SUMMARY OF SAFETY AND PROBABLE BENEFIT

I. GENERAL INFORMATION

Device Generic Name: Gastric electrical stimulator

Device Trade Name: Enterra™ Therapy System

Applicant's Name and Address:
Medtronic, Inc.
Neurological Division
800 53rd Avenue NE
Minneapolis, Minnesota 55421

Humanitarian Device Exemption (HDE) Number: H990014

Date of Humanitarian Use Device Designation: September 23, 1999

Date of Panel Recommendation:
The Enterra™ Therapy System was not submitted to the Gastroenterology and Urology Devices Panel for review (refer to Section XI for discussion).

Date of Good Manufacturing Practices Inspection:
Each manufacturing site and the date of the most recent inspection at each is listed below:

Medtronic MedRel - Humacoa, Puerto Rico - November 1998
Medtronic Milaca - Milaca, Minnesota - November 1998
Medtronic B.V. - Kerkrade, The Netherlands - February 1997
Medtronic Neurological - Minneapolis, Minnesota - January 1999

Date of Notice of Approval to Applicant: March 31, 2000

II. INDICATIONS FOR USE

The Enterra™ Therapy System is indicated for the treatment of chronic, intractable (drug refractory) nausea and vomiting secondary to gastroparesis of diabetic or idiopathic etiology.

III. DEVICE DESCRIPTION

The Enterra™ Therapy System is an implanted gastric stimulation system that consists of these components: the implanted pulse generator (Model 7425G Neurostimulator), two unipolar intramuscular stomach leads (Model 4301 Lead), the stimulator programmer (Model 7432 Physician Programmer), and the memory cartridge (Model 7457 MemoryMod Software Cartridge).

The implantable pulse generator, stimulator programmer, and memory cartridge were previously approved for marketing under Premarket Approval Application P840001/S37. The Model 4301 Lead is the only component of the Enterra™ Therapy System that has not been approved or cleared under a prior marketing application, although it is similar in design and features to other previously approved leads for stimulation.

The Model 7425G Neurostimulator is renamed from the Model 7425 Itrel III implanted pulse generator. Similarly, the Model 4301 Lead is renamed from the Model 4300 Lead. The earlier version of each component was used in the WAVESS clinical study described in Section IX of this summary. All components are identical in terms of materials, engineering, and technical specifications, with the only change being the device name.

The intramuscular stomach leads, implanted via laparoscopy, are placed on the greater curvature of the stomach. The implanted pulse generator (IPG) is implanted in a subcutaneous pocket, generally created in the abdominal area, and is then connected to the leads. The IPG provides the energy source that delivers the electrical pulse to the stomach muscle through the stomach leads.

Via the stimulator programmer, the IPG stimulates the stomach muscle at a set of stimulation parameters determined by the physician. The default parameters, used in the clinical studies described in Section IX, are as follows:

amplitude:	5 mA
pulse width:	330 µsec
frequency:	14 Hz
cycle ON time:	0.1 sec
cycle OFF time:	5.0 sec

IV. CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

This device is contraindicated in patients whom the physician determines is not a candidate for surgical procedures and/or anesthesia due to physical or mental conditions.

Warnings and Precautions

The warnings and precautions can be found in the Physician Labeling attached.

V. ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Adverse effects data were collected on patients with drug-refractory gastroparesis of diabetic or idiopathic etiologies in two clinical studies conducted in the United States, Canada, and Europe. The table below summarizes those adverse events reported through September 30, 1999.

Table 1 - Summary of Adverse Events (N = 51)

Event	# Events	# Patients	% of Patients
Device- or Implant-Related			
Lead impedance out of range	7	6	12
Device infections [1]	2	2	4
Device erosion [2]	1	1	2
Device migration [3]	2	1	2
Stomach wall perforation [4]	1	1	2
Underlying Disease-Related			
Upper GI symptoms	81	23	45
Extra abdominal pain	33	14	27
Feeding tube complications	23	14	27
Lower GI symptoms	17	9	20
Dehydration	15	8	16
Bone and joint related	11	8	16
Acute diabetic complications	9	6	12
Dysphagia	5	1	2
Cardiovascular/renal related	2	2	4
Other Therapy Complications			
Feeding tube or IV complications	23	14	27
Miscellaneous			
Urinary tract infections	4	4	8
Stress incontinence	2	2	4
Fever	6	4	8
Other infections: sinus, pink eye, herpes zoster	3	3	6

1. The device system was removed in both patients; a new system was subsequently implanted in one of these patients.

2. The device system was removed in one patient; a new system was subsequently implanted.

3. The device system was twice surgically revised, but not removed, in the same patient.

4. The device system was removed and not re-implanted or replaced with a new system.

Three types of device related adverse events required surgical intervention. These events were device infection (N = 3), stomach wall perforation (N = 1) and migration of the pulse generator (N = 1).

Other Potential Risks
The implantation and/or use of the Enterra™ Therapy System carries other potential risks, which are described below:

1. undesirable change in stimulation, possibly related to cellular changes around the electrodes, shifts in electrode position, loose electrical connections, or lead fractures;

2. hemorrhage, hematoma, and possible GI complications resulting from the surgical procedure to implant the pulse generator and leads;

3. persistent pain at the pulse generator site;

4. seroma at the pulse generator site;

5. allergenic or immune system response to the implanted materials; and

6. loss of therapeutic effect.

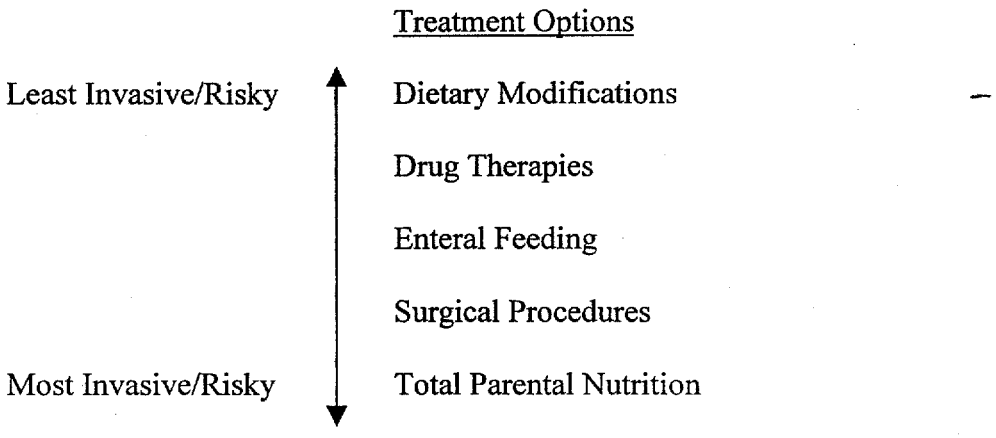
VI. ALTERNATIVE PRACTICES AND TREATMENTS

Gastroparesis is a debilitating disease in which patients suffer from a number of upper GI symptoms including nausea, vomiting, early satiety, bloating, postprandial fullness, epigastric pain and burning, and cardiac pain and burning. Severe symptoms, particularly vomiting and nausea, can significantly impair a patients daily activities and quality of life.

Current medical practice for the treatment and/or management of gastroparesis consists of dietary modifications, drug therapies, enteral feeding, parenteral feeding and surgery. These treatments are successful for some patients, but have significant drawbacks.

The treatment continuum for gastroparesis described by Kendall[2] is illustrated in the figure below. Patients may initially be treated with various dietary modifications including frequent low fat meals. However, if dietary modifications alone are unsuccessful, antiemetic and prokinetic drugs, or combinations thereof, are generally tried. If symptoms cannot be controlled with medication, supplemental nutrition via enteral or parenteral feeding may be required to maintain hydration and nutritional status.

Figure 1 - Treatment Continuum for Chronic Nausea and Vomiting Secondary to Gastroparesis (Kendall, 1993)[2]



Prokinetic drugs are intended to promote gastric motility, i.e., to return abnormally slow gastric emptying states to normal. Antiemetic drugs are intended to alleviate symptoms of nausea and vomiting, but have no effect on motility.[3]

Table 2a - Prokinetic Drugs

Prokinetic Agents Generic Name
Cisapride
Bethanechol
Metoclopramide
Domperidone
Erythromycin

Table 2b - Antiemetic Drugs

Antiemetic Agents Generic Name
Metoclopramide HCl
Granisetron HCl
Ondansetron HCl
Dimenhydrinate
Diphenhydramine HCl
Prochlorperazine
Promethazine HCl
Thietylperazine Malate
Trimethobenzamide HCl

None of the prokinetic drugs are labeled for improved gastric emptying in gastroparesis. Metoclopramide is the only antiemetic or prokinetic drug indicated for use in the treatment of symptoms of diabetic gastroparesis.

Surgical procedures are occasionally employed to manage symptoms of gastroparesis while maintaining the ability for enteral feeding. Surgical procedures, including gastrectomy, pyloroplasty, and gastrojejunostomy, have had limited success in managing symptoms of gastroparesis.[4]

When drug therapies or surgery are ineffective, supplemental enteral feeding via gastric or jejunal feeding tubes or total parenteral nutrition (TPN) may be required to meet the patient's nutritional needs.

For those patients who cannot be adequately treated or managed by current medical practice, the Enterra™ Therapy System has no satisfactory alternative. It is this group of patients for which the Enterra™ Therapy System is indicated.

VII. MARKETING HISTORY

The Medtronic Enterra™ Therapy System is not currently in commercial distribution. However, certain components of the Enterra™ Therapy System, i.e., the Model 7425G implantable pulse generator, Model 7432 programmer, and Model 7457 software, were approved by FDA for spinal cord stimulation and for sacral nerve stimulation to treat urge incontinence and are commercially available.

VIII. SUMMARY OF PRE-CLINICAL TESTING

As noted above, all of the components of the Enterra™ Therapy System, except for the Model 4301 Leads, were previously cleared under a prior marketing application; therefore, additional pre-clinical testing was not required for these components. Thus, the pre-clinical information submitted for the Enterra™ Therapy System consisted of mechanical, electrical, biocompatibility, and shelf life information on the Model 4301 Leads only.

Mechanical Testing

The mechanical characteristics of the Model 4301 Leads were evaluated with the following tests: crimp strength, composite lead strength, lead body flex life, sliding characteristics, connector compatibility, and non-deformation strength. Testing was conducted on finished, sterilized components. For some tests, the Model 4750 Lead was used instead of the Model 4301 Lead. The Model 4750 Lead is similar in design to the 4301 Lead - it is a unipolar intramuscular lead with an adjustable electrode surface that is provided with a neuromuscular stimulation lead connector.

A. Crimp Strength

The purpose of this test was to verify that the crimp junction/joint strength is sufficient to withstand tensile loads experienced during lead implantation. In this test, a load was applied to the sample at a specific joint. The specific joints, devices used, and number of samples is identified in the table below:

Table 3 - Crimp Strength Test

Joint at which Load is Applied	Model Tested	Number of Samples
electrode tip/electrode coil	Model 4750	22
electrode coil/conductor coil	Model 4750	22
conductor coil/connector pin assembly with monofilament	Model 4301	30
conductor coil/connector pin assembly without monofilament	Model 4301	30

For this test, the applied load was set to 0 N and was increased to the minimum specification load requirement of 12 N. The load was maintained for 1 minute. After this time, if no breakage was observed, the load was increased until the point of failure. The acceptance criterion was for the test sample to exceed the minimum specification load requirement prior to failure. The results demonstrated that all samples met this criterion.

B. Composite Lead Strength

The purpose of this test was to verify that the lead strength is sufficient to withstand anticipated forces experienced during lead handling and placement and *in-vivo* forces experienced during device usage. In this test, a tensile load of 10 N was applied between the lead connector pin and polypropylene monofilament for a period of 10 seconds. The test was performed prior to and after a 10-day soak in 0.9% saline solution. The intent of the saline soak was to simulate exposure of the lead to *in vivo* conditions. A total of 30 samples were used. The acceptance criterion for this test was that the device remained mechanically and electrically functional. The results demonstrated that all samples met this criterion.

C. Lead Body Flex Life

The purpose of this test was to verify that the lead remains functional when subjected to flexural forces anticipated during *in vivo* usage. In this test, test samples were mounted in a lead flex fixture and flexed over a bending radius of 6 mm at a rate of 120 cycles/minute. The specific components of the lead tested were: electrode coil, conductor coil, and lead body. A total of 13 samples of the Model 4750 lead were used. The justification for the use of the Model 4750 lead in this test is the fact that this aspect of the Model 4750 and 4301 leads is identical. The acceptance criterion was that no mechanical failures were observed with the lead body. The results demonstrated that all samples met this criterion.

D. Sliding Characteristics

The purpose of this test was to verify that the sliding sheath can be moved easily in order to adjust the area of exposed electrode coil. In this test, the maximum force required to move the sheath was measured. The ease of movement was also recorded. A total of 22 lead subassemblies were used. The acceptance criteria were that the maximum sliding force did not exceed 1N and that the sheath did not catch on the lead body. The results demonstrated that all samples met these criteria.

E. Connector Compatibility

The purpose of this test was to verify that the lead is mechanically compatible with the Medtronic Itrel Implantable Pulse Generator (IPG). In this test, the lead connector was

inserted into the connector module of the IPG, and subsequently removed. The force required to insert and withdraw the lead was measured. A total of 30 Medtronic 4301 leads and 30 IPGs were used. The acceptance criterion was that insertion and withdrawal force is less than 13.3 and 11.1 N, respectively. The results demonstrated that all samples met this criterion.

F. Non-Deformation Strength

The purpose of this test was to verify that the lead can withstand a tensile load experienced during its use. In this test, a tensile load of 2.5 N was applied to the test sample for 10 seconds. The samples were examined for visual, dimensional, and electrical integrity. A total of 30 samples were used in this test. The acceptance criteria were for the test sample to not have any permanent deformation or visual or electrical changes or defects. The results demonstrated that all samples met these criteria.

Electrical Testing

The electrical characteristics of the Model 4301 Leads were evaluated with the following tests: DC resistance, intermittency, and sealing integrity. Testing was conducted on finished, sterilized components.

A. DC Resistance

The purpose of this test was to verify the integrity of the electrical conduction path of the lead. In this test, the resistance between the connector pin and the electrode tip of the lead was measured. A total of 30 samples of the Model 4301 lead were used. The acceptance criterion was that the resistance was within 40-74Ω. The results demonstrated that all samples met this criterion.

B. Intermittency

The purpose of this test was to verify that the lead provides a stable and continual electrical connection between the lead connector pin and electrode tip. In this test, the lead was connected to an oscilloscope. The power supply was set to 10 V. The oscilloscope was used to identify an intermittency greater than 50 μs. A total of 30 samples of the Model 4301 lead were used. The acceptance criterion was that there was no electrical intermittency longer than 50 μs. The results demonstrated that all samples met this criterion.

C. Sealing Integrity

The purpose of this test was to verify that the connection between the Model 4301 lead connector and the Itrel IPG connector module remains electrically isolated from surrounding fluid. In this test, the lead connector was inserted into the connector module of the IPG. The system was then placed in a 0.9% NaCl solution for a period of 10 days. The AC impedance between the connector pin and surrounding fluid was measured. A total of 30 samples of the Medtronic 4301 lead and 15 IPGs were used. The acceptance criterion was that the measured impedance be greater than 50 kΩ. The results demonstrated that all samples met this criterion.

Biocompatibility Testing
The specific materials used in the Model 4301 Leads are polyurethane, silicone, polypropylene, platinum/iridium, and stainless steel. The specific materials, including supplier, have been certified to be identical to those used in previously cleared devices for similar intended use, duration of use, and placement of use. Therefore, no additional biocompatibility testing of the device materials was required.

Shelf Life
Shelf life for the Medtronic 4301 Leads was identified at 2 years. This shelf life was based on two main factors: (1) packaging testing, which validated the integrity of the sterility of the device over the two year period; and (2) similarity in materials and manufacture of the Model 4301 Leads to previously approved Medtronic leads, such as the Model 3387 Leads, which were approved with a shelf life of 4 years under P960009, and have a documented history of use.

Animal Testing
Electrical stimulation of the stomach muscle and its possible correlation to gastric electrical activity was investigated in prior animal studies. Specifically, Familoni, et al.[1] evaluated electrical stimulation in canines to evaluate effects of gastric stimulation patterns on motility. Four pairs of electrodes were implanted in the serosa of the stomach in six dogs and were stimulated at frequencies ranging from 3 to 30 cycles/minute (cpm) at a pulse width of 300 microsecond. Gastric electric activity and contractions were monitored before and during electrical stimulation. Contractile response to stimulation at four to five times the intrinsic gastric slow wave frequency was significantly greater than at frequencies near the intrinsic slow wave frequency ($p<0.05$). The authors concluded that stimulation at higher frequencies in the range of 20-30 cpm resulted in higher motility indices versus lower frequencies. Animal studies were not conducted with the Medtronic Enterra™ Therapy System.

IX. SUMMARY OF CLINICAL STUDIES

Patients with drug-refractory gastroparesis of diabetic or idiopathic etiologies were evaluated in the following clinical studies conducted in the United States, Canada, and Europe: the World Wide Anti-Vomiting Electrical Stimulation Study (WAVESS) and a Compassionate Use Study.

A. WAVESS Study

The WAVESS study was a double-blind, randomized cross-over study that enrolled a total of 33 subjects. The study was designed to collect both safety and effectiveness information.

Study Objective
The primary endpoint of the study was a reduction in vomiting frequency, as measured by patient diaries. The treatment was considered successful if a reduction in vomiting frequency by at least

80% was observed during the cross-over period of the study with the ON-mode stimulation, when compared to the OFF-mode stimulation.

The secondary endpoints in the study were quality of life (with the Medical Outcomes Study Short-Form 36 Health Survey), body weight , hypoglycemic attacks (diabetic group only), subjective symptoms documented by a clinical status interview, glycosylated hemoglobin, and gastric emptying.

Entry Criteria

The inclusion criteria for the study included:

- symptomatic gastroparesis ≥ 1 year, as documented by an initial gastric emptying test;
- refractory or intolerant to at least two anti-emetic and prokinetic drug classes;
- on stable medical therapy, and, if applicable, stable nutritional support during the month prior to enrollment;
- frequency of vomiting > 7 vomiting episodes per week, as documented with a baseline patient diary; and
- delayed gastric emptying, defined by greater than 60% retention at two hours and > 10% retention at four hours, as measured by standardized gastric emptying testing.

The exclusion criteria included:

- organ transplant;
- organic obstruction;
- pseudo obstruction;
- prior gastric surgery;
- scleroderma amyloidosis;
- history of seizures;
- peritoneal or unstable dialysis;
- chemical dependency;
- pregnancy;
- primary eating or swallowing disorders;
- psychogenic vomiting;
- implanted electronic medical devices; and
- age > 70 or < 18.

Study Enrollment

The number of subjects who completed each stage of the WAVESS study is described in the table below:

Table 4 - Enrollment in WAVESS Study

Number of Subjects:	at enrollment	implanted > 30 days	implanted > 60 days	implanted > 6 months	implanted > 12 months
(N)	33	33	33	25	15

Demographics

A total of 33 subjects were enrolled in the WAVESS study. The demographic information on these subjects is presented below:

Table 5 - Patient Demographics

	Diabetic (n=17)	Idiopathic (n=16)	Total (n=33)
gender (M/F)	9/8	0/16	9/24
age, mean	38.1	41.1	39.6
BMI, mean	24.7	22.9	23.7
gastric retention (mean/median) %			
@ 2 hours	79.7/80.0	73.1/76.5	76.5/78.0
@ 4 hours	53.2/51.0	34.3/28.0	44.0/34.00

Study Design

Subjects satisfying entry criteria received gastric stimulation systems which included an implanted pulse generator connected to two unipolar leads which were implanted in the muscle wall of the stomach on the greater curvature at the limit of the corpus-antrum. All subjects received a Model 7425G implantable pulse generator and a pair of Model 4301 leads. The stimulation parameters used in the study were: Intensity: 5 mA, Pulse Width: 330 μsec, Frequency: 14 Hz. The pulse generator was set to deliver a pair of pulses at these parameters every five seconds continuously 24 hours per day.

The study was conducted in two phases:

1. Phase I was a double blind crossover study with evaluations prior to implant and at 30 days and 60 days. Subjects were randomly assigned to stimulation ON and OFF for the first month after implant and were crossed to OFF and ON for the second month. Subjects were blinded as to which stimulation sequence they received.

2. Phase II was an unblinded open label study with follow-up at six and twelve months. After the cross-over period was complete, the subjects were asked which month of the cross-over stimulation they prefered. After the selection was made, the study blind was broken. The subjects then received stimulation consistent with their preference.

The primary and all of the secondary endpoints except for gastric emptying were measured at baseline, and 30 days, 60 days, six months, and twelve months post-randomization. Gastric emptying was measured at baseline, and six and twelve months post-randomization.

B. Effectiveness Information

The primary and secondary effectiveness results described below were obtained from the WAVESS study.

1. Primary Effectiveness Results - Vomiting Frequency

There was no difference in the vomiting frequency with stimulation ON or OFF during the two month double blind cross over study (see Table 6), although both periods showed a decrease in vomiting when compared to baseline. This lack of difference in improvement suggests that there were factors, other than gastric stimulation, which contribued to the change in vomiting frequency.

Table 6 - Vomiting Frequency, WAVESS Phase I, all Subjects (N=33)

Vomiting Episodes per Week	Baseline	ON	OFF	Difference (OFF-ON)	% Difference
mean, (N ± SD)	47.6 ± 52.6	23.0 ± 35.5	29.0 ± 38.2	6.0 ± 22.4	21
median, (N)	26.3	12.0	14.0	2.0	14.3

As noted above, at the end of the Phase I study period, each subject was asked which month of stimulation was preferred. Twenty one subjects preferred the ON mode, seven preferred the OFF mode, and five had no preference. Each of these subjects had the option of requesting that stimulation be turned OFF or ON at any time during the Phase II period.

Although 33 subjects completed the two-month cross-over period of the study (through Phase I), data at six months is provided for only 25 patients. Of these 25 subjects, some subjects had the device turned to the ON mode immediately at the end of the Phase I period, while others had the device turned ON later. By the end of the fourth month post-randomization, all 25 subjects had the device turned ON. As a result, the vomiting frequency at 6 months documented in the tables below was obtained from subjects who received stimulation for at least 3 months (including the Phase II cross-over period). At the time at which the data set was locked, 6 month follow-up data were only available for 25 of the 33 patients.

Vomiting frequency results at six and 12 months post-implantation are shown in Tables 7-9. Table 7 includes data for all subjects, while Tables 8 and 9 include data for the idiopathic and diabetic gastroparesis groups, respectively. There was no statistical difference in vomiting frequency as compared to baseline for either group.

Table 7 - Vomiting Frequency, WAVESS Phase II, all Subjects

	Baseline	6 Months	% Difference	Baseline	12 Months	% Difference
number of subjects	25	25		15	15	
mean number of episodes, ± SD	44.6 ± 50.7	19.2 ± 43.7	-57	42.7 ± 53.9	10.1 ± 9.8	-76
median number of episodes	26.5	5.0	-81	18.5	4.5	-76
# of subjects with > 50% vomiting reduction vs. baseline, N (%)	-	17 (68)	-	-	14 (93)	-
# of subjects with > 80% vomiting reduction vs. baseline, N (%)	-	14 (56)	-	-	8 (53)	-

Table 8 - Vomiting Frequency, WAVESS Phase II, Idiopathic Gastroparesis Subjects

	Baseline	6 Months	% Difference	Baseline	12 Months	% Difference
number of subjects	14	14		10	10	
mean number of episodes, ± SD	32.7 ± 44.4	12.1 ± 25.1	-63	41.3 ± 53.3	13.8 ± 23.7	-67
median number of episodes	22.5	3.0	-87	23.0	5.3	-77
# of subjects with > 50% vomiting reduction vs. baseline, N (%)	-	9 (64)	-	-	9 (90)	-
# of subjects with > 80% vomiting reduction vs. baseline, N (%)	-	8 (57)	-	-	5 (50)	-

Table 9 - Vomiting Frequency, WAVESS Phase II, Diabetic Gastroparesis Subjects

	Baseline	6 Months	% Difference	Baseline	12 Months	% Difference
number of subjects	11	11		5	5	
mean number of episodes, ± SD	59.8 ± 56.1	28.2 ± 60.1	-53	45.5 ± 61.5	2.8 ± 4.2	-94
median number of episodes	28	6.0	-79	18.0	1.0	-94
# of subjects with > 50% vomiting reduction vs. baseline, N (%)	-	8 (73)	-	-	5 (100)	-
# of subjects with > 80% vomiting reduction vs. baseline, N (%)	-	6 (56)	-	-	3 (60)	-

2. Secondary Effectiveness Results

Secondary effectiveness endpoints measured in the study included: subjective symptoms as documented by a clinical status interview, quality of life, tolerance of solid meals, body weight, gastric retention, and rate of hypoglycemic attacks (for diabetic group only).

- For the subjective symptoms, patients were interviewed at the follow-up visits to the physician and asked to compare their level of vomiting, nausea, early satiety, and abdominal pain, with respect to the previous interview period.

- Quality of life (QoL) was measured with the Medical Outcomes Study Short-Form 36 (SF-36) Health Survey[10, 11]. A total of 10 indices (8 health-related and 2 summary) were used. These were: physical functioning, physical role, body pain, general health, vitality, social functioning, emotional role, mental health, physical component summary (PCS), and mental component summary (MCS).

- The number of hypoglycemic attacks (diabetic gastroparesis group only) and the ability to tolerate solid meals was documented in a patient diary.

- The body weight of the patient was recorded in the follow-up visits to the physician.

- Gastric retention was measured with a gastric emptying test (GET), in which the subject ate a radio-marked solid meal. The amount of food remaining in the stomach was measured at two and four hours. It should be noted that an abnormal gastric emptying rate, as measured by a baseline GET, was one of the requirements for the definition of gastroparesis and enrollment in this study.

Overall, the study indicated trends toward improvement in most of these secondary endpoints. For example, the results of secondary endpoint evaluations indicate that many patients experienced improvements in quality of life (73%) and ability to tolerate solid meals (73%).

C. Compassionate Use Study

The Compassionate Use study was an open label, non-randomized study that included a total of 18 subjects. This study was designed to provide safety information on gastric stimulation.

Study Objective
The purpose of the compassionate use study was to treat patients with drug-refractory gastroparesis who did not meet the entry criteria of the WAVESS study.

The number of subjects who completed each stage of the compassionate use study is described in the table below:

Table 10 - Enrollment in Compassionate Use Study

Number of Subjects:	at enrollment	implanted > 30 days	implanted > 60 days	implanted > 6 months	implanted > 12 months
(N)	18	15	7	6	4

Study Design
Subjects received the Enterra™ Therapy System, which included an implanted pulse generator connected to two unipolar leads which were implanted in the muscle wall of the stomach on the greater curvature at the limit of the corpus-antrum. All subjects received a model 7425G implantable pulse generator and a pair of model 4301 leads. The stimulation parameters used in the study were: Intensity: 5 mA, Pulse Width: 330 μsec, Frequency: 14 Hz. The pulse generator was set to deliver a pair of pulses at these parameters every five seconds continuously 24 hours per day. The stimulation parameters could be adjusted at any time by the physician to optimize treatment therapy.

In contrast to the WAVESS study design, the Compassionate Use Study consisted solely of an unblinded open label study. Upon implantation of the device within each subject, the stimulation therapy was immediately initiated without a randomized ON/OFF cross-over period. The safety results for the Compassionate Use Study are included in Section V of this summary.

D. Data from Published Literature

Reports in the literature[5, 6, 7, 8, 9] have documented the therapeutic effects of gastric stimulation on patients with diabetic and idiopathic gastroparesis. In general, these studies were small and not controlled. However, the studies suggest that gastric electrical stimulation may provide some benefit to this group of patients.

One feasibility study, the GEMS (gastro electro-mechanical stimulation) trial, was initiated to demonstrate the feasibility of the Enterra™ Therapy System to treat gastroparesis of idiopathic and diabetic etiologies. Both early and long-term results have been reported [6, 7, 8]. A total of 29 patients with drug refractory gastroparesis responded positively to temporary stimulation and received the Enterra™ Therapy Systems at centers in the US, Canada, and Europe. Of these 29 patients, follow-up data was published on 18 patients[8]. The median weekly vomiting frequency for this group declined from 30 at baseline to 0 at the last follow up (mean of 30 months). At this last follow up, two of the 29 patients were lost to follow up, and three died of causes unrelated to stimulation. Of the remaining 24, three underwent gastrectomy due to poor results, and three had the system explanted due to infection or erosion. Overall, the results of the GEMS study indicate that Enterra™ Therapy System may provide a long-term benefit to patients with gastroparesis.

X. CONCLUSIONS DRAWN FROM PRE-CLINICAL AND CLINICAL STUDIES

The pre-clinical safety and performance studies demonstrate that the design of the Enterra™ Therapy System is appropriate for this intended use. The design of this stimulation system is similar to the design of currently marketed stimulation systems approved for spinal cord and deep brain stimulation. Further, the Enterra™ Therapy System utilizes components, except for the Model 4301 leads, which were approved or cleared in previous applications. As a result, much of the pre-clinical information has already been provided. The mechanical and electrical testing demonstrated that the device met the specific performance specifications and is reasonably safe for its intended use. Since the Model 4301 leads utilize materials used in previously approved device, the biocompatibility of these materials has been demonstrated.

The Phase I and II data demonstrated some improvement in the reduction in vomiting with respect to the baseline evalution period, and some improvement in secondary endpoints. Data obtained from the WAVESS and compassionate use studies revealed the same type of adverse events associated with other implantable electrical stimulation devices. These adverse events were treatable and did not cause significant morbidity and mortality.

Patients for whom this therapy is indicated are refractory to antiemetic and prokinetic drug therapies. Alternative treatments, such as supplemental enteral feeding, TPN, and GI surgical procedures have significant drawbacks. The Enterra™ Therapy System provides an alternative for this group of patients who have limited treatment options. The Enterra™ Therapy System may be turned off by the physician at any time, and the components may be removed, thus, making the treatment completely reversible.

Overall, the pre-clinical safety and performance studies provide reasonable assurance that the device materials and design are appropriate for this intended use. The limited clinical data suggest that the device will not expose patients to an unreasonable or significant risk of illness or injury, and that the probable benefit to health from using the device outweighs the risk of injury or illness, especially considering the probable risks and benefits of currently available alternative forms of treatment for this disease.

XI. PANEL RECOMMENDATIONS

The Medtronic Enterra™ Therapy System was not submitted to the Gastroenterology and Urology Devices Advisory Panel for review. The implantable pulse generator, the stimulator programmer, and memory cartridge were previously approved for marketing under Premarket Approval Application P840001/S37. While its design and features are similar to other leads previously approved for stimulation, the Model 4301 lead is the only component of the Enterra™ Therapy System that has not been approved or cleared under a prior marketing application. As a result, there was a significant amount of clinical experience with most of the components used in the Enterra™ Therapy System. Based on the prior knowledge of the safety and performance of the device system, it was determined that the HDE application need not be submitted to the advisory panel.

XII. CDRH DECISION

CDRH has determined that, based on the data submitted in this HDE application, the Medtronic Enterra™ Therapy System will not expose patients to an unreasonable or significant risk of illness or injury, and the probable benefit to health from using the device outweighs the risk of illness or injury, and issued an approval order on March 31, 2000.

XIII. APPROVAL SPECIFICATIONS

Physician Labeling:

Model 4301, Unipolar Intramuscular Lead
Model 7425G Enterra™ Therapy Quadripolar Neurostimulator Physician and Hospital Staff Manual
Model 7432 Physician Programmer
Model 7457 MemoryMod Software Cartridge

Patient Labeling:

Patient Manual, Enterra Therapy Gastric Electrical Stimulation System

XIV. REFERENCES

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