

SUMMARY OF SAFETY AND EFFECTIVENESS

I. GENERAL INFORMATION

Generic Name: Implantable Electrical Stimulator for Incontinence

Trade Name: Medtronic® InterStim® System for Urinary Control

Applicant: Medtronic Neurological Division
800 53rd Avenue N.E.
Minneapolis, MN 55421-1200

PMA Supplement Number: P970004/S4

Date of Panel Recommendation: Not Panel Reviewed

Date of Notice of Approval to Applicant: APR 15 1999

The original system (Irel II) was approved on September 29, 1997, for the indication of urinary urge incontinence in patients who have failed or could not tolerate more conservative treatments. The InterStim System received FDA approval (for urge incontinence) under P970004/S2 (approved: July 8, 1998). The Model 3057 test lead received FDA approval under P970004/S3 (approved: November 2, 1998).

The sponsor submitted this PMA supplement to expand the clinical indications. The updated clinical data to support the expanded indications to treat urinary retention and symptoms of urgency/frequency are provided in this summary. The preclinical test results were presented in the original PMA application. For more information on the data, which supported the original indication, the summary of safety and effectiveness data to the original PMA should be referenced. Written requests for copies of the summary of safety and effectiveness data can be obtained from the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Drive, rm. 1-23, Rockville, MD 20857 under Docket #98M-0037. This information can also be accessed via the FDA CDRH Internet home page located at <http://www.fda.gov/cdrh/pmapage.html>.

II. INDICATIONS FOR USE

The Medtronic InterStim System for Urinary Control is indicated for the treatment of urinary urge incontinence, urinary retention, and significant symptoms of urgency/frequency in patients who have failed or could not tolerate more conservative treatments.

III. CONTRAINDICATIONS

Patients are contraindicated for implantation of the InterStim System if:

- ◆ They have not demonstrated an appropriate response to test stimulation, or
- ◆ They are unable to operate the implantable pulse generator (IPG).

Refer to the labeling for a list of warnings and precautions.

IV. DEVICE DESCRIPTION

The Medtronic InterStim System for Urinary Control is a stimulation system that comprises:

Implantable components, including

- ◆ a power source (Model 3023 implantable pulse generator or IPG)
- ◆ an extension (Model 3095) and lead system (Model 3080 or 3886) to deliver the electrical pulses

Control devices to non-invasively adjust the implanted IPG, including

- ◆ a console programmer (Model 7432)
- ◆ a patient programmer (Model 3031) with optional antenna (Model 7440)
- ◆ a control magnet (Model 7452)
- ◆ a memory module (MemMod) software cartridge (Model 3051)

Accessories for test stimulation and implantation, including

- ◆ test stimulation lead (Model 3057), foramen needles, cables, ground pads
- ◆ a test stimulator (Model 3525)

The clinical data was acquired using the Itriel II Sacral Nerve Stimulation System and Model 041830 test stimulation lead. The InterStim IPG System and Model 3057 test stimulation lead are equivalent in electrical performance to the devices used in the clinical trial. Therefore the clinical data is valid and applicable to the use of the InterStim IPG System and Model 3057 test stimulation lead.

1. *Model 3023 Implantable Pulse Generator (IPG)*

The InterStim Model 3023 IPG is the electrical power source for sacral nerve stimulation (SNS) therapy. The InterStim IPG is typically implanted in the right or left lower quadrant. The IPG is capable of delivering electrical stimulation pulses with a variety of parameters, modes, and polarities.

The Model 3023's unique access code allows programming only via the InterStim Model 3051 MemoryMod. The stimulation parameters of the implanted InterStim IPG can be non-invasively set and adjusted to optimize the therapy outcome for each patient. Initial parameters and adjustments are made by radio-frequency (RF) telemetry from the Model 7432 Console Programmer used with the Model 3051

programming software. The Model 7432's programming head is placed over the site of the IPG, and can send and receive information via RF to and from the IPG. Model 3023 IPGs, when properly reviewed by the programmer, are capable of providing telemetry data transmissions such as model and serial number identification, total stimulation time, number of patient activations, and lead impedance.

2. *Model 3095 Extension*

The Model 3095 Extension connects the IPG to either the Model 3886 or Model 3080 SNS lead. The extension is subcutaneously implanted, and connects to the lead at the patient's side and to the IPG, implanted typically in the lower abdomen.

3. *Model 3886 Lead*

The Model 3886 lead is a quadripolar lead, terminating distally in four equally-spaced electrodes. On the proximal end are four electrical contacts spaced to mate with the Model 3095 Extension. The Model 3886 lead kit contains all the accessories required for implantation of the lead for sacral nerve stimulation.

4. *Model 3080 Lead*

The Model 3080 lead is nearly identical to the Model 3886 lead, with the exception that the Model 3080 lead is provided with one silicone anchor attached (glued) to the lead body. This anchor is identical in design and function to the individual anchors supplied in the 3886 kit. As with the 3886, the Model 3080 lead kit contains accessories required to implant the lead for sacral nerve stimulation.

5. *Model 7432 Console Programmer*

The Model 7432 Console Programmer is used in conjunction with the Model 3051 Memory Mod Software Cartridge to non-invasively adjust the stimulation parameters of the IPG. The programmer's programming head is placed over the site of the IPG, and can send and receive information via RF telemetry to and from the IPG.

6. *Model 3051 Memory Module (MemMod) Software Cartridge*

The InterStim Model 3051 Memory Module Software Cartridge is inserted in the Model 7432 Console Programmer and provides the software information for programming or interrogating an InterStim Model 3023 IPG.

7. *Model 3031 Patient Programmer*

The InterStim Model 3031 Patient Programmer is a handheld, battery operated programmer used by patients to non-invasively monitor and control their implanted InterStim IPG. The InterStim Model 3031 allows patients to turn the IPG ON or OFF, to increase/decrease amplitude within physician-set limits, and to check IPG

battery status. An optional antenna can be used with the patient programmer when the IPG is in a location that is difficult for the patient to reach.

8. *Model 7452 Control Magnet*

The control magnet is used to turn an implanted IPG ON or OFF or to switch the IPG amplitude between two programmable settings.

9. *Model 7440 Optional Antenna*

The Medtronic Model 7440 Optional Antenna is an external antenna that is placed on the skin over the implanted Model 3023 IPG. It makes programming with the patient programmer easier, particularly if the location of the IPG is difficult for the patient to reach or if the patient has difficulty holding the patient programmer over the implanted IPG. The Model 7440 antenna takes the place of the antenna that is built into the Model 3031 programmer to allow communication between the programmer and the IPG without having the programmer directly over the implanted IPG site.

10. *Model 3625 Test Stimulator*

The Model 3625 Test Stimulator is an external stimulation source that is used for test stimulation either during a test stimulation procedure or intraoperatively during chronic lead implant to assess lead placement and nerve response. The output capabilities of the test stimulator (amplitude, rate, and pulse width) are the same as that of the Model 3023 IPG. The test stimulator is about the size of a garage door opener, and is operated by a nine volt battery.

11. *Test Stimulation Lead, Foramen Needles, Cables, Ground Pads*

The Model 3057 test stimulation lead consists of a coiled, insulated, stranded stainless steel wire. The distal electrode is a section of the coiled wire stripped of insulation. The proximal end of the lead attaches, via cables, to the Model 3625 Test stimulator, which provides stimulation for temporary sacral nerve stimulation. This lead is percutaneously placed in the sacral foramen through a foramen needle. The lead is removed by gentle traction. The ground pad provides an electrical ground to complete the electrical circuit for unipolar test stimulation.

V. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

InterStim therapy is delivered in two stages: test stimulation to assess effect of sacral nerve stimulation on patients' symptoms, and implantation of the InterStim System (if indicated). The major potential adverse effects associated with these two stages are listed below.

Test Stimulation

- ◆ suspected lead migration (11.8%)
- ◆ technical problem (2.6%)
- ◆ new pain (2.1%)
- ◆ suspected device problem (1.1%)
- ◆ persistent skin irritation (0.7%)
- ◆ adverse change in bowel function (0.4%)
- ◆ infection at test stimulation lead site (0.3%)
- ◆ adverse change in voiding function (0.3%)
- ◆ transient electrical shock (0.1%)

Implantable SNS Devices

- ◆ surgical revision (33%)
- ◆ pain at IPG site (15.3%)
- ◆ new pain (9.0%)
- ◆ suspected lead migration (8.4%)
- ◆ infection (6.1%)
- ◆ transient electric shock (5.5%)
- ◆ pain at lead site (5.4%)
- ◆ adverse change in bowel function (3.0%)
- ◆ technical problem (1.7%)
- ◆ suspected device problem (1.6%)
- ◆ change in menstrual cycle (1.0%)
- ◆ adverse change in voiding function (0.6%)
- ◆ persistent skin irritation (0.5%)
- ◆ suspected nerve injury (0.5%)
- ◆ device rejection (0.5%)

Refer to the safety section of this summary for a more complete discussion of the adverse events associate with this device.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Non-surgical treatment options for urgency/frequency patients include diet modification, pharmacologics, and behavioral techniques such as timed voiding, pelvic muscle exercises, and biofeedback. For patients with retention, treatment options include self or indwelling catheterization. Surgical interventions include augmentation cystoplasty and bladder removal/urinary diversion. Patients who fail conservative therapy and elect not to undergo surgery, default to managing their voiding dysfunction through frequent voiding, fluid restriction, catheterization, and by making significant lifestyle adjustments.

VII. MARKETING HISTORY

The Medtronic InterStim System received the CE Mark and has been commercially available outside of the U.S. for sacral nerve stimulation for the indication of functional urinary disorders such as urge incontinence, urgency/frequency, retention, and pelvic pain since November, 1995. Medtronic SNS leads and accessories have been commercially available outside the U.S. since 1994. The Model 3057 test stimulation lead received the CE mark in July 1998.

The Model 3625 Test Stimulator has been commercially available in the U.S. and outside the U.S. for Spinal Cord Stimulation (SCS) and Peripheral Nerve Stimulation (PNS) for the treatment of chronic pain since 1988.

The InterStim System has been marketed in the U.S. since September 1997 (P970004).

VIII. SUMMARY OF STUDIES

Non-Clinical Studies

Since the time of approval of the original PMA, the changes in devices approved include:

1. Addition of the Model 041826 Ground Pad Bulk Accessory (P970004/S1).
2. Addition as an alternative to the Itriel II IPG, the use of the InterStim IPG and respective control devices (P970004/S2).
3. Addition of the Model 3057 Test Stimulation Lead as alternative to Model 041830 PNE lead (P970004/S3).

The results of the testing completed for these devices, as disclosed in the original PMA and subsequent supplements, demonstrate that the InterStim System performs satisfactorily.

Animal studies were performed and summarized per the original PMA for the Itriel II IPG for sacral nerve stimulation (P970004). These data are valid and applicable to indications of urinary retention and symptoms of urgency/frequency since the stimulation output, functionality, and method of implantation are identical for all patient populations in the clinical study.

Clinical Studies

Sacral nerve stimulation is the application of electrical stimulation to the sacral nerves via a totally implantable system including a lead, a power source (the pulse generator or IPG), and an extension which connects the lead to the IPG. The therapy is based on the observation that electrical stimulation of sacral nerves can modulate neural reflexes that influence bladder, sphincter, and pelvic floor behavior.

1. Study Design/Methods

This study is a prospective, randomized clinical trial, which was undertaken to evaluate the safety and efficacy of the Medtronic InterStim System for the treatment of urinary retention and symptoms of urgency/frequency. The study included an extensive baseline evaluation, temporary test stimulation, and randomization to either a treatment group (immediate implant) or control group (delay to implant). All qualified delay group patients were offered the opportunity for the implant after 6 months follow-up.

The clinical investigation was conducted with 23 investigators worldwide who recruited patients from the general urologic population. Patients qualified for study enrollment based on meeting specific inclusion and exclusion criteria during the baseline assessment.

Based on the baseline data, patients were categorized into one of three patient groups: urge incontinence, retention, or urgency/frequency. Primary voiding diary variables were established for assessing the effectiveness of the therapy for each of the patient groups.

For the retention population, the primary efficacy variable was:

- ◆ Catheter volume per catheterization which refers to the urine volume obtained at the time of catheterization.

For the urgency/frequency population, the primary efficacy variables were:

- ◆ Number of voids/day
- ◆ Volume voided/void
- ◆ Degree of urgency prior to void.

Following the baseline assessment, all subjects who signed an informed consent underwent the test stimulation procedure, which consisted of temporary sacral nerve stimulation to evaluate the effects of the InterStim therapy on the patients' symptoms. Patients were qualified for randomization based upon the results of the test stimulation and were then randomly assigned to the treatment group (implant arm of the study) or control group (delay to implant). After 6 months follow-up in the delay group, patients could cross over to the treatment group if desired and considered medically appropriate.

Follow-up evaluations took place at 1, 3, 6, and 12 months post-implant and every 6 months thereafter through study completion. Control group patients were followed at 3 and 6 months post-randomization, then if appropriate, crossed over to the treatment (implant) arm of the study. Voiding diaries were collected at baseline and all scheduled follow-ups. In addition, urodynamic testing was conducted at baseline and 6 months, and two types of quality of life assessments were administered at baseline and at each follow-up visit after 3 months.

2. *Clinical Study Results*

Effectiveness is evaluated separately for each indication (i.e., patients in retention and patients with symptoms of urgency/frequency). Safety is assessed based on a larger population which included all patients enrolled in the study regardless of their presenting symptoms: urge incontinence, retention, and urgency/frequency (test stimulation, n=581 (914 test stimulation procedures); implant, n=219).

Effectiveness: Retention Study Population

One hundred seventy-seven (177) retentive patients were enrolled in the clinical study. Of these, 68 patients met the criteria for randomization and entered the Treatment and Control arms of the study. To qualify for randomization, patients were required to demonstrate $\geq 50\%$ reduction in catheter volume/catheterization during test stimulation as compared to baseline (no stimulation).

Efficacy results for the retention study population for which evaluable data has been received are as follows:

- ◆ Group sequential data analysis of 6-month efficacy data randomized patients - treatment vs. control (n=51)
- ◆ 6-month efficacy analysis for all implanted retention patients (n = 47 implanted patients)
- ◆ 6-month (stimulation inactivation) Therapy Evaluation Test results – evaluate patients as their own control (stimulation activated versus inactivated) (n = 34 implanted patients)
- ◆ 12-month efficacy analysis (n = 38 implanted patients)
- ◆ 18-month efficacy analysis (n = 24 implanted patients).

In addition to the voiding diary analysis, secondary efficacy outcomes included analysis of urodynamic evaluation data and quality of life assessments (the SF-36 Health Survey and Beck Depression Inventory).

Of the 109 patients who did not qualify for randomization, 33 did not complete voiding diaries for reasons related to technical difficulties or lack of efficacy, and were subsequently exited from the study. The remaining 76 completed test stimulation diaries but did not qualify for randomization because reductions in retention symptoms were $< 50\%$, and therefore did not meet the randomization criteria.

a) Effectiveness: Treatment vs. Control at 6 Months

The group of 68 randomized retention patients was followed to 6 months at the time of database closure. Of these 68 patients, 6 months results were available from 29 implant patients and from 22 control patients, for a total of 51 randomized patients.

The results of statistical analysis for the primary efficacy variable of catheterization volume/catheterization are summarized below:

Catheter Volume/Catheterization

	Volume (ml)	Volume (ml)	Elimination	≥ 50% Reduction	Retention	Exacerbation
Treatment (n=29)	339 ± 176 ml	49 ± 106 ml	69%	14%	14%	3%
Control (n=22)	350 ± 152 ml	319 ± 195 ml	9%	0%	55%	36%

*p<0.0001 for each follow-up comparison

Statistical analysis comparing results collected from the implant and control group indicate that the improvement rankings in the treatment group were significantly different from the improvement rankings in the control (p<0.0001) for catheter volume per catheterization. At 6 months, 69% (n=20) of the 29 implanted patients had completely eliminated catheterization and an additional 14% demonstrated ≥ 50% reduction in catheter volume per catheterization. Successful results were therefore achieved by 83% of treatment group retention patients as compared to 9% of the control group retention patients at 6 months.

b) Effectiveness: All Implanted Retention Patients, 6, 12, and 18 Months Post-Implant

Catheter Volume/Catheterization

	Volume (ml)	Volume (ml)	Elimination	≥ 50% Reduction	Retention	Exacerbation
6 months (n=47)	335 ± 167 ml	81 ± 134 ml	53%	19%	19%	6%
12 months (n=38)	313 ± 162 ml	59 ± 104 ml	61%	16%	11%	8%
18 months (n=24)	305 ± 141 ml*	74 ± 132 ml	58%	13%	13%	4%

*p<0.0001 for each follow-up comparison, respectively

The percentage of implanted patients who had a successful result (elimination or ≥ 50% reduction in catheterization) at each follow-up interval were 72% at 6 months, 77% at 12 months, and 71% at 18 months.

In addition to the reduction in catheter volume per catheterization at 12 months, corresponding changes indicative of improved bladder function included:

- ◆ Decreased number of catheterizations/day (5.9 to 1.7), p<0.0001,
- ◆ Decreased total catheter volume/day (1724 to 271 ml), p<0.0001,
- ◆ Decreased maximum catheter volume (555 to 83 ml), p<0.0001,

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- ◆ Increased number of voids/day (3.3 to 5.9), $p=0.002$,
- ◆ Increased total volume voided/day (514 to 1540 ml), $p<0.0001$,
- ◆ Increased volume voided/void (182 to 263 ml), $p=0.049$,
- ◆ Increased percent felt empty (48% to 84%), $p=0.006$,
- ◆ Improved urine stream force (3.5 fair-poor to 2.4 good-fair), $p=0.0004$,
- ◆ Decreased overflow incontinent events/day (4.0 to 1.6), $p=0.009$,
- ◆ Decreased moderate or heavy overflow incontinent events/day (2.2 to 1.1), $p=0.047$,
- ◆ Decreased absorbent pads/diapers replaced due to overflow incontinence (2.8 to 1.2), $p=0.008$.

Therapy Evaluation Test

To further document the effects of the InterStim therapy on voiding function, 34 implanted retention patients completed the Therapy Evaluation Test where stimulation therapy was temporarily programmed OFF by the investigator at 6 months post-implant. Discontinuation of stimulation therapy resulted in a statistically significant increase in retention toward baseline levels. This indicates that the reduction in retention symptoms observed with stimulation ON is attributable to the InterStim therapy, the effects of the therapy are reversible, and the therapy is not associated with deterioration of bladder function at 6 months post-implant.

Secondary Outcomes: Urodynamic Evaluation and Quality of Life

Three urodynamic assessments were completed at baseline and at 6 months follow-up post-implant for treatment and control group patients: simple uroflowmetry, water cystometry, and detrusor pressure/uroflow study. These tests indicate that the InterStim therapy does not compromise urologic function through 6 months.

The Beck Depression Inventory and the SF-36 Health Survey were used to assess the impact of the device on quality of life. There were no statistically significant differences between the treatment and control groups with respect to the Beck Depression Inventory. Of the eight conceptual areas of the SF-36 Health Survey, only the bodily pain component demonstrated statistically significant improvement ($p=0.03$) in the treatment group versus the control group.

Effectiveness: Urgency/frequency Population

Two hundred twenty (220) patients were enrolled as urgency/frequency patients in the clinical study. Of these, 80 patients met the criteria for randomization and entered the treatment and control arms of the study. Efficacy analysis was performed on patients who completed at least 6 months of follow-up. The data were analyzed using the primary voiding diary variables: number of voids/day, volume voided/void, and degree of urgency prior to void.

At database closure, efficacy results for the urgency/frequency study population was as follows:

- ◆ Group sequential data analysis of 6-month efficacy data randomized patients - treatment vs. control (n=51)
- ◆ 6-month efficacy analysis for all implanted urgency/frequency patients (n = 46)
- ◆ 6-month (stimulation inactivation) Therapy Evaluation Test results – evaluate patients as their own control (stimulation activated versus inactivated) (n = 37 implanted patients)
- ◆ 12-month efficacy analysis (n = 33 implanted patients)
- ◆ 18-month efficacy analysis (n = 24 implanted patients)

In addition to the voiding diary analysis, secondary efficacy outcomes included analysis of urodynamic evaluation data and quality of life assessments (the SF-36 Health Survey and Beck Depression Inventory).

All 220 urgency/frequency patients underwent a test stimulation procedure, and 80 patients were subsequently qualified for randomization into the implant and delay groups of the study. To qualify for randomization, patients were required to demonstrate $\geq 50\%$ reduction in one of the three primary voiding diary variables with stimulation as compared to baseline results (no stimulation).

Of the 140 patients who did not qualify for randomization, 20 did not complete voiding diaries and were exited from the study. The remaining 120 patients completed test stimulation diaries but did not qualify for randomization because reductions in urgency/frequency symptoms were $<50\%$ as compared to baseline status, and therefore did not meet the randomization criteria.

a) Effectiveness: Treatment vs. Control at 6 Months

The group of 80 randomized urgency/frequency patients was followed to 6 months at the time of database closure. Of these 80 patients, 6 months results were available from 25 implant patients and from 26 control patients, for a total of 51 randomized patients. The results of statistical analysis at 6 months for the primary efficacy variables are summarized below:

(1) Number Voids/Day

Analysis of the diary results for the number of voids per day demonstrates significant improvement at 6 months in the treatment group patients when compared to the control group patients.

	Baseline	6 Months		Percentage of Patients with Improvement			
		Number	%	Number	%	Urgency	Frequency
Treatment (n=25)	16.9 ± 9.7	9.3 ± 5.1	40%	16%	32%	8%	4%
Control (n=26)	15.2 ± 6.6	15.7 ± 7.6	4%	0%	32%	64%	0%

* p<0.0001 for each follow-up comparison

Statistical analysis comparing results collected from the implant and control group indicate that the improvement rankings in the treatment group were significantly different from the improvement rankings in the control group ($p < 0.0001$) for the number of voids/day.

(2) Voided Volume/Void

Analysis of the diary results for average volume voided per void demonstrates significant improvement in the volume voided at 6 months in the treatment group patients when compared to the control group patients.

	Baseline	6 Months	Improved	Unchanged	Worsened	Failed
Treatment (n=25)	118 ± 74 ml	226 ± 124 ml	64%	28%	4%	4%
Control (n=26)	124 ± 66 ml	123 ± 75 ml	8%	23%	69%	0%

* $p < 0.0001$ for each follow-up comparison

Statistical analysis comparing results collected from the implant and control group indicate that the improvement rankings in the treatment group were significantly different from the improvement rankings in the control group ($p < 0.0001$) for the volume voided per void at 6 months.

(3) Degree of urgency prior to void

Analysis of the diary results for urgency prior to void demonstrates significant increases in the average volume at 6 months in the treatment group patients when compared to the control group patients.

	Baseline	6 Months	Clinical Success (Degree of Urgency Prior to Void)
Treatment (n=25)	2.2 ± 0.6	1.6 ± 0.9	88%
Control (n=26)	2.4 ± 0.5	2.3 ± 0.5	32%

* $p = 0.01$ for the follow-up comparison

Changes in the degree of urgency were correlated with changes in voided volumes to define the impact of sacral nerve stimulation on urgency/frequency behavior. The goal of sacral nerve stimulation was to enable urgency/frequency patients to sense urinary urgency at a more appropriate volume of urine (as opposed to completely eliminating urgency).

At 6 months, 22 (88%) of the 25 implanted patients documented clinical success which was defined as an increase in voided volume with either the same or

reduced degree of urgency. Of the 25 Control Group patients, 8 (32%) demonstrated clinical success. The ratio of clinical success and clinical failure as measured between the implant and control groups indicates that the implanted patients experienced a significantly-reduced degree of urgency at 6 months (p=0.00011).

b) Effectiveness: All Implanted Urgency/Frequency Patients, 6, 12, and 18 Months Post-Implant

The following compares the percentage of urgency/frequency patients that demonstrated clinical success at 6, 12, and 18 months post-implant.

Diary Variable*	% of Patients (6 Months) n=46	% of Patients (12 Months) n=33	% of Patients (18 Months) n=24
Number of Voids/Day	34%	33%	42%
Volume Voided /Void	54%	61%	54%
Degree of urgency prior to void (0 _{none} , 3 _{severe})	83%	82%	79%

* # Voids/day: $\geq 50\%$ reduction in # voids/day

Volume voided/void: $\geq 50\%$ increase in volume voided/void

Degree of urgency prior to void: Increased voided volumes with the same or reduced degree of urgency.

Patients implanted with the InterStim System also documented the following changes indicative of improved bladder function:

- ◆ increase in maximum voided volume (291 to 452 ml), p<0.0001
- ◆ decrease in pelvic/bladder discomfort ranking from moderate down to mild (2.0 to 0.6), p<0.0001
- ◆ increase in the percent felt empty after voiding (34.6% to 78.7%), p<0.0001
- ◆ improved force of urine stream from fair to good (2.9 down to 1.7), p<0.0001
- ◆ decrease in incontinent episodes/day (10.6 to 4.1), p=0.02

Therapy Evaluation Test

Statistical analysis of voiding diary results collected during the Therapy Evaluation Test demonstrated a return to baseline symptoms of severe urgency/frequency when stimulation therapy was turned OFF at 6 months post-implant. These results indicate the improvement in urgency/frequency symptoms is attributable to the InterStim therapy alone, the effects of the therapy are reversible, and the therapy is not associated with deterioration of bladder function.

Secondary Outcomes: Urodynamic Evaluation and Quality of Life

Three urodynamic assessments were completed at baseline and at 6 months follow-up post-implant for treatment and control group patients: simply uroflowmetry, water

cystometry, and detrusor pressure/flow study. These tests indicate that InterStim therapy does not compromise urologic function through 6 months.

The Beck Depression Inventory and the SF-36 Health Survey were used to assess the impact of the device on quality of life. There were no statistically significant differences between the treatment and control groups with respect to the Beck Depression Inventory. Seven of the eight conceptual areas of the SF-36 Health Survey demonstrated statistically significant improvement in the treatment group versus the control group.

3. Safety

Safety of the InterStim therapy for retention and urgency/frequency is based on pooling of safety data from the entire study population of 581 patients (includes all three indications: urge incontinence, retention, and urgency/frequency) for 914 temporary test stimulation procedures and all 219 implanted patients for chronic stimulation.

Test Stimulation

Summary of Test Stimulation Study Population	
581	Enrolled patients (184 urge incontinent, 177 retention, 220 urgency/frequency)
914	Test stimulation procedures completed on 581 enrolled patients (290 urge incontinent, 260 retention, 364 urgency/frequency)
135	Patients with therapy or device-related events (23.2%)
181	Total therapy + device related adverse events reported during 166 (18.2%) of test stimulations
	92 (50.8%) required no intervention
	88 (48.6%) required non-surgical intervention
	1 (0.6%) required surgical intervention (labeling addresses)
19.8%	Test stimulation event rate from 914 procedures (181 events/914 procedures)
181	Device+therapy related adverse events resolved at database closure (100%)
17	Patient-related events (not related to devices or use of stimulation therapy)
17	Patient-related events resolved at database closure (100%)
65.0%	Patients qualified for randomization with one test stimulation procedure (169/260)
21.5%	Patients who qualified for randomization after 2 nd test stimulation procedure (56/260)
13.5%	Patients who qualified for randomization with 3 or more test stimulation procedures (35/260)

Repeat test stimulation procedures were performed for a variety of reasons including inadequate response to test stimulation, incomplete voiding diaries, and inadequate improvement in symptoms at a particular sacral foramen site.

Events associated with test stimulation are summarized below:

Event	Number	Percentage	Resolved
Suspected Lead Migration	108	11.8%	108
Technical Problem	24	2.6%	24
New Pain	19	2.1%	19
Suspected Device Problem	10	1.1%	10
Persistent Skin Irritation	6	0.7%	6
Adverse Change in Bowel Function	4	0.4%	4
Infection at Test Stimulation Lead Site	3	0.3%	3
Adverse Change in Voiding Function	3	0.3%	3
Other*	3	0.3%	3
Transient Electric Shock	1	0.1%	1
Total			181

* Other adverse events included affected equilibrium, poor rubber pad adhesion, and syncope.

Implant

Relevant statistics derived from the 219-patient implant safety experienced are summarized below:

260	Randomized patients (112 urge incontinent, 68 retention, 80 urgency/frequency)
219	Total implanted patients (100 urge incontinent, 55 retention, 64 urgency/frequency)
113	Implanted patients with Device or Therapy-related events (51.6%)
201	Device-related and therapy-related events
	8.0% (16) required no intervention
	38.3% (77) required non-surgical intervention
	53.7% (108) required hospitalization or surgical intervention (labeling addresses)
29.0%	Probability of 1 adverse event resulting in surgical intervention at 12 months
41.1%	Probability of 1 adverse event resulting in surgical intervention at 24 months
183	Resolved events at database closure (91.0%)
73	Resolved by surgical revision (33.3%)
93	Patient-related events (not related to devices or use of stimulation therapy)
73	Patients had 115 surgeries after initial implant to resolve 108 therapy and device related events
7	Permanent explants: pain at IPG or implant site (3), infection (2), new pain (1), change in bowel function (1)
Unipolar used in 86.2% of cases; Bipolar used in 13.8% of cases	

Overall, 91.0% (183) of the 201 events were fully resolved at the time of database closure. The *surgical revision rate* associated with the InterStim System is 33.3% (73 of 219 implanted patients).

A comprehensive list of post-implant adverse events is summarized below:

Post-implant Adverse Event	Non-Surgical	Surgical	Total	Subjects	Events Received
Pain at IPG Site	46	2	9	35	43
New Pain	23	3	13	7	19
Suspected Lead Migration	19	1	1	17	18
Infection	18	0	4	14	18
Pain at Lead Site	15	4	6	5	12
Transient Electric Shock	14	3	8	3	13
Suspected Device Problem	14	0	3	11	12
Change in Bowel Function	7	0	2	5	7
Technical Problem	4	1	0	3	4
Persistent Skin Irritation	2	0	2	0	2
Change in Menstrual Cycle	2	0	2	0	2
Suspected Nerve Injury	1	0	1	0	1
Change in Voiding Function	1	0	1	0	1
Device Rejection	1	0	0	1	1
Other**	34	2	25	7	30
Total	201	16	77	108	183

* Categories are not mutually exclusive

** Change in sensation of stimulation (9), Grand mal seizure when stimulation inactivated (1), Hematoma or seroma (1), Urinary hesitancy (1), IPG turns ON and OFF (2), Lack of orgasm (1), Lack of efficacy (2), Numbness and tingling (3), Foot/leg movement (6), Strong anal sensation (1), Unable to perceive stimulation (2), Stress urinary incontinence (1), Swollen feeling in abdomen (1), Vaginal cramps (1), Superficial connection (1), Possible skin perforation at IPG (1)

Note: Post-Implant Adverse Events occurred in 113 of the 219 Implants.

IX. CONCLUSIONS DRAWN FROM STUDIES

Sacral nerve stimulation was previously approved for marketing for the indication of urge incontinence (P970004) on September 29, 1997. The results of the randomized study in this PMA Supplement demonstrate the safety and effectiveness of sacral nerve stimulation for the indications of retention and urgency/frequency. Since the device is indicated for patients that have failed or could not tolerate more conservative treatments, the risks associated with implanting the device are outweighed by the potential benefits for these specific patients. Laboratory, animal, and clinical data provide reasonable assurance of the safety and effectiveness of the Medtronic InterStim System when used as indicated in accordance to the directions for use.

X. PANEL RECOMMENDATION

The Gastroenterology/Urology Devices Advisory Panel was not consulted on this submission based on the Agency's own experience and the knowledge derived from the Panel's review of the original application for urge incontinence. In addition, the adverse event profile is comparable to the prior indication based on a comparison of the Summaries of Safety and Effectiveness.

XI. CDRH DECISION

The conditions of Approval that accompanied the September 29, 1997, FDA approval order for the urinary urge incontinence application required the sponsor to conduct a post-approval study to further assess safety and effectiveness. CDRH determined that, based on the modified labeling and the ongoing post approval study from the original application of the InterStim System (which took all three indications into consideration), the application was approvable without an additional post approval study.

FDA determined that the applicant's manufacturing facilities complied with the Good Manufacturing Practices Regulation.

CDRH issued an approval order for the application on APR 15 1999.

XII. APPROVAL SPECIFICATIONS

Directions for Use: See 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.