from increased pacing rates concurrent with increases in activity and/or minute ventilation.
- Accepted patient conditions warranting chronic cardiac pacing which include:
 - Symptomatic paroxysmal or permanent second or third-degree AV block.
 - Symptomatic bilateral bundle branch block.
 - Symptomatic paroxysmal or transient sinus node dysfunctions with or without associated AV conduction disorders.
 - Bradycardia-tachycardia syndrome to prevent symptomatic bradycardia or some forms of symptomatic tachyarrhythmias.
 - Vasovagal syndromes or hypersensitive carotid sinus syndromes.

- Medtronic.Kappa 400 Series pacemakers are also indicated for dual chamber and atrial tracking modes in patients who may benefit from maintenance of AV synchrony. Dual chamber modes are specifically indicated for treatment of conduction disorders that require restoration of both rate and AV synchrony, which include:
 - Various degrees of AV block to maintain the atrial contribution to cardiac output.
 - VVI intolerance (e.g., pacemaker syndrome) in the presence of persistent sinus rhythm.

Device Description

The Medtronic.Kappa 400 Series pacemakers are multi-programmable, rate responsive, implantable pacemakers. Rate response is controlled through an activity-based sensor, a minute ventilation-based sensor, or an integrated sensor combination (activity and minute ventilation together).

The following models are available:

- The Models K_{DR}401 and K_{SR}401 accept bipolar and unipolar leads compatible with the IS-1¹ connector standard.
- The Models K_{DR}403 and K_{SR}403 accept low-profile 3.2 mm bipolar leads or bipolar and unipolar leads compatible with the IS-1¹ connector standard.

All models require at least one bipolar lead in either chamber for minute ventilation (MV) based rate responsive pacing (i.e., the integrated sensor or MV sensor-only rate response).

The Medtronic.Kappa 400 Series pulse generators are programmed using the Medtronic. Vision™ Model 9952E software and Medtronic Model 9790 programmer with Model 9891 baseline software.

Minute Ventilation (MV)

Minute ventilation is determined by the measurement of transthoracic impedance. This measurement is conducted by injecting a 1 mA (peak to peak), 30 µsec biphasic current excitation between the ring electrode of a bipolar lead and the pulse generator case. The resulting voltage between the tip and case is measured to derive the transthoracic impedance. The resulting impedance values are integrated over time to estimate MV. The MV value is used to maintain two averages: the short term average (STA) and the long term average (LTA). The difference between the LTA and STA provides the MV value which drives the sensor rate. The short term average is calculated using a 32 second time constant, and the LTA is calculated using an 18 hour time constant.

In the Medtronic.Kappa KDR 400 Series dual-chamber devices, the transthoracic impedance can be measured using either the atrial or ventricular lead. This allows flexibility in selection of lead types (unipolar vs. bipolar) since only one bipolar lead is required, which can be placed in either chamber. The Medtronic.Kappa 400 Series single chamber devices require a bipolar lead in the chamber to be paced in order to provide MV-based (MV or integrated sensor) pacing.

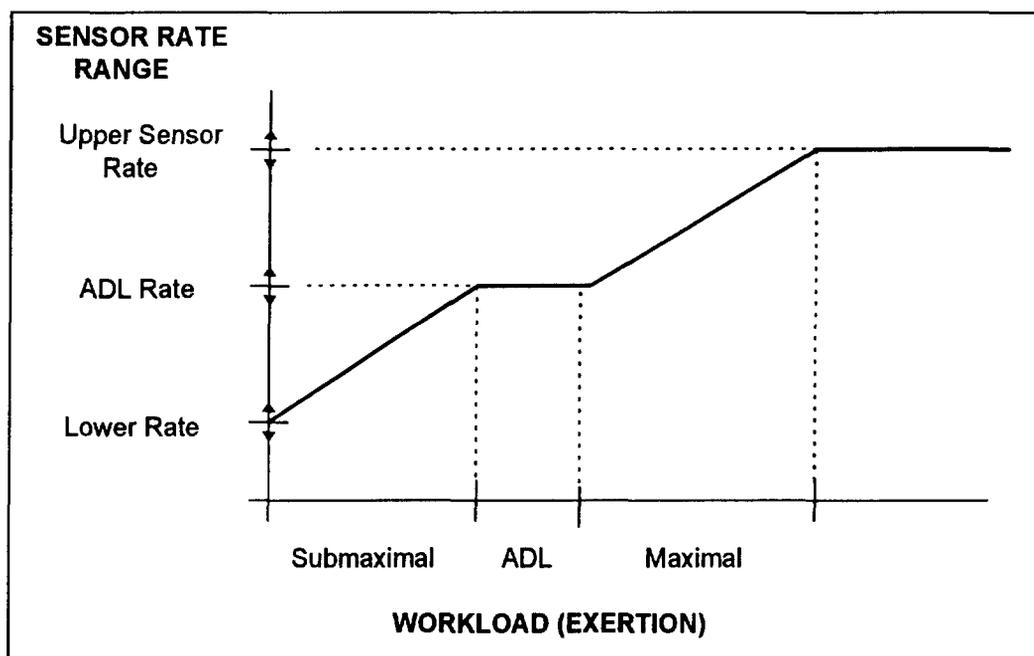
¹ IS-1 refers to an International Connector Standard (see Document No. ISO 5841-3; 1992) whereby pulse generators and leads so designated are assured of meeting the electrical and mechanical parameters specified in the IS-1 International Standard.

Activity Sensor

The activity sensor consists of a piezoelectric crystal mounted on the inside of the pulse generator shield (can). The crystal generates a voltage proportional to the amount of deflection experienced (caused by activity-induced pressure waves within the body). The sensitivity of the activity sensor is determined by the Activity Threshold parameter. The Activity Threshold determines the minimum intensity of detected physical activity to which the pacemaker responds. Five (5) Activity Threshold settings are available, with the Low setting providing the most sensitive response to activity detection.

Rate Transfer Function

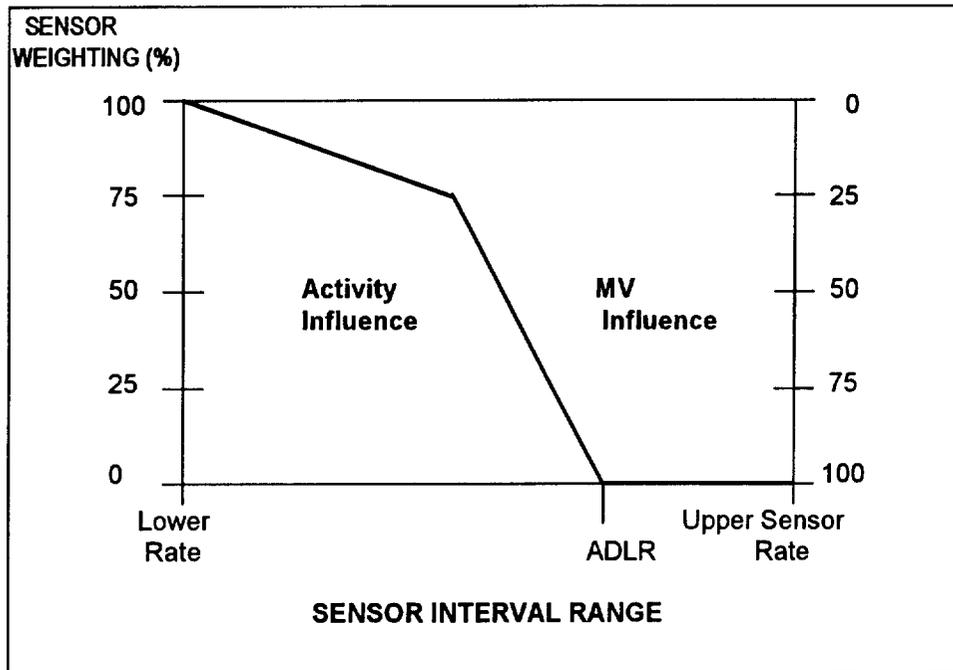
Previous Medtronic rate responsive pulse generators, make use of linear rate response curves from the Lower Rate (LR) to the Upper Sensor Rate (USR). Medtronic.Kappa KDR/KSR400 Series differs from past devices by defining a third rate parameter in addition to the LR and USR: the Activities of Daily Living Rate (ADLR). The ADLR is to be programmed to a value that is appropriate for the patient during typical daily activities (the shipping value is 95ppm). The ADLR breaks the rate transfer function into two independent zones: the lower workload, or submaximal zone exists from LR to ADLR, and the higher workload, or maximal zone spans the rates from ADLR to USR. Each of these zones is independently controllable.



Sensor Integration

In integrated sensor rate response modes, the Medtronic.Kappa KDR/KSR 400 Series pulse generators integrate the input from the activity and MV sensors to produce the sensor target rate. At rates near the programmed lower rate, the activity sensor primarily contributes to the sensor rate. At rates approaching the programmed ADL rate, the contribution from the activity sensor diminishes

and the MV contribution increases. At rates above the ADL rate, only the MV sensor contributes to the sensor rate.



Rate Profile Optimization

With Rate Profile Optimization programmed On, the clinician can prescribe a target rate profile using the ADL Response and Exertion Response parameters to match the patient's lifestyle or activity levels. Programming the ADL Response to a more active setting redefines the target rate profile to spend more time pacing at or above the ADL Rate, thereby increasing rate responsiveness in the submaximal rate range. Similarly, programming the Exertion Response to a more frequent setting redefines the target rate profile to spend more time pacing near the Upper Sensor Rate, thereby increasing rate responsiveness in the maximal rate range.

After programming, Rate Profile Optimization then compares the patient's actual sensor rate histograms to the target profile on a daily basis. The submaximal and maximal rate response slopes are then adjusted as necessary in order to achieve the target rate profile programmed.

Contraindications

Medtronic.Kappa 400 Series pacemakers are contraindicated for the following applications:

- Dual chamber atrial pacing in patients with chronic refractory atrial tachyarrhythmias.
- Asynchronous pacing in the presence (or likelihood) of competitive paced and intrinsic rhythms.
- Co-implant in a patient with an implanted cardioverter-defibrillator (ICD) because it may cause unwanted delivery of ICD therapy.

Warnings

Programming and Pacemaker Operation

- **Minute ventilation sensor** limits detection of respiratory cycles shorter than 1.25 seconds (greater than 48 breaths per minute).
- **Rate responsive modes.** Do not use rate responsive modes in those patients who cannot tolerate pacing rates above the programmed Lower Rate.
- **Single chamber atrial modes.** Do not use single chamber atrial modes in patients with impaired AV nodal conduction because ventricular capture cannot be assured.

Pacemaker Dependent Patients

- **Diagnostic modes.** Never program diagnostic modes (ODO, OVO, and OAO) for pacemaker-dependent patients. For such patients, use the programmer's inhibit function for brief interruption of outputs.
- **Electrogram (EGM)** of the patient's intrinsic activity should be obtained with care since the patient is without pacing support when using the programmer's inhibit function.
- **Polarity override** - Overriding the bipolar verification prompt with bipolar polarity when a unipolar lead is connected results in NO PACING OUTPUT.
- **Loss of capture** during threshold margin test (TMT) at a 25% reduction in pulse width (or at a 50% reduction in pulse width if Extended TMT is On) indicates that the stimulation safety margin is inadequate.
- Ventricular safety pacing should always be used for pacemaker-dependent patients.

Medical Therapy

- **THERAPEUTIC DIATHERMY can cause fibrillation, burning of the myocardium, and irreversible damage to the pulse generator due to induced currents.**
- Magnetic resonance imaging of pacemaker patients has resulted in significant adverse effects.

Precautions

Storage and Resterilization

Medtronic pacemakers are intended for single use only. Do not resterilize and reimplant explanted pacemakers.

The chart below gives recommendations on handling and storing the package. Medtronic has sterilized the pacemaker with ethylene oxide prior to shipment. Resterilizing the pacemaker is

necessary if the seal on the sterile package is broken. Resterilization does not affect the “Use Before” date.

Handling and Storage: Acceptable

Store and transport within Environmental Temperature limits: 0°F (-18°C) to +131°F (55°C).

Note: A full or partial electrical reset condition may occur at temperatures below 0°F (-18°C).

Unacceptable

Do not implant the device if it has been dropped on a hard surface from a height of 12 inches (30 cm) or more.

Resterilization: Acceptable

Resterilize if the sterile package seal is broken. Place the device in an ethylene oxide permeable package and resterilize with ethylene oxide. Allow the device to aerate ethylene oxide residues. Refer to sterilizer instructions for details. Use an acceptable method for determining sterility, such as biological indicators.

Unacceptable

Do not resterilize the device or the torque wrench using:

- an autoclave,
- gamma radiation,
- organic cleaning agents, e.g., alcohol, acetone, etc., or
- ultra-sonic cleaners.

Do not exceed 140°F (60°C) or 17 psi (103 kPa) when sterilizing.

Do not resterilize the device more than two times.

Lead Evaluation and Lead Connection

- **Connector compatibility.** Do not use any lead with this pacemaker without first verifying connector compatibility. Using incompatible leads can damage the connector or result in a leaking or intermittent connection.
- **Pacing and sensing safety margins.** Consider lead maturation when choosing pacing amplitudes, pacing pulse widths, and sensing levels.
- **Hex wrench.** Do not use a hex wrench with a blue handle or right angle. These wrenches have torque capabilities greater than is designed for the lead connector.

Programming and Pacemaker Operation

- **Abdominal implantation.** Do not use integrated or minute ventilation sensor-driven pacing when the pacemaker is implanted abdominally. Accurate measurement of minute ventilation has not been demonstrated for abdominal placements.

- **Epicardial leads.** Do not use epicardial leads for integrated or minute ventilation sensor-driven pacing. Epicardial leads have not been demonstrated to measure minute ventilation.
- **Shipping values.** Do not use shipping values for pacing amplitude and sensitivity without verifying that they provide adequate safety margins for the patient.
- **Constant current devices.** Do not use constant current devices (such as the Model 5880A, 5375, 5348, or 5346 External Pacemaker) to test lead performance. They may damage the pacemaker's constant voltage output circuits.
- **Crosstalk** occurs in dual chamber systems when atrial pacing output pulses are sensed by the ventricular lead. Crosstalk results in self-inhibition and is more likely to occur at high sensor-driven pacing rates, high atrial amplitudes, and wide atrial pulse widths. To prevent self-inhibition caused by crosstalk, program Ventricular Safety Pacing (VSP) On or lengthen the Ventricular Blanking period.
- **Elective Replacement Indicator (ERI).** Once ERI is set, the pacemaker must be replaced within three months.
- **Full electrical reset** is indicated by VVI pacing at a rate of 65 ppm without the elective replacement indicator set.
- **Slow retrograde conduction**, especially with conduction time greater than 400 ms, may induce pacemaker-mediated tachycardia (PMT).
- **PMT intervention.** Even with the feature turned On, PMTs may still require clinical intervention such as pacemaker reprogramming, magnet application, drug therapy, or lead evaluation.

Rate Increases

- **External pressure** on the pacemaker may cause an increase in the pacing rate up to the programmed ADL Rate in integrated sensor modes and the Upper Sensor Rate in activity-only sensor modes. This might occur when the patient is lying on the pacemaker while sleeping, or by pressing the programmer head over the pacemaker.
- **Twiddler's syndrome**, i.e., patient manipulation of the device after implant, may cause the pacing rate to increase temporarily if the pacemaker is programmed to the integrated sensor or activity-only sensor mode.
- **Muscle stimulation**, e.g., due to unipolar pacing, may result in pacing rates up to the ADL Rate in integrated sensor modes and the Upper Sensor Rate in activity-only sensor modes.

Unipolar Sensing

- **Continuous myopotentials** cause reversion to asynchronous operation when sensed in the refractory period. Sensing of myopotentials is more likely when atrial sensitivity settings of 0.5 through 1.0 mV and ventricular sensitivity settings of 1.0 and 1.4 mV are programmed.

Environmental and Medical Therapy Hazards

Patients should be directed to exercise reasonable caution in avoidance of devices which generate a strong electric or magnetic field. If the pacemaker inhibits or reverts to asynchronous operation at the programmed pacing rate or at the magnet rate while in the presence of electromagnetic interference (EMI), moving away from the source or turning it off will allow the pacemaker to return to its normal mode of operation.

Hospital and Medical Environments

- **Electrosurgical cautery** could induce ventricular arrhythmias and/or fibrillation, or may cause asynchronous or inhibited pacemaker operation. If use of electrocautery is necessary, the current path and ground plate should be kept as far away from the pacemaker and leads as possible.
- **External defibrillation** may damage the pacemaker or may result in temporary and/or permanent myocardial damage at the electrode-tissue interface as well as temporary or permanent elevated pacing thresholds. Attempt to minimize current flowing through the pacemaker and lead system by following these precautions when using external defibrillation on a pacemaker patient:
 - Position defibrillation paddles as far from the pacemaker as possible (minimum of 5 inches [13 cm]). Attempt to minimize current flowing through the pacemaker and leads by positioning the defibrillation paddles perpendicular to the implanted pacemaker/lead system.
 - Use the lowest clinically appropriate energy output (watt seconds).
 - Confirm pacemaker function following any defibrillation.
- **Respiration rate monitors**, or other external equipment that applies electrical current across the patient's thorax, may result in pacing rates up to the Upper Sensor Rate in the integrated sensor or minute ventilation-only sensor modes. If external monitoring equipment is used, program the pacemaker to an activity-only sensor mode or non-rate responsive mode prior to turning the equipment on.
- **High radiation sources** such as cobalt 60 or gamma radiation should not be directed at the pacemaker. If a patient requires radiation therapy in the vicinity of the pacemaker, place lead shielding over the device to prevent radiation damage and confirm its function after treatment.

- **Lithotripsy** may permanently damage the pacemaker if the device is at the focal point of the lithotripsy beam. If lithotripsy must be used, program the pacemaker to a single chamber non-rate responsive mode (VVI/AAI or VOO/AOO) prior to treatment; and keep the pacemaker at least 1 to 2 inches (2.5 to 5 cm) away from the focal point of the lithotripsy beam.
- **Magnetic resonance imaging (MRI)**. Pacemaker patients subjected to MRI should be closely monitored and programmed parameters should be verified upon cessation of MRI. MRI of pacemaker patients should be carefully weighed against the potential adverse affects. Clinicians should carefully weigh the decision to use MRI with pacemaker patients. Limited studies of the effects of MRI on pacemakers have shown that:
 - Magnetic and radio frequency (RF) fields produced by MRI may adversely affect the operation of the pacemaker and may inhibit pacing output.
 - Magnetic fields may activate magnet mode operation and cause asynchronous pacing.
 - Reported² effects of MRI on pacing include increased ventricular pacing beyond the rate limit.
- **Mechanical ventilation** may cause pacing rate changes up to the Upper Sensor Rate in the integrated sensor or minute ventilation-only sensor modes. To prevent the pacing rate from changing due to mechanical ventilation, program the pacemaker to an activity-only sensor mode or a non-rate responsive mode.
- **Radio frequency ablation** procedure in a patient with a Medtronic.Kappa 400 Series pacemaker may cause any of the following:
 - Asynchronous pacing above or below the programmed rate.
 - Reversion to an asynchronous operation.
 - Pacemaker electrical reset.
 - Premature triggering of the elective replacement indicator.

RF ablation risks may be minimized by:

1. Programming a non-rate responsive, asynchronous pacing mode prior to the RF ablation procedure.
2. Avoiding direct contact between the ablation catheter and the implanted lead or pacemaker.
3. Positioning the ground plate so that the current pathway does not pass through or near the pacemaker system, i.e., place the ground plate under the patient's buttocks or legs.

² Holmes, Hayes, Gray, et al. The effects of magnetic resonance imaging on implantable pulse generators. PACE. 1986; 9 (3): 360-370.

4. Having a Medtronic programmer available for temporary pacing.
5. Having defibrillation equipment available.

Home and Occupational Environments

- **High voltage power transmission lines** may generate enough EMI to interfere with pacemaker operation if approached too closely.
- **Communication equipment** such as microwave transmitters, linear power amplifiers, or high-power amateur transmitters may generate enough EMI to interfere with pacemaker operation if approached too closely.
- **Commercial electrical equipment** such as arc welders, induction furnaces, or resistance welders may generate enough EMI to interfere with pacemaker operation if approached too closely.
- **Home appliances** which are in good working order and properly grounded do not usually produce enough EMI to interfere with pacemaker operation. There are reports of pacemaker disturbances caused by electric hand tools or electric razors used directly over the pacemaker implant site.
- **Electronic Article Surveillance (EAS)** equipment such as retail theft prevention systems may interact with pacemakers. Patients should be advised to walk directly through and not to remain near an EAS system longer than is necessary.

Cellular Phones

Medtronic.Kappa 400 Series pacemakers have been tested to the frequency ranges used by the cellular phones included in Table 1. Based on this testing, these pacemakers should not be affected by the normal operation of such cellular phones.

These pacemakers contain a filter that allows usage, without interaction, of cellular phones using the transmission technologies listed in Table 1. These transmission technologies represent most of the cellular phones in use worldwide. Patients can contact their local cellular phone service provider to confirm that the provider uses one of these technologies.

Table 1 Cellular Phone Transmission Technologies

| Transmission Technology | Frequency Range |
|----------------------------------|------------------------|
| Analog | |
| FM (Frequency Modulation) | 824 - 849 MHz |
| Digital TDMA^a | |
| North American Standards | |
| TDMA - 11 Hz | 806 - 821 MHz |
| NADC ^b (TDMA - 50 Hz) | 824 - 849 MHz |
| PCS ^c 1900 | 1850 - 1910 MHz |
| International Standards | |
| GSM ^d | 880 - 915 MHz |
| DCS ^e 1800 | 1710 - 1785 MHz |
| Digital CDMA | |
| CDMA - DS ^f | 824 - 894 MHz |

^a Time Division Multiple Access

^b North American Digital Cellular

^c Personal Communication System

^d Global System for Mobile Communications

^e Digital Cellular System

^f Code Division Multiple Access - Direct Sequence

Adverse Events

Clinical study of the Medtronic Kappa 400 Series and DX2 pacemakers (DX2 is an earlier version of the Kappa 400 pacemaker) included 229 devices implanted in 229 patients worldwide (96 Medtronic.Kappa 400 and 133 DX2). Total device exposure was 1590 device months (151 Medtronic.Kappa 400 and 1439 DX2). For Medtronic.Kappa 400, individual patient exposure averaged 1.6 months (ranging from 0 to 3.3 months), and for DX2, exposure averaged 10.8 months (ranging from 0.7 to 15.6 months). Experience with the Medtronic.Kappa 400 device and the DX2 were combined for the safety evaluation.

There were a total of 5 deaths in the studies; all were reviewed and judged to be non-device related. Heart failure was a major factor in three deaths while a cerebrovascular accident was the cause of the fourth. The fifth was caused by end-stage chronic obstructive pulmonary disease and congestive heart failure. Four of these deaths occurred more than 1 month post implant.

Five (5) devices were explanted, 4 due to infection, and 1 due to pulse generator failure.

Observed Adverse Events

Table 2 reports the adverse events on a per patient and a per device-year basis in descending order of frequency. Of these events, 22 were device related (4 Medtronic.Kappa 400 and 18 DX2).

Table 2. Adverse Events Reported

All patients implanted (n = 229 devices in 229 patients, 133 device years)

| Adverse Events Reported | # of Patients (device related) | % of Patients | # of Events (device related) | Events per device-year |
|---|--------------------------------|---------------|------------------------------|------------------------|
| Any adverse events | 77 | 34% | 114 | 85.7% |
| Any Device-related Event | 18 | 7.9% | 22 | 16.5% |
| Paroxysmal Atrial Flutter/Fibrillation | 14 (2) | 6.1% | 14 (2) | 10.5% |
| Palpitations | 10 (1) | 4.4% | 12 (1) | 9.0% |
| Syncope | 8 | 3.5% | 10 | 7.5% |
| Dyspnea/Shortness of Breath | 8 (1) | 3.5% | 9 (1) | 6.8% |
| Chest Pain/Angina Pectoris | 8 | 3.5% | 8 | 6.0% |
| Other | 6 (1) | 2.6% | 6 (1) | 4.5% |
| Deaths (all were non-device related) | 5 | 2.2% | 5 | 3.8% |
| Pocket Infection | 5 (5) | 2.2% | 5 (5) | 3.8% |
| Lead Dislodgment | 5 | 2.2% | 5 | 3.8% |
| Pocket Hematoma | 3 (3) | 1.3% | 3 (3) | 2.3% |
| Persistent Atrial Flutter/Fibrillation | 3 | 1.3% | 4 | 3.0% |
| Inadequate Lead/Pacemaker Connection | 3 (3) | 1.3% | 3 (3) | 2.3% |
| Heart Failure | 3 (1) | 1.3% | 3 (1) | 2.3% |
| Dizziness | 3 | 1.3% | 3 | 2.3% |
| Sustained Ventricular Tachycardia | 2 | 0.9% | 2 | 1.5% |
| Pneumothorax | 2 | 0.9% | 2 | 1.5% |
| Muscle Stimulation/ Phrenic Nerve Diaphragm | 2 | 0.9% | 2 | 1.5% |
| Fatigue | 2 (1) | 0.9% | 2 (1) | 1.5% |
| Ventricular Ectopy | 2 | 0.9% | 2 | 1.5% |
| Elevated Pacing Thresholds | 2 | 0.9% | 2 | 1.5% |
| No Output ³ | 1 (1) | 0.4% | 1 (1) | 0.4% |
| Ventricular Undersensing | 1 | 0.4% | 1 | 0.8% |
| Random Component Failure | 1 (1) | 0.4% | 1 (1) | 0.8% |
| Perforation of Myocardium | 1 | 0.4% | 1 | 0.8% |
| Pacemaker Syndrome | 1 (1) | 0.4% | 1 (1) | 0.8% |
| Oversensing | 1 (1) | 0.4% | 1 (1) | 0.8% |
| Myocardial Infarction | 1 | 0.4% | 1 | 0.8% |
| Junctional Rhythm | 1 | 0.4% | 1 | 0.8% |
| Inappropriate Rate Response | 1 | 0.4% | 1 | 0.8% |
| Hypotension | 1 | 0.4% | 1 | 0.8% |
| Failure to Capture, Loss of Capture | 1 | 0.4% | 1 | 0.8% |
| Exit Block | 1 | 0.4% | 1 | 0.8% |

³ Event occurred in earlier version of product. Design changes were made to eliminate reoccurrence.

Potential Adverse Events

Adverse events (in alphabetical order), including those reported in Table 2, associated with pacing systems include:

- Cardiac perforation
- Cardiac tamponade
- Death
- Erosion through the skin
- Hematoma/seroma
- Infection
- Myopotential sensing
- Nerve and muscle stimulation
- Rejection phenomena (local tissue reaction, fibrotic tissue formation, pulse generator migration)
- Threshold elevation
- Transvenous lead-related thrombosis

Alternative Practices and Procedures

While surgery or drug therapy may be alternatives to cardiac pacing in certain instances, cardiac pacing is often the standard treatment for the indications described above. Other commercially available single chamber or dual chamber pacemakers provide alternatives to the Medtronic.Kappa 400 Series pulse generators.

Marketing History

The Medtronic.Kappa 400 Series pacemakers are currently distributed commercially outside the United States. Specifically, this product is approved for sale in Canada, Japan, Australia, and the European Community. As of January 1998, over 8000 Medtronic.Kappa 400 Series devices have been sold and/or implanted outside the United States. This device has not been withdrawn from the market in any country for any reason related to the safety and effectiveness of the device.

Summary of Studies

Nonclinical Laboratory Studies

Nonclinical testing of the Medtronic.Kappa 400 devices and the Remote Assistant were conducted to ensure that the components and the finished device perform in accordance with their design specifications.

These nonclinical tests show that the Medtronic.Kappa 400 devices and Remote Assistant passed all validation tests, function within specification under normal operating conditions, and function appropriately when subjected to severe mechanical and electrical conditions.

Hazard analysis

Hazard analyses have been performed on all new features and critical components included in the Medtronic.Kappa 400 Series pacing system, including the integrated circuits, firmware, and software. The hazard analyses were incorporated into design and development processes of the pacing system to ensure that critical failures modes or potentially hazard situations have been identified and adequately eliminated or mitigated.

Battery Testing

The Medtronic.Kappa 400 Series pulse generators utilize two different power sources. The dual chamber pulse generators use the Promeon Sigma 303 lithium-iodine. The single chamber pulse generators use the Promeon Sigma 263 lithium-iodine cell.

Both battery types were subjected to accelerated discharge (62 Sigma 303 samples and 96 Sigma 263 samples), application discharge (12 Sigma 303 samples and 24 Sigma 263 samples) and environmental tests (16 Sigma 303 samples and 16 Sigma 263 Samples). Normal and expected behavior of lithium-iodine batteries was observed.

Integrated Circuits

Qualification of the Micro-controller IC used in the Medtronic.Kappa 400 Series pulse generators was not repeated due to its use in the currently approved Medtronic Thera pulse generators.

The minute ventilation controller IC and RAM/ROM Memory IC were qualified using samples of 77 units and 76 units respectively. Electrical stability of the ICs were assessed through accelerated life testing. Each minute ventilation controller IC was stressed at 4.2V and 150°C for 184 hours minimum. Similarly, each RAM/ROM Memory IC was stressed at 4.2V and 125°C for 1000 hours minimum. Results of these tests established appropriate IC performance.

Hybrid

The hybrids used for the Medtronic.Kappa 400 Series dual chamber and single chamber pulse generator configurations are electrically identical. Therefore the qualification testing is applicable to both configurations.

Electrical qualification testing was performed on a sample of 154 electronic modules. Electrical stability of the hybrid module was assessed through accelerated life testing. Each unit was stressed at 3.3V and 125°C for 500 hours minimum. Results from all samples were within specified tolerances. Current drain characterization was also performed and deemed appropriate.

It should also be noted that all components populating the hybrid are tested and individually qualified for use per Medtronic specifications.

Connector Testing

The Medtronic.Kappa 400 Series dual chamber and single chamber pulse generators are available in IS-1 or 3.2mm (IS-1 compatible) unipolar/bipolar connector module configurations.

Compatibility testing was conducted on sixty-six devices (22 Model KDR401, 22 Model KSR401, and 22 KSR403 devices). Testing included a) IS-1 Go-Gage testing, b) IS-1 insertion testing, c)

Medtronic IS-1/3.2 mm lead insertion and extraction testing, and d) connector electrical leakage testing. These connector configurations were found to meet all qualification testing requirements.

Environmental and Mechanical Testing

Environmental and mechanical qualification testing was performed on twenty-two (22) KDR401 dual chamber pulse generators. Six (6) KSR401 single chamber devices were included in the testing for characterizational purposes only and are considered qualified by similarity.

The test devices were subjected to 1) environmental stress tests including: temperature storage - 18°C and 55°C for a minimum of six hours), mechanical vibration (5 Hz to 500 Hz to 5 Hz at 2.5 g), and mechanical shock (600 g, 1 msec/effective free-fall height of 18 inches), and 2) telemetry mapping. Full functionality of each device was verified at the completion of all environmental tests.

Electromagnetic Compatibility (EMC) Testing

Electromagnetic Compatibility (EMC) testing was performed using the twenty-six (26) KDR401 dual chamber pulse generators. Four (4) KSR401 single chamber devices were included in the testing for characterizational purposes only and are considered qualified by similarity.

The test devices were subjected to radiated electric fields, sinusoidal currents, electrosurgical cautery currents, and transthoracic (high level) defibrillation pulses. In addition, characterizational testing was performed subjecting the devices to cellular phones transmission frequencies.

The Medtronic.Kappa 400 Series pulse generators were found to meet performance specifications for exposure to radiated electric fields.

No devices were observed to exhibit rates above or below the specified test tolerances, and the pulse amplitude and duration of all devices were observed to remain within acceptable tolerances when subjected to sinusoidal currents with the exception of one device which exhibited atrial inhibition during 400Hz testing due to a component failure.

Observed effects of electrosurgical cautery currents on Medtronic.Kappa 400 Series devices included; switching to ERI operation, delay of up to 105 seconds for pulse amplitudes to return to nominal values, and atrial inhibition and safety pacing up to 20 seconds after cessation of exposure. This behavior is considered acceptable since none of the test devices were damaged due to exposure and all devices maintained ventricular pacing support during exposure to electrosurgical cautery currents.

The Medtronic.Kappa 400 Series pulse generators were found to meet the performance specifications for devices exposed to in-vitro transthoracic defibrillation currents. No anomalies were observed during testing. One device exhibited a partial POR during exposure to transthoracic defibrillation pulses and was successfully reprogrammed to test parameters. This operation is expected and is addressed in the product manual. All devices were fully functional and survived with no damage following defibrillation exposure.

None of the Medtronic.Kappa 400 Series pulse generators exhibited susceptibility upon exposure to simulated (817/836/900/950 MHz) and actual cellular phone signals with the exception of one device which exhibited atrial inhibition and upper rate ventricular pacing when exposed to an actual 828 Mhz cellular phone signal. Subsequent retesting did not replicate this behavior.

Parameter Stability

Testing was performed on the Medtronic.Kappa 400 Series single and dual chamber pulse generators to determine the stability of the device pacing parameters when exposed to varying environmental conditions. Pacing rate, amplitude, pulse width, and sensitivity were evaluated under varying load impedance, supply (battery) voltage, and temperature conditions. Activity and Minute Ventilation (MV) rate response acceleration and deceleration were evaluated under varying temperature and supply voltage conditions.

The test results demonstrate that the device parameters met specifications and remained stable under varying temperature, pacing load and supply voltage conditions.

Firmware Testing

The firmware for the Medtronic.Kappa 400 Series pulse generators was developed in accordance with the applicable Medtronic development processes. Three levels of testing were performed on the firmware, including unit, integration and verification testing. All firmware tests passed.

Pacing Features Testing

Testing of the Medtronic.Kappa 400 Series pacing features occurred using one or more of the following test platforms: a) firmware testing, b) analog testing, c) software testing, d) system testing, and e) canine testing. The platform used is dependent on the specific parameters being tested.

Testing performed on the enhanced pacing features (including new or modified rate response, lead recognition, threshold margin tests, and automatic and user-selectable diagnostic features) of the Medtronic.Kappa 400 Series pulse generators demonstrated that they performed as intended in various environments, including the firmware, device, system, and canine environments.

Packaging Qualification

Qualification testing was conducted on twenty-two (22) dual chamber device package inner trays (all other package configurations are identical to those used in currently approved products). This testing consisted of a) environmental stress tests including extreme temperature/humidity conditions, extreme vibration, stacking, and drop testing, and b) visual inspection of sterile package seals and package materials and contents. All 22 of the Medtronic.Kappa 400 Series dual chamber inner tray packages tested met the package design test requirements.

Model 9462 Remote Assistant Testing

Qualification of the Medtronic Model 9462 Remote Assistant included verification of adherence to product mechanical, electrical, and software specifications through physical examination and functional testing. Environmental testing was performed to insure that the device operation would not be adversely affected due to expected use and handling conditions. Based on this testing, Medtronic considers the Model 9462 Remote Assistant fully qualified for use with the Medtronic.Kappa 400 Pacing System.

System Testing

System testing of the Medtronic.Kappa 400 Series pacing system evaluated the use of the pulse generators with the programmers, software, patient monitors, Remote Assistant device, and pacing system analyzers to assure their operation is within the limits of their respective specifications. Issues associated with the technical literature and/or software were identified and resolved during testing.

Animal Testing

A canine study was conducted to verify the function and performance of the Medtronic DX2 dual chamber pulse generator in four(4) canines. Since that report, additional follow ups were conducted which showed that the system continued to operate as expected and no new anomalies were noted.

Since the therapy provided by the Medtronic.Kappa 400 is identical to that provided by DX2, the testing conducted on the DX2 platform provides the data to support the safe and effective operation of the Medtronic.Kappa 400 device. However, canine testing was performed on four (4) more canines having Medtronic.Kappa 400 devices to document the continued safety and appropriate operation of the major features provided in the Medtronic.Kappa 400 devices.

All general pulse generator functions of the DX2 and Kappa 400 pulse generators under observation were found to operate according to specification.

Software Testing

The Medtronic.Vision (Model 9952E) Software was developed and tested in accordance with Medtronic's formal procedures for software development and testing. These procedures include development of a Software Requirements Specification, a detailed design specification, a Hazard Analysis, a retest strategy, and a Verification Test Specification. The software was tested per the Verification Test Specification. Errors, anomalies, and inconsistencies were noted in Engineering Report Forms and all corrections were made. Following final retest of the software, a final configuration audit was performed by Software Quality Engineering to ensure that all documents and code were properly controlled and released.

Biocompatibility

The company did not conduct additional biocompatibility testing because the Medtronic.Kappa 400 series devices use identical materials used on currently available Medtronic US commercial products.

Conclusion Concerning Nonclinical Laboratory Tests

The manufacturer conducted a hazard analysis on all new features and critical components and then conducted testing to evaluate these and other device features. All test results were found to be acceptable.

Clinical Studies

Two clinical studies were conducted to support the Medtronic.Kappa 400 device. The first study was conducted using an earlier version of this device referred to as DX2. The second study was

conducted on the Medtronic.Kappa 400 device itself, data from this second study was used primarily to support the rate responsive characteristics of the device.

Clinical data were accrued under a common investigational plan for the Medtronic DX2 device, approved under G950215. The study began on February 5, 1996. As of June 27, 1997, 133 DX2 devices were implanted in 133 patients at 37 investigational sites. The average implant duration was 10.8 months with a maximum implant duration of 15.6 months. The mean age of patients implanted with this device was 65.7 years old, with a standard deviation of 13.8 years.

The Medtronic.Kappa 400 investigational plan was conducted as an extension of the G950215 investigational device exemption. This study began on June 10, 1997. As of October 6, 1997, there were 96 devices implanted in 96 patients at 14 investigational sites. There was a total of 150.8 device months of experience with the Medtronic.Kappa 400 device. The mean age of patients implanted with this device was 67.1 years, with a standard deviation of 12.83 years.

Objectives

The following table lists the primary objectives of the investigational studies as well as those data used to support these objectives.

| Objective | Primary Data Source Used |
|---|--------------------------|
| 1. There should be no serious unanticipated adverse events related to the device, the software, or the Remote Assistant. | DX2 |
| 2. Survival from device related clinical events at 3 months should be greater than or equal to 67% with 95% confidence. | DX2 |
| 3. The percentage of patients in the Integrated Sensor mode (not taken out of the mode due to a mode related event) at 3 months should be greater than or equal to 75% with 95% confidence. | Kappa 400 |
| 4. The optimized Integrated sensor indicated rate during the three minute hallwalk at one month and three months should reach within 10 ppm of the programmed ADL (Activities of Daily Living) rate in 65% of the patients with 95% confidence. | Kappa 400 |
| 5. The optimized Integrated sensor indicated maximum rate during the symptom limited treadmill CAEP test at one month and three months should reach within 20 ppm of the programmed upper rate in 65% of the patients with 95% confidence. | Kappa 400 |
| 6. The percentage of patients that have actual sensor histograms that closely match the target sensor histogram at three months (optimization has stabilized) should be greater than or equal to 75% with 95% confidence. | Kappa 400 |
| 7. The percentage of patients with the Rate Response optimization feature on (not turned off due to a clinical performance issue) at three months should be 67% with 95% confidence. | Kappa 400 |
| 8. The Auto-Initialization should successfully complete in 95% of | DX2 |

| Objective | Primary Data Source Used |
|---|--------------------------|
| patients (in whom there is not a lead related event which prevents initialization) with 95% confidence. | |
| 9. The rate of failure of the lead recognition feature should be less than or equal to 5% (for patients in whom there is not a lead related event which prevents lead recognition) with 95% confidence. | DX2 |
| 10. The patient should be able to successfully trigger the Remote Assistant in 65% of documented attempts with 95% confidence. | DX2 |

Methods

This study was a prospective evaluation of the DX2 and Kappa 400 devices using the results of the TheraDR and Legend Plus clinical studies as Objective Performance Criteria, where applicable. Patient data for this report was collected at Implant, Pre-discharge, One Month, Three Months, and Six Months post implant.

Pacemaker diagnostic information, along with the hallwalk, treadmill and Holter monitor data were the primary methods used to evaluate the pacemakers features. Treadmill test results and associated ECG and programmer strips for each patient were reviewed by the Investigator or Medtronic personnel or both.

Holter monitoring records for each patient were reviewed by the Investigator or Medtronic personnel or by both. Comments made in patient's diaries were also reviewed. Marker boxes were applied with many of the Holter monitors. These boxes supplied the telemetered pacemaker marker signals to a channel of the Holter monitors. In these cases, the full disclosure was printed with both the ECG and marker signal to assist with a more accurate evaluation of the 24 hour monitor.

Patient selection included the general dual chamber pacing population. All implants were required to be pectoral (not abdominal) and patients with an implantable defibrillator were excluded. At least one of the implanted leads implanted (atrial or ventricular) was required to be bipolar and, for optimal functioning of the minute ventilation sensor, patients with breathing rates higher than 48 breaths per minute were excluded.

A common protocol was used to collect patient history, implant and post-operative data from all study patients. Holter monitoring, hallwalks and treadmill exercise tests were performed to confirm proper sensing and pacing as well as to evaluate the rate response function.

Results of the Study

During the investigation of the DX2 devices, it was noted that some devices were processing very little to no minute ventilation counts which prevented some patients from receiving rate response rates beyond their programmed ADL rate when programmed to Integrated Sensor mode. Design changes were incorporated in the Medtronic.Kappa 400 device to eliminate this issue. Clinical studies were then undertaken on the Medtronic.Kappa 400 device to primarily evaluate its rate response performance (objectives 4 and 5).

Objective 1 During the study of the DX2 devices, there were no serious unanticipated

- adverse events related to the device, software, or remote assistant.
- Objective 2** The actual DX2 device related clinical event free survival rate was 88.7%.
- Objective 3** One hundred percent (100%) of Kappa 400 patients programmed to integrated sensor mode remained in integrated sensor mode at 3 months.
- Objective 4** At one month 73.9% of Kappa 400 patients met the submaximal criteria of reaching within 10 ppm of the ADL rate. At three months, 64.5% of patients met this criteria.
- Objective 5** At one month 78.4% of Kappa 400 patients met the maximal criteria of reaching within 20 ppm of programmed upper sensor rate. At three months 76.0% of patients met this criteria.
- Objective 6** At three months, 96.8% of Kappa 400 patients had actual sensor histograms that closely matched their programmed target histograms.
- Objective 7** The survival of rate profile in the Kappa 400 population was 98.8% at three months.
- Objective 8** Auto-Initialization worked in 100% of the DX2 devices which did not have a lead (or connection) problem or a missing pre-discharge visit.
- Objective 9** In the DX2 population, correct lead polarities were achieved in all cases but two. In one situation, a 3.2 mm lead had been connected to an IS-1 device and the device configured the lead unipolar instead of bipolar. In the second scenario, lead polarity configuration was programmed manually due to an inadequate lead to pacemaker connection.
- During the Kappa 400 investigation, a unipolar lead was inadvertently configured bipolar due to measurement interference caused by high energy released by an ablation system.
- For initial market release of the Kappa 400 device, the automatic lead polarity recognition feature has been removed.
- Objective 10** The remote assistant was successfully triggered in 98.6% of the attempts.

As noted above, the 1 and 3 month submaximal as well as the 3 month maximal rate response objectives were not met during the study. Twenty-seven (27) of the 28 patients who failed the submaximal test did so by obtaining heart rates greater than 10 ppm of the programmed ADL during the 3 minute hallwalk test. A review of the long term sensor rate histogram diagnostics indicated that pacing rates achieved during the hallwalk test were more characteristic of these patients exertional exercise activity than the submaximal activity, which the protocol intended to observe. With the 6 patients who failed to meet the maximal exercise objective at 3 months, review of the sensor rate histograms indicated that these patients were capable of achieving pacing rates within 20 ppm of their programmed upper sensor rate during their normal ambulatory activities.

The following represents the clinical data summary as reported in the product labeling:

The Medtronic.Kappa 400 device was evaluated in a multi-center (14 US centers) prospective study of the Integrated Sensor Mode (Activity + Minute Ventilation) exercise rate response and usability.

Methods: Rate response was evaluated using system diagnostic outputs during submaximal exercise (hallwalk, three minute time point) and maximal exercise. Chronotropic assessment

exercise protocol (CAEP) treadmill data were used in the analysis of maximal effort heart rates. Submaximal exercise tests were carried out at 1 month (N=65) and 3 months (N=31) post implant. Usability (continued use of the feature) was assessed as the percent of patients for which the Integrated Sensor Mode and Rate Profile Optimization were in continued use at 3 months. Stability of Rate Profile Optimization was assessed as the percent of patients with a rate histogram (heart rate range) within the target for both activity of daily living (ADL \pm 3%) range and upper sensor rate (USR \pm 1.5%) range at 3 months.

Description of Patients: A total of 96 patients were enrolled and implanted. Median age was 70 yr. (range: 18 to 89 yr.). Patients met the indications for dual chamber pacing: sick sinus syndrome in 37, sinus bradycardia in 36, and normal AV conduction in 25 patients (patients could have more than one indication). All implants were pectoral. At least one of the leads (atrial or ventricular) was bipolar to support the minute ventilation sensor. Mean duration of implant was 1.6 mos. with a range of 0 to 3.3 mos. and a total experience of 151 patient mos.

Table 3. Results of Exercise Testing

Number (and percent) of patients meeting the target criteria

All patients completing exercise testing (n=48), number, % and 95% confidence intervals

| Test (target) ^a | 1 month | | 3 months | |
|--|---------|-------------------------------|----------|-------------------------------|
| | Number | Percent [95% CI] ^b | Number | Percent [95% CI] ^b |
| Submaximal exercise test (within 10 ppm of ADL) | 48/65 | 74% [62%, 84%] | 20/31 | 65% [45%, 81%] |
| CAEP exercise treadmill test (within 20 ppm of USR) | 40/51 | 78% [65%, 89%] | 19/25 | 76% [54%, 91%] |

^a Protocol objectives for the Submaximal (within 10 ppm of ADL) and CAEP (within 20 ppm of USR) exercise tests (lower 95% CI > 65% were met only for the CAEP test at 1 month).

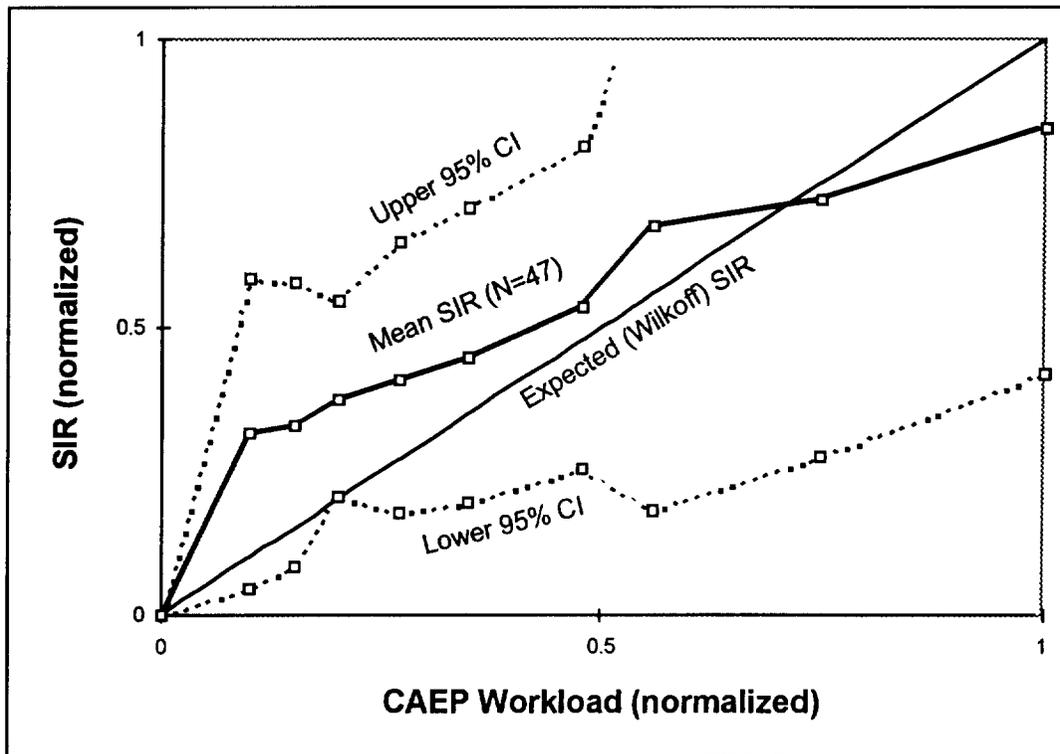
^b Confidence intervals [95% CI] calculated based on the binomial (exact) method.

Assessment conducted at the 3 month follow-up of continued use of the feature showed 85 of 85 patients remained programmed to the Integrated Sensor Mode and 95 of 96 remained programmed to Rate Profile Optimization "On". Stability of Rate Profile Optimization targets were met in 30 of 31 patients at 3 months.

Figure 1 shows the normalized sensor indicated rate (mean and 95% CI for SIR) vs. the normalized workload during the CAEP tests at 1 month.

Figure 1. Sensor Indicated Rate (SIR) vs. Expected Rate during CAEP - 1 Month

All patients completing at least stage 4, N=47, Max SIR at each stage (2 min), Expected (Wilkoff) rate, mean and 95% CI



As indicated in Table 3, the SIR reached at 100% workload during the CAEP was below the programmed upper sensor rate (85% of expected in Figure 1).

Programming of the rate adaptive function of the Medtronic.Kappa 400 includes two independent zones allowing separate selection of slopes for low and high patient activity levels. The CAEP data did indicate a higher SIR at low activity (compared to Wilkoff), but did not establish a clinical benefit for the higher early rate response.

Gender Bias Analysis

There were 80 (60.2%) males and 53 (39.9%) females for a total of 133 DX2 study patients. Furthermore, there were 70 (72.9%) males and 26 (27.1%) females for a total of 96 Medtronic.Kappa 400 patients. Inclusion and exclusion criteria were chosen to avoid gender bias. "The preponderance of male patients reflected both the gender referral pattern for cardiac disease and the severity of the disease in the centers involved. In addition, the comparability of the gender distribution is supported by U.S. epidemiological data obtained nationwide in a 1988 survey of 122,310 individuals where the age-adjusted pacemaker prevalence in males was 1.5 times that in females (60% male: 40% female)"⁴.

⁴ Chorus RM/Opus RM SS&E - P950029 March 3, 1997

Safety and effectiveness data were analyzed by gender and no statistically significant differences were noted.

Conclusions Drawn from the Studies

Both the bench testing and clinical testing demonstrate a reasonable assurance that the Medtronic.Kappa 400 series devices are safe and effective when used in accordance with their labeling.

Panel Recommendation

Pursuant to section 515(f) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory panel for review and recommendation because the information in the PMA substantially duplicated information previously reviewed by this panel.

CDRH Decision

FDA issued an approval order on January 30, 1998.

Approval Specifications

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the Labeling.

Post-approval Requirements and Restrictions: See approval order.

DEVICE DESCRIPTION

The Medtronic.Kappa 400 Series pacemakers are dual chamber, multi-programmable, rate responsive, implantable pacemakers. Rate response is controlled through an activity-based sensor, a minute ventilation-based sensor, or an integrated sensor combination (activity and minute ventilation together)

The following models are available:

- The KDR401 accepts bipolar and unipolar leads compatible with the IS-1 connector standard.
- The KDR403 accepts low-profile 3.2 mm bipolar leads or bipolar and unipolar leads compatible with IS-1 connector standard.

Both models require at least one bipolar lead in either chamber for minute ventilation (MV) based rate responsive pacing (i.e., the integrated sensor or MV sensor-only rate response).

The Medtronic.Kappa 400 Series pulse generators are programmed using the Medtronic. Vision™ Model 9952E software and Medtronic Model 9790 programmer with Model 9891 baseline software.

INDICATIONS AND USAGE

Medtronic.Kappa 400 pacemakers are indicated for the following:

- Rate adaptive pacing in patients who may benefit from increased pacing rates concurrent with increases in activity and/or minute ventilation. (see “Clinical Studies” on page 1-20 for further details).
- Accepted patient conditions warranting chronic cardiac pacing which include:
 - Symptomatic paroxysmal or permanent second or third-degree AV block.
 - Symptomatic bilateral bundle branch block.
 - Symptomatic paroxysmal or transient sinus node dysfunctions with or without associated AV conduction disorders.
 - Bradycardia-tachycardia syndrome to prevent symptomatic bradycardia or some forms of symptomatic tachyarrhythmias.
 - Vasovagal syndromes or hypersensitive carotid sinus syndromes.
- Medtronic.Kappa 400 Series pacemakers are also indicated for dual chamber and atrial tracking modes in patients who may benefit from maintenance of AV synchrony. Dual chamber modes are specifically indicated for treatment of conduction disorders that require restoration of both rate and AV synchrony, which include:
 - Various degrees of AV block to maintain the atrial contribution to cardiac output.
 - VVI intolerance (e.g., pacemaker syndrome) in the presence of persistent sinus rhythm.

CONTRAINDICATIONS

Medtronic.Kappa 400 Series pacemakers are contraindicated for the following applications:

- Dual chamber atrial pacing in patients with chronic refractory atrial tachyarrhythmias.
- Asynchronous pacing in the presence (or likelihood) of competitive paced and intrinsic rhythms.
- Co-implant in a patient with an implanted cardioverter-defibrillator (ICD) because it may cause unwanted delivery of ICD therapy.

WARNINGS

Programming and Pacemaker Operation

- **Minute ventilation sensor** limits detection of respiratory cycles shorter than 1.25 seconds (greater than 48 breaths per minute). Refer to “Activity, Minute Ventilation, and Integrated Sensor” on page 3-5 for further information.
- **Rate responsive modes.** Do not use rate responsive modes in those patients who cannot tolerate pacing rates above the programmed Lower Rate.
- **Single chamber atrial modes.** Do not use single chamber atrial modes in patients with impaired AV nodal conduction because ventricular capture cannot be assured.

Pacemaker Dependent Patients

- **Diagnostic modes.** Never program diagnostic modes (ODO, OVO, and OAO) for pacemaker-dependent patients. For such patients, use the programmer’s inhibit function for brief interruption of outputs.
- **Electrogram (EGM)** of the patient’s intrinsic activity should be obtained with care since the patient is without pacing support when using the programmer’s inhibit function.
- **Polarity override** - Overriding the bipolar verification prompt with bipolar polarity when a unipolar lead is connected results in NO PACING OUTPUT.
- **Loss of capture** during threshold margin test (TMT) at a 25% reduction in pulse width (or at a 50% reduction in pulse width if Extended TMT is On) indicates that the stimulation safety margin is inadequate. Refer to “Threshold Margin Test” on page 4-6 for further information.
- Ventricular safety pacing should always be used for pacemaker-dependent patients. Refer to “Ventricular Safety Pacing” on page 3-17 for further information.

Medical Therapy

- **THERAPEUTIC DIATHERMY can cause fibrillation, burning of the myocardium, and irreversible damage to the pulse generator due to induced currents.**
- Magnetic resonance imaging of pacemaker patients has resulted in significant adverse effects. Refer to "Magnetic Resonance Imaging (MRI)" on page 1-12 for further information.

PRECAUTIONS

Storage and Resterilization

Medtronic pacemakers are intended for single use only. Do not resterilize and reimplant explanted pacemakers.

The chart below gives recommendations on handling and storing the package. Medtronic has sterilized the pacemaker with ethylene oxide prior to shipment. Resterilizing the pacemaker is necessary if the seal on the sterile package is broken. Resterilization does not affect the "Use Before" date.

Handling and Storage: Acceptable

Store and transport within Environmental Temperature limits: 0°F (-18°C) to +131°F (55°C).

Note: A full or partial electrical reset condition may occur at temperatures below 0°F (-18°C).

Unacceptable

Do not implant the device if it has been dropped on a hard surface from a height of 12 inches (30 cm) or more.

Resterilization: Acceptable

Resterilize if the sterile package seal is broken. Place the device in an ethylene oxide permeable package and resterilize with ethylene oxide. Allow the device to aerate ethylene oxide residues. Refer to sterilizer instructions for details. Use an acceptable method for determining sterility, such as biological indicators.

Unacceptable

Do not resterilize the device or the torque wrench using:

- **an autoclave,**
- **gamma radiation,**
- **organic cleaning agents, e.g., alcohol, acetone, etc., or**
- **ultra-sonic cleaners.**

Do not exceed 140°F (60°C) or 17 psi (103 kPa) when sterilizing.

Do not resterilize the device more than two times.

Lead Evaluation and Lead Connection

- **Connector compatibility.** Do not use any lead with this pacemaker without first verifying connector compatibility. Using incompatible leads can damage the connector or result in a leaking or intermittent connection.
- **Pacing and sensing safety margins.** Consider lead maturation when choosing pacing amplitudes, pacing pulse widths, and sensing levels. Refer to “Programming Considerations” on page 2-14.
- **Hex wrench.** Do not use a hex wrench with a blue handle or right angle. These wrenches have torque capabilities greater than is designed for the lead connector (see “Connecting Leads to Pacemaker” on page 2-6 for lead connection instructions).

Programming and Pacemaker Operation

- **Abdominal implantation.** Do not use integrated or minute ventilation sensor-driven pacing when the pacemaker is implanted abdominally. Accurate measurement of minute ventilation has not been demonstrated for abdominal placements.
- **Epicardial leads.** Do not use epicardial leads for integrated or minute ventilation sensor-driven pacing. Epicardial leads have not been demonstrated to measure minute ventilation.
- **Shipping values.** Do not use shipping values for pacing amplitude and sensitivity without verifying that they provide adequate safety margins for the patient.
- **Constant current devices.** Do not use constant current devices (such as the Model 5880A, 5375, 5348, or 5346 External Pacemaker) to test lead performance. They may damage the pacemaker’s constant voltage output circuits.
- **Crosstalk** occurs in dual chamber systems when atrial pacing output pulses are sensed by the ventricular lead. Crosstalk results in self-inhibition and is more likely to occur at high sensor-driven pacing rates, high atrial amplitudes, and wide atrial pulse widths. To prevent self-inhibition caused by crosstalk, program Ventricular Safety Pacing (VSP) On or lengthen the Ventricular Blanking period.
- **Elective Replacement Indicator (ERI).** Once ERI is set, the pacemaker must be replaced within three months. Refer to “Elective Replacement Indicator” on page 4-9 for more information.
- **Full electrical reset** is indicated by VVI pacing at a rate of 65 ppm without the elective replacement indicator set. Refer to “Electrical Reset” on page 4-8 for more information.
- **Slow retrograde conduction**, especially with conduction time greater than 400 ms, may induce pacemaker-mediated tachycardia (PMT).

- **PMT intervention.** Even with the feature turned On, PMTs may still require clinical intervention such as pacemaker reprogramming, magnet application, drug therapy, or lead evaluation. Refer to “PMT Intervention” on page 3-16 for further information.

Rate Increases

- **External pressure** on the pacemaker may cause an increase in the pacing rate up to the programmed ADL Rate in integrated sensor modes and the Upper Sensor Rate in activity-only sensor modes. This might occur when the patient is lying on the pacemaker while sleeping, or by pressing the programmer head over the pacemaker. Refer to “External Pressure on the Pacemaker” on page 2-14 for further information.
- **Twiddler’s syndrome**, i.e., patient manipulation of the device after implant, may cause the pacing rate to increase temporarily if the pacemaker is programmed to the integrated sensor or activity-only sensor mode.
- **Muscle stimulation**, e.g., due to unipolar pacing, may result in pacing rates up to the ADL Rate in integrated sensor modes and the Upper Sensor Rate in activity-only sensor modes.

Unipolar Sensing

- **Continuous myopotentials** cause reversion to asynchronous operation when sensed in the refractory period. Sensing of myopotentials is more likely when atrial sensitivity settings of 0.5 through 1.0 mV and ventricular sensitivity settings of 1.0 and 1.4 mV are programmed.

Environmental and Medical Therapy Hazards

Patients should be directed to exercise reasonable caution in avoidance of devices which generate a strong electric or magnetic field. If the pacemaker inhibits or reverts to asynchronous operation at the programmed pacing rate or at the magnet rate while in the presence of electromagnetic interference (EMI), moving away from the source or turning it off will allow the pacemaker to return to its normal mode of operation.

Hospital and Medical Environments

- **Electrosurgical cautery** could induce ventricular arrhythmias and/or fibrillation, or may cause asynchronous or inhibited pacemaker operation. If use of electrocautery is necessary, the current path and ground plate should be kept as far away from the pacemaker and leads as possible. Refer to “Electrosurgical Cautery” on page 2-19 for more information.
- **External defibrillation** may damage the pacemaker or may result in temporary and/or permanent myocardial damage at the electrode-tissue interface as well as temporary or permanent elevated

pacing thresholds. Attempt to minimize current flowing through the pacemaker and lead system by following these precautions when using external defibrillation on a pacemaker patient:

- Position defibrillation paddles as far from the pacemaker as possible (minimum of 5 inches [13 cm]). Attempt to minimize current flowing through the pacemaker and leads by positioning the defibrillation paddles perpendicular to the implanted pacemaker/lead system.
- Use the lowest clinically appropriate energy output (watt seconds).
- Confirm pacemaker function following any defibrillation.
- **Respiration rate monitors**, or other external equipment that applies electrical current across the patient's thorax, may result in pacing rates up to the Upper Sensor Rate in the integrated sensor or minute ventilation-only sensor modes. If external monitoring equipment is used, program the pacemaker to an activity-only sensor mode or non-rate responsive mode prior to turning the equipment on.
- **High radiation sources** such as cobalt 60 or gamma radiation should not be directed at the pacemaker. If a patient requires radiation therapy in the vicinity of the pacemaker, place lead shielding over the device to prevent radiation damage and confirm its function after treatment.
- **Lithotripsy** may permanently damage the pacemaker if the device is at the focal point of the lithotripsy beam. If lithotripsy must be used, program the pacemaker to a single chamber non-rate responsive mode (VVI/AAI or VOO/AOO) prior to treatment; and keep the pacemaker at least 1 to 2 inches (2.5 to 5 cm) away from the focal point of the lithotripsy beam.
- **Magnetic resonance imaging (MRI)**. Pacemaker patients subjected to MRI should be closely monitored and programmed parameters should be verified upon cessation of MRI. MRI of pacemaker patients should be carefully weighed against the potential adverse affects. Clinicians should carefully weigh the decision to use MRI with pacemaker patients. Limited studies of the effects of MRI on pacemakers have shown that:
 - Magnetic and radio frequency (RF) fields produced by MRI may adversely affect the operation of the pacemaker and may inhibit pacing output.
 - Magnetic fields may activate magnet mode operation and cause asynchronous pacing.
 - Reported¹ effects of MRI on pacing include increased ventricular pacing beyond the rate limit.
- **Mechanical ventilation** may cause pacing rate changes up to the Upper Sensor Rate in the integrated sensor or minute ventilation-only sensor modes. To prevent the pacing rate from

¹Holmes, Hayes, Gray, et al. The effects of magnetic resonance imaging on implantable pulse generators. PACE. 1986; 9 (3): 360-370.

changing due to mechanical ventilation, program the pacemaker to an activity-only sensor mode or a non-rate responsive mode.

- **Radio frequency ablation** procedure in a patient with a Medtronic.Kappa 400 Series pacemaker may cause any of the following:
 - Asynchronous pacing above or below the programmed rate.
 - Reversion to an asynchronous operation.
 - Pacemaker electrical reset.
 - Premature triggering of the elective replacement indicator.

RF ablation risks may be minimized by:

1. Programming a non-rate responsive, asynchronous pacing mode prior to the RF ablation procedure.
2. Avoiding direct contact between the ablation catheter and the implanted lead or pacemaker.
3. Positioning the ground plate so that the current pathway does not pass through or near the pacemaker system, i.e., place the ground plate under the patient's buttocks or legs.
4. Having a Medtronic programmer available for temporary pacing.
5. Having defibrillation equipment available.

Home and Occupational Environments

- **High voltage power transmission lines** may generate enough EMI to interfere with pacemaker operation if approached too closely.
- **Communication equipment** such as microwave transmitters, linear power amplifiers, or high-power amateur transmitters may generate enough EMI to interfere with pacemaker operation if approached too closely.
- **Commercial electrical equipment** such as arc welders, induction furnaces, or resistance welders may generate enough EMI to interfere with pacemaker operation if approached too closely.
- **Home appliances** which are in good working order and properly grounded do not usually produce enough EMI to interfere with pacemaker operation. There are reports of pacemaker disturbances caused by electric hand tools or electric razors used directly over the pacemaker implant site.
- **Electronic Article Surveillance (EAS)** equipment such as retail theft prevention systems may interact with pacemakers. Patients should be advised to walk directly through and not to remain near an EAS system longer than is necessary.

Cellular Phones

Medtronic.Kappa 400 Series pacemakers have been tested to the frequency ranges used by the cellular phones included in Table 1-1. Based on this testing, these pacemakers should not be affected by the normal operation of such cellular phones.

These pacemakers contain a filter that allows usage, without interaction, of cellular phones using the transmission technologies listed in Table 1-1. These transmission technologies represent most of the cellular phones in use worldwide. Patients can contact their local cellular phone service provider to confirm that the provider uses one of these technologies.

Table 1-1. Cellular Phone Transmission Technologies

| Transmission Technology | Frequency Range |
|----------------------------------|-----------------|
| Analog | |
| FM (Frequency Modulation) | 824 - 849 MHz |
| Digital TDMA^a | |
| North American Standards | |
| TDMA - 11 Hz | 806 - 821 MHz |
| NADC ^b (TDMA - 50 Hz) | 824 - 849 MHz |
| PCS ^c 1900 | 1850 - 1910 MHz |
| International Standards | |
| GSM ^d | 880 - 915 MHz |
| DCS ^e 1800 | 1710 - 1785 MHz |
| Digital CDMA | |
| CDMA - DS ^f | 824 - 894 MHz |

^a Time Division Multiple Access

^b North American Digital Cellular

^c Personal Communication System

^d Global System for Mobile Communications

^e Digital Cellular System

^f Code Division Multiple Access - Direct Sequence

ADVERSE EVENTS

Clinical study of the Medtronic Kappa 400 Series and DX2 pacemakers (DX2 is an earlier version of the Kappa 400 pacemaker) included 229 devices implanted in 229 patients worldwide (96 Medtronic.Kappa 400 and 133 DX2). Total device exposure was 1590 device months (151 Medtronic.Kappa 400 and 1439 DX2). For Medtronic.Kappa 400, individual patient exposure averaged 1.6 months (ranging from 0 to 3.3 months) and for DX2, exposure averaged 10.8 months (ranging from 0.7 to 15.6 months).

Experience with the Medtronic.Kappa 400 device and the DX2 were combined for the safety evaluation.

There were a total of 5 deaths in the studies; all were reviewed and judged to be non-device related. Heart failure was a major factor in three deaths, while a cerebrovascular accident was the cause of the fourth. The fifth was caused by end-stage chronic obstructive pulmonary disease and congestive heart failure. Four of these deaths occurred more than 1 month post implant.

Five (5) devices were explanted, 4 due to infection, and 1 due to pulse generator failure.

Observed Adverse Events

Table 1-2 reports the adverse events on a per patient and a per device-year basis in descending order of frequency. Of these events, 22 were device related (4 Medtronic.Kappa 400 and 18 DX2).

Table 1-2. Adverse Events Reported

All patients implanted (n = 229 devices in 229 patients, 133 device years)

| Adverse Events Reported | # of Patients (device related) | % of Patients | # of Events (device related) | Events per device-year |
|---|--------------------------------|---------------|------------------------------|------------------------|
| Any adverse events | 77 | 34% | 114 | 85.7% |
| Any Device-related Event | 18 | 7.9% | 22 | 16.5% |
| Paroxysmal Atrial Flutter/Fibrillation | 14 (2) | 6.1% | 14 (2) | 10.5% |
| Palpitations | 10 (1) | 4.4% | 12 (1) | 9.0% |
| Syncope | 8 | 3.5% | 10 | 7.5% |
| Dyspnea/Shortness of Breath | 8 (1) | 3.5% | 9 (1) | 6.8% |
| Chest Pain/Angina Pectoris | 8 | 3.5% | 8 | 6.0% |
| Other | 6 (1) | 2.6% | 6 (1) | 4.5% |
| Deaths (all were non-device related) | 5 | 2.2% | 5 | 3.8% |
| Pocket Infection | 5 (5) | 2.2% | 5 (5) | 3.8% |
| Lead Dislodgment | 5 | 2.2% | 5 | 3.8% |
| Pocket Hematoma | 3 (3) | 1.3% | 3 (3) | 2.3% |
| Persistent Atrial Flutter/Fibrillation | 3 | 1.3% | 4 | 3.0% |
| Inadequate Lead/Pacemaker Connection | 3 (3) | 1.3% | 3 (3) | 2.3% |
| Heart Failure | 3 (1) | 1.3% | 3 (1) | 2.3% |
| Dizziness | 3 | 1.3% | 3 | 2.3% |
| Sustained Ventricular Tachycardia | 2 | 0.9% | 2 | 1.5% |
| Pneumothorax | 2 | 0.9% | 2 | 1.5% |
| Muscle Stimulation/ Phrenic Nerve Diaphragm | 2 | 0.9% | 2 | 1.5% |
| Fatigue | 2 (1) | 0.9% | 2 (1) | 1.5% |
| Ventricular Ectopy | 2 | 0.9% | 2 | 1.5% |
| Elevated Pacing Thresholds | 2 | 0.9% | 2 | 1.5% |
| No Output ² | 1 (1) | 0.4% | 1 (1) | 0.4% |
| Ventricular Undersensing | 1 | 0.4% | 1 | 0.8% |
| Random Component Failure | 1 (1) | 0.4% | 1 (1) | 0.8% |
| Perforation of Myocardium | 1 | 0.4% | 1 | 0.8% |
| Pacemaker Syndrome | 1 (1) | 0.4% | 1 (1) | 0.8% |
| Oversensing | 1 (1) | 0.4% | 1 (1) | 0.8% |

² Event occurred in earlier version of product. Design changes were made to eliminate reoccurrence.

| Adverse Events Reported | # of Patients (device related) | % of Patients | # of Events (device related) | Events per device-year |
|-------------------------------------|--------------------------------|---------------|------------------------------|------------------------|
| Myocardial Infarction | 1 | 0.4% | 1 | 0.8% |
| Junctional Rhythm | 1 | 0.4% | 1 | 0.8% |
| Inappropriate Rate Response | 1 | 0.4% | 1 | 0.8% |
| Hypotension | 1 | 0.4% | 1 | 0.8% |
| Failure to Capture, Loss of Capture | 1 | 0.4% | 1 | 0.8% |
| Exit Block | 1 | 0.4% | 1 | 0.8% |

Potential Adverse Events

Adverse events (in alphabetical order), including those reported in Table 1-2, associated with pacing systems include:

- Cardiac perforation
- Cardiac tamponade
- Death
- Erosion through the skin
- Hematoma/seroma
- Infection
- Myopotential sensing
- Nerve and muscle stimulation
- Rejection phenomena (local tissue reaction, fibrotic tissue formation, pulse generator migration)
- Threshold elevation
- Transvenous lead-related thrombosis

CLINICAL STUDIES

The Medtronic Kappa 400 device was evaluated in a multi-center (14 US centers) prospective study of the Integrated Sensor Mode (Activity + Minute Ventilation) exercise rate response and usability.

Methods: Rate response was evaluated using system diagnostic outputs during submaximal exercise (hallwalk, three minute time point) and maximal exercise. Chronotropic assessment exercise protocol (CAEP) treadmill data were used in the analysis of maximal effort heart rates. Submaximal exercise tests were carried out at 1 month (N=65) and 3 months (N=31) post implant. Usability (continued use of the feature) was assessed as the percent of patients for which the Integrated Sensor Mode and Rate Profile Optimization were in continued use at 3 months. Stability of Rate Profile Optimization was assessed as the percent of patients with a rate histogram (heart rates range) within the target for both activity of daily living (ADL \pm 3%) range and upper sensor rate (USR \pm 1.5%) range at 3 months.

Description of Patients: A total of 96 patients were enrolled and implanted. Median age was 70 yr. (range: 18 to 89 yr.). Patients met the indications for dual chamber pacing: sick sinus syndrome in 37, sinus bradycardia in 36, and normal AV conduction in 25 patients (patients could have more than one indication). All implants were pectoral. At least one of the leads (atrial or ventricular) was bipolar to

support the minute ventilation sensor. Mean duration of implant was 1.6 mos. with a range of 0 to 3.3 mos. and a total experience of 151 patient mos.

Table 1-3. Results of Exercise Testing

Number (and percent) of patients meeting the target criteria

All patients completing exercise testing (n=48), number, % and 95% confidence intervals

| Test (target) ^a | 1 month | | 3 months | |
|--|---------|-------------------------------|----------|-------------------------------|
| | Number | Percent [95% CI] ^b | Number | Percent [95% CI] ^b |
| Submaximal exercise test (within 10 ppm of ADL) | 48/65 | 74% [62%, 84%] | 20/31 | 65% [45%, 81%] |
| CAEP exercise treadmill test (within 20 ppm of USR) | 40/51 | 78% [65%, 89%] | 19/25 | 76% [54%, 91%] |

^a Protocol objectives for the Submaximal (within 10 ppm of ADL) and CAEP (within 20 ppm of USR) exercise tests (lower 95% CI > 65% were met only for the CAEP test at 1 month).

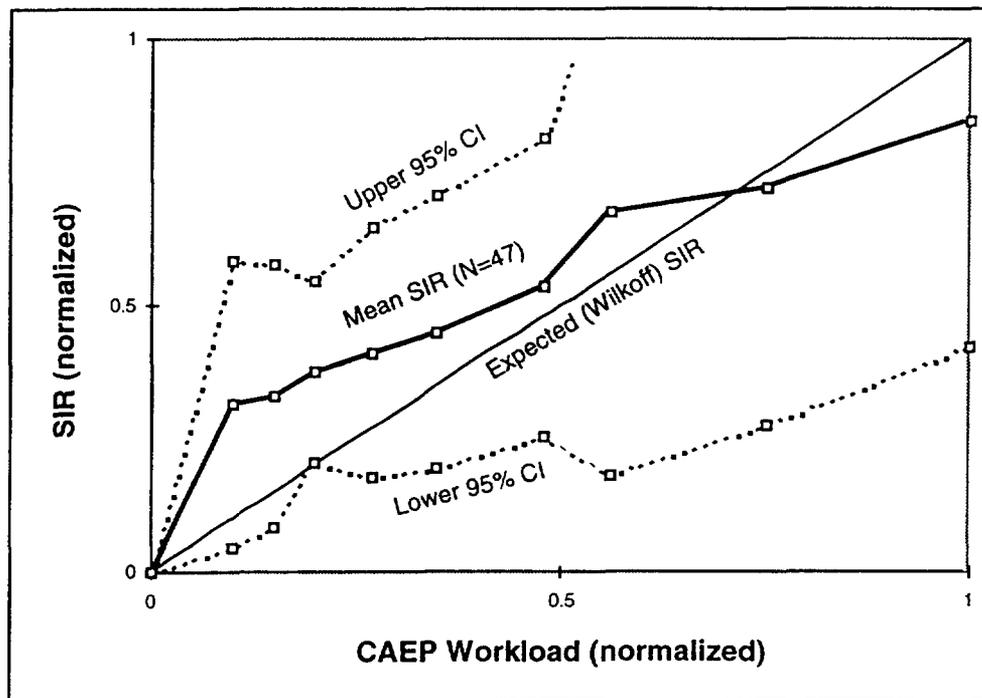
^b Confidence intervals [95% CI] calculated based on the binomial (exact) method.

Assessment conducted at the 3 month follow-up of continued use of the feature showed 85 of 85 patients remained programmed to the Integrated Sensor Mode and 95 of 96 remained programmed to Rate Profile Optimization "On". Stability of Rate Profile Optimization targets were met in 30 of 31 patients at 3 months.

Figure 1-1 shows the normalized sensor indicated rate (mean and 95% CI for SIR) vs. the normalized workload during the CAEP tests at 1 month.

Figure 1-1. Sensor Indicated Rate (SIR) vs. Expected Rate during CAEP - 1 Month

All patients completing at least stage 4, N=47, Max SIR at each stage (2 min), Expected (Wilkoff) rate, mean and 95% CI



As indicated in Table 1-1, the SIR reached at 100% workload during the CAEP was below the programmed upper sensor rate (85% of expected in Figure 1-1).

Programming of the rate adaptive function of the Medtronic.Kappa 400 includes two independent zones allowing separate selection of slopes for low and high patient activity levels. The CAEP data did indicate a higher SIR at low activity (compared to Wilkoff), but did not establish a clinical benefit for the higher early rate response.