Physician's Manual

Paired VNS Therapy® Serenity System® Model 1000 Generator & Model 3000 Lead

For Healthcare Professionals

September 2012

CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use.

NOTE: This identifies the parts included in this Physician's Manual. The information contained in any one part is not intended to serve as a substitute for a complete and thorough understanding of the material presented in all of the physician's manual sections for the Paired VNS Therapy Serenity System and its component parts, nor does this represent full disclosure of all pertinent information concerning use of this product, potential safety complications, or efficacy outcomes. Copies of all Paired VNS Therapy Serenity System manuals must be included for full disclosure; copies are available from MicroTransponder Inc.

Released Version A

Table of Contents

List of Figures & Tables

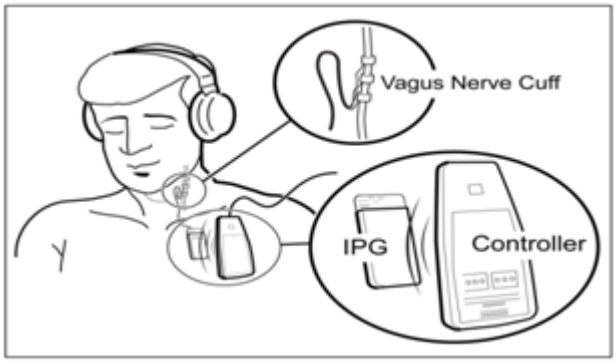
1. BRIEF DEVICE DESCRIPTION

The Paired VNS Therapy Serenity System is an active implantable device that is comprised of four main components: (1) an Implantable Pulse Generator (IPG), (2) an implantable lead, (3) Tinnitus Application & Programming software (TAPS), and (4) a Wireless Transmitter (WT, a communication and trigger system). The IPG and lead comprise the implantable components; the TAPS and WT comprise the non-implantable components.

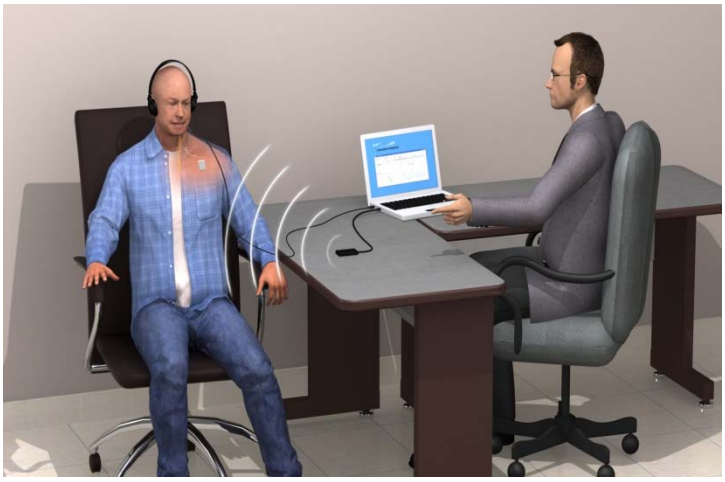
The Paired VNS Therapy Serenity System, when used as intended, provides a drug-free way to treat chronic tinnitus by pairing tone therapy with Vagus Nerve Stimulation (VNS). The lead electrodes are attached to the left vagus nerve in the neck. The lead is tunneled from the neck to the pectoral region, where it is connected to the IPG, and the IPG is surgically placed subcutaneously (or sub-muscularly) in the pectoral region. The Tinnitus Application & Programming Software (TAPS), via the Wireless Transmitter,, allows the physician to program the output settings of the IPG, including amplitude, frequency, and pulse width, to stimulate the vagus nerve while simultaneously providing tones through a laptop and headphones to the patient's ears. Once the physician and site personnel have set the system settings and verified operation, the patient will be trained in proper use of the device to initiate daily stimulation at their own home. The complete device system, called the Serenity System, is shown in Figure 1.1. The IPG is seen in figure 1.2.

Figure 1.1 (A) Device Placement, (B) In-Office Set-up, and (C) Home Set-up

A.



B.



C.

Figure 1.2 Implantable Pulse Generator (IPG)

The IPG and Lead are described in detail throughout this manual. The Wireless Transmitter and TAPS are described in further detail in the Paired VNS Therapy Serenity Non-Implantable Physician's Manual. However, since an understanding of the complete system is helpful for understanding the implantable components, the Wireless Transmitter and TAPS are summarized further below.

Wireless Transmitter (WT)

The WT has a cable with a USB connector that plugs into the laptop and converts the information from TAPS into a radio-frequency (RF) signal that is transmitted to the IPG. The WT converts the digital signals from the computer and software into RF signals that can be transmitted through the air and skin to the device and also receives RF signals back from the IPG. The IPG then translates the signal and acts on the commands given to it from TAPS. The WT will have a cable of at least 6 feet long and will communicate with the device at up to 1 meter from the WT. It is powered via the USB connection and does not require any additional power source, such as battery, or additional power connection. The WT is shown in Figure 1.3.

Figure 1.3 Wireless Transmitter

Tinnitus Application & Programming Software (TAPS)

The TAPS allows the physician to control the tone frequencies, amplitude and relative timing of the tones to the stimulation, in addition to setting the IPG stimulation parameters. The TAPS also stores the therapy history. The TAPS (loaded and tested on a provided laptop), headphones, and WT will be taken home by the patient, so that therapy can be continued at home. When taken home, most features of the software shall be locked out so that the patient cannot change the stimulation parameters or tone therapy, but only initiate a therapy session. The TAPS system also allows the status of the IPG to be checked for battery level, lead impedance, etc.

1.1. Symbols and Definitions

This physician's manual and accompanying device labeling use these symbols and definitions:

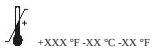
 Notice for reader to pay special attention to details that follow

 Serial Number

 Use by / Expiration Date (last day of indicated month)

 Single Use Only / Do Not Reuse

 Date of Manufacture

 Storage Temperature

 Contents Sterilized by Ethylene Oxide

 No MRI

 Consult Instructions for Use Sidebar Note (cross-references and other useful information)

 Non-Pyrogenic

RX Only Prescription Statement Symbol – US Federal law restricts this device to sale or use by or on the order of a physician.

2.0 INTENDED USE / INDICATION

The MicroTransponder Paired VNS Therapy Serenity System is intended to be used to simultaneously stimulate the vagus nerve and provide tones to the ears in order to reduce or eliminate a patient's perception of tinnitus (ringing in the ears).

3.0 CONTRAINDICATIONS

- **Vagotomy**—The Paired VNS Therapy Serenity System cannot be used in patients after a bilateral or left cervical vagotomy.
- **Diathermy**—Do not use shortwave diathermy, microwave diathermy, or therapeutic ultrasound diathermy (hereafter referred to as diathermy) on patients implanted with a Paired VNS Therapy Serenity System. Diagnostic ultrasound is not included in this contraindication.

  Energy delivered by diathermy may be concentrated into or reflected by implanted products such as the Paired VNS Therapy Serenity System. This concentration or reflection of energy may cause heating.

  Heating of the Paired VNS Therapy Serenity System resulting from diathermy could cause temporary or permanent nerve, tissue, or vascular damage. This damage may result in pain or discomfort, loss of vocal cord function, or even possibly death if there is damage to blood vessels.

  Because diathermy can concentrate or reflect its energy off any size implanted object, the hazard of heating is possible when any portion of the Paired VNS Therapy Serenity System remains implanted, including just a small portion of the Lead or electrode. Injury or damage can occur during diathermy treatment whether the Paired VNS Therapy Serenity System is turned "ON" or "OFF."

  Diathermy is further prohibited because it may also damage the Paired VNS Therapy Serenity System components resulting in loss of therapy, requiring additional surgery for system explantation and replacement. All risks associated with surgery or loss of therapy would then be applicable.

  Advise patients to inform all healthcare professionals that they should not be exposed to diathermy treatment.

4.0 WARNINGS

Physicians should inform patients about all potential risks and adverse events discussed in this physician's manual.

- **Use—**The Paired VNS Therapy Serenity System should only be prescribed and monitored by physicians who have specific training and expertise in the management of tinnitus and the use of this device. The System should only be implanted by physicians who are trained

in surgery of the carotid sheath and have received specific training in the implantation of this device.

- **Not curative—**Physicians should warn patients that the Paired VNS Therapy Serenity System has not been determined to be a cure for tinnitus. Patients should be counseled to understand that individual results will likely vary. Beneficial results might not become evident for months or may never occur.

- **Unapproved uses—**The safety and efficacy of the Paired VNS Therapy Serenity System have not been established for uses outside the “Intended Use / Indications” section of this physician’s manual, including (but not limited to) patients with:

    - Acute suicidal thinking or behavior
    - History of schizophrenia, schizoaffective disorder or delusional disorders
    - History of rapid cycling bipolar disorder
    - History of previous therapeutic brain surgery or CNS injury
    - Progressive neurological diseases other than tinnitus
    - Cardiac arrhythmias or other abnormalities
    - History of dysautonomias
    - History of respiratory diseases or disorders, including dyspnea and asthma
    - History of ulcers (gastric, duodenal, or other)
    - History of vasovagal syncope
    - Only one vagus nerve
    - Other concurrent forms of brain stimulation
    - Pre-existing hoarseness
    - Under 18 years of age

- **Worsening depression/suicidality—**Patients being treated with adjunctive Paired VNS Therapy who have moderate or severe depression should be observed closely for clinical worsening and suicidality, especially at the time of Paired VNS Therapy stimulation parameter changes or drug or drug dose changes, including either increases or decreases in the stimulation parameters or concomitant treatments. Consideration should be given to changing the therapeutic regimen of Paired VNS Therapy or concomitant treatments, including possibly discontinuing Paired VNS Therapy or the concomitant therapy, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient’s presenting symptoms.

- **Dysfunctional cardiac conduction systems—**The safety and effectiveness of the Paired VNS Therapy Serenity System in patients with predisposed dysfunction of cardiac conduction systems (re-entry pathway) have not been established. Evaluation by a cardiologist is recommended if the family history, patient history, or electrocardiogram suggests an

abnormal cardiac conduction pathway. Serum electrolytes, magnesium, and calcium should be documented before implantation. Additionally, postoperative bradycardia can occur among patients with certain underlying cardiac arrhythmias. Post-implant electrocardiograms and holter monitoring are recommended if clinically indicated.

It is important to follow recommended implantation procedures and intraoperative product testing described in the *Implantation Procedure* part of this manual. During intraoperative Lead Impedance Diagnostics of the Cyberonics VNS Therapy System, infrequent incidents of bradycardia and/or asystole have occurred. Although these events have not occurred during implantation of the MicroTransponder paired VNS Therapy Serenity System, they are events that could possibly occur. If asystole, severe bradycardia (heart rate < 40 bpm), or a clinically significant change in heart rate is encountered during a Lead Impedance Check or during initiation of stimulation, physicians should be prepared to follow guidelines consistent with Advanced Cardiac Life Support (ACLS).

Additionally, postoperative bradycardia can theoretically occur among patients with certain underlying cardiac arrhythmias (although none have been reported with the Paired VNS Therapy Serenity System). If a patient has experienced asystole, severe bradycardia (heart rate < 40 bpm), or a clinically significant change in heart rate during a Lead Impedance Check at the time of initial device implantation, the patient should be placed on a cardiac monitor during initiation of stimulation.

The safety of this therapy has not been systematically established for patients experiencing bradycardia or asystole during Paired VNS Therapy Serenity System implantation.

- **Swallowing difficulties—**Difficulty swallowing (dysphagia) may occur with active stimulation, and aspiration may result from the increased swallowing difficulties. Patients with pre-existing swallowing difficulties are at greater risk for aspiration. Appropriate aspiration precautions should be taken for such patients.

- **Dyspnea or shortness of breath—**Dyspnea (shortness of breath) may occur with active Paired VNS Therapy. Any patient with underlying pulmonary disease or insufficiency, such as chronic obstructive pulmonary disease or asthma, may be at increased risk for dyspnea and should have their respiratory status evaluated prior to implantation and monitored following initiation of stimulation.

- **Obstructive sleep apnea—**Patients with obstructive sleep apnea (OSA) may have an increase in apneic events during stimulation. Lowering stimulus frequency or prolonging “OFF” time may prevent exacerbation of OSA. Vagus nerve stimulation may also cause new onset sleep apnea in patients who have not previously been diagnosed with this disorder. It is recommended that patients being considered for Paired VNS Therapy who demonstrate signs or symptoms of OSA, or who are at increased risk for developing OSA, should undergo the appropriate evaluation(s) prior to implantation.

 None of the above three items (swallowing difficulties, dyspnea, obstructive sleep apnea) should be issues for the Paired VNS Therapy Serenity System, since stimulation sessions only occur for 2.5 hours while the patient is awake and for shorter periods (1/2 second vs. 30 seconds). However, this information is included for completeness since it is reported in unpaired VNS Therapy use.

• **Device malfunction—**Device malfunction could cause painful stimulation or direct current stimulation. Either event could cause nerve damage and other associated problems. Patients should be instructed to use the Magnet to stop stimulation if they suspect a malfunction, and then to contact their physician immediately for further evaluation. Prompt surgical intervention may be required if a malfunction occurs.

• **Magnetic resonance imaging (MRI)**—Patients with the Paired VNS Therapy Serenity System, or any part of the implanted Paired VNS Therapy Serenity System, should not have MRI procedures performed. No testing has yet been completed on MRI compatibility of the Paired VNS Therapy Serenity System. Therefore the Serenity System should be completely explanted or removed prior to MRI being performed.

• **Excessive stimulation—**Excessive stimulation at an excess duty cycle (when "ON" time is greater than "OFF" time) has resulted in degenerative nerve damage in laboratory animals.

• **Device manipulation—**Patients who manipulate the IPG and Lead through the skin (Twiddler's Syndrome) may damage or disconnect the Lead from the IPG and/or possibly cause damage to the vagus nerve. Patients should be warned against manipulating the IPG and Lead.

Note: See the "Physician Training/ Information" section of the *Implantation Procedure* part of this physician's manual.

5.0 PRECAUTIONS

Physicians should inform patients about all potential risks and adverse events discussed in this physician's manual.

5.1 General

• Appropriate physician training is very important. **Prescribing physicians** should be experienced in the diagnosis and treatment of tinnitus and should be familiar with the programming and use of the Paired VNS Therapy Serenity System.

• **Physicians who implant the Paired VNS Therapy Serenity System** should be experienced performing surgery in the carotid sheath and should be trained in the surgical technique relating to implantation of the Paired VNS Therapy Serenity System.

• **Use during pregnancy—**The safety and effectiveness of the Paired VNS Therapy Serenity System have not been established for use during pregnancy. There are no adequate and well-controlled studies of Paired VNS Therapy in pregnant women.

• The Paired VNS Therapy Serenity System is indicated for use only in stimulating the left vagus nerve in the neck area inside the carotid sheath. The Paired VNS Therapy Serenity System is indicated for use only in stimulating the **left vagus nerve below where the superior and inferior cervical cardiac branches separate from the vagus nerve.** The safety and efficacy of the Paired VNS Therapy Serenity System have not been established for stimulation of the right vagus nerve or of any other nerve, muscle, or tissue.

• It is important to follow infection control procedures. Infections related to any implanted device are difficult to treat and may require that the device be explanted. The patient should be given antibiotics preoperatively. The surgeon should ensure that all instruments are sterile prior to the operation.

Frequent irrigation of both incision sites with generous amounts of bacitracin or equivalent

solution should be performed prior to closure. To minimize scarring, these incisions should be closed with cosmetic closure techniques. Also, antibiotics should be administered postoperatively at the discretion of the physician.

- **Effects on other medical devices—**The Paired VNS Therapy Serenity System has not been tested with and may affect the operation of other implanted devices, such as cardiac pacemakers and implanted defibrillators. Possible effects include, but are not limited to, sensing problems and inappropriate device responses.

- **Reversal of Lead polarity has been associated with an increased chance of bradycardia** in animal studies of unpaired VNS. It is important that the electrodes are attached to the left vagus nerve in the correct orientation.

- The patient can use a neck brace for the first week to help ensure proper Lead stabilization.

- A reset of the device will program the device OFF (output current = 0.0 mA).

When an IPG is reset, its stimulation output is disabled (0.0mA); however, all settings and device history are preserved. After a successful reset, the IPG stimulation output may be re-enabled to resume operation at the previously programmed settings.

Note: For more information on diagnostic testing, see the “Troubleshooting” section.

- Laryngeal irritation may result from stimulation. Patients who smoke may have an increased risk of laryngeal irritation.

- **Potential effects of Lead breaks**—Lead fractures may prevent patients from receiving therapy. If a Lead fracture is suspected, perform diagnostic testing to evaluate continuity within the system. If diagnostics suggest that a fracture is present, consider turning the Serenity IPG to zero milliamps (0 mA) of output current. Continuing stimulation with a fractured Lead may result in dissolution of the conductor material resulting in adverse events, such as pain, inflammation, and vocal cord dysfunction. The benefits and risks of leaving the Serenity IPG ON (actively stimulating) when a Lead fracture is present should be evaluated and monitored by the medical professional treating the patient.
- **Some complications** may be associated with damage to the vagus nerve.
- Hoarseness may be caused by device malfunction, nerve constriction, or nerve fatigue. Nerve constriction should be apparent within a few days after implantation and may require explantation of the Lead. Nerve fatigue usually occurs after intense stimulation parameters have been used, and might not be associated with any other adverse event. If fatigue is suspected, the Serenity IPG should be turned OFF for several days until hoarseness subsides.

- Persistent hoarseness *not* associated with stimulation suggests possible nerve irritation and should be immediately investigated.

Trauma to the vagus nerve at the implantation site could result in permanent vocal cord dysfunction.

5.2 Sterilization, Storage, and Handling

The IPG and Lead have been sterilized using ethylene oxide (EO) gas, and are supplied in a sterile package to permit direct introduction into the operating field. An expiration (or use-before) date is marked on each package. A sterilization process indicator is included in each package. Products labeled as sterile should be used only if the color of the indicator is green or brown.

The implantable portions of the Paired VNS Therapy Serenity System are nonpyrogenic.

- **Store the Paired VNS Therapy Serenity System** between -20°C (-4°F) and +55°C (+131°F). Temperatures outside this range can damage components.
- **Do not store the Paired VNS Therapy Serenity System** where it is exposed to water or other liquids. Moisture can damage the seal integrity of the package materials.
- **Do not implant a device** if any of the following has occurred:
  - The device has been dropped, because dropping it could damage IPG components.
  - The color of the sterilization process indicator within the inner package is not green or brown for product sterilized by EO.
  - The outer or inner storage package has been pierced or altered, because this could have rendered it non-sterile.
  - The expiration (use-before) date has expired, because this can adversely affect the device's longevity and sterility.
- **Do not ultrasonically clean the IPG**, because doing so may damage IPG components.
- **Do not re-sterilize any Paired VNS Therapy Serenity System product**. Return any opened devices to MicroTransponder.

The IPG and Lead are single-use-only devices. **Do not re-implant an explanted IPG or Lead for any reason**, because sterility, functionality, and reliability cannot be ensured, and infections may occur.

Note: See the exterior package label to ascertain the method of sterilization, which is indicated by the EO sterility symbol (see "Symbols and Definitions" section of this manual).

Note: See the "Other environmental hazards" section of this manual.
Explanted IPGs and Leads should be returned to MicroTransponder for examination and proper disposal. Before returning the IPG or Lead, disinfect the device components with Betadine®, Cidex® soak, or other similar disinfectant, and double-seal them in a pouch or other container properly labeled with a biohazard warning.

Do not incinerate the IPG; it contains a sealed chemical battery, and an explosion could result.

5.3. Lead Evaluation and Connection

- **Do not use a lead other than** the MicroTransponder Model 3000 Lead with the Serenity IPG because such use may damage the IPG or injure the patient.
- Exercise extreme caution if testing the Lead using **line-powered equipment** because leakage current can injure the patient.

- Do not insert a Lead in the IPG Lead receptacle(s) without first visually **verifying that the setscrew(s) is sufficiently retracted** to allow insertion. Avoid backing the setscrew(s) out further than needed for Lead insertion.
- To avoid damaging (stripping) the setscrew(s) and/or dislodging the setscrew plug(s), insert the hex screwdriver into the center of the setscrew plug, keeping it perpendicular to the IPG.
- Inserting the hex screwdriver into the septum can aid in relieving a vacuum that may be created during lead insertion or withdrawal.

5.4. Environmental and Medical Therapy Hazards

Patients should exercise reasonable caution in avoiding devices that generate a strong electric or magnetic field. If an IPG ceases operation while in the presence of electromagnetic interference (EMI), moving away from the source may allow it to return to its normal mode of operation.

5.4.1. Hospital and medical environments

Paired VNS Therapy Serenity System operation **should always be checked** by performing device diagnostics after any of the procedures mentioned in this manual. Additional precautions for these procedures are described below.

- **For clear imaging, patients may need to be specially positioned for mammography procedures** because of the location of the IPG in the chest. (Most routine diagnostic procedures, such as fluoroscopy and radiography, are not expected to affect system operation.)
- **Therapeutic radiation** may damage the IPG's circuitry, although no testing has been done to date and no definite information on radiation effects is available. Sources of such radiation include therapeutic radiation, cobalt machines, and linear accelerators. The radiation effect is cumulative, with the total dosage determining the extent of damage. The effects of exposure to such radiation can range from a temporary disturbance to permanent damage, and may not be detectable immediately.
- **External defibrillation** may damage the IPG. Attempt to minimize current flowing through the IPG and Lead system by following these precautions:
    - Position defibrillation paddles perpendicular to the IPG and Lead system and as far from the IPG as possible.
    - Use the lowest clinically appropriate energy output (watt-seconds).
    - Confirm IPG function after any internal or external defibrillation.
- Use of electrosurgery [electrocautery or radio frequency (RF) ablation devices] may damage the IPG. During the VNS implantation procedure, do not use electrosurgical equipment after the IPG has been introduced to the sterile field. When performing other surgical procedures on a patient implanted with a Serenity IPG, attempt to minimize the current flowing through the IPG and Lead system by following these precautions:

- Position the electrosurgery electrodes as far as possible from the IPG and Lead.
- Avoid electrode placement that puts the IPG or Lead in the direct path of current flow or within the part of the body being treated.
- Confirm that the IPG functions as programmed after electrosurgery.

- Electrostatic Discharge (ESD) may damage the IPG. Care should be taken when using the hex screwdriver to avoid touching the metal shaft when the screwdriver is engaged with the setscrew of the IPG. This shaft can serve as a path to conduct electrostatic discharges into the device circuitry.

Caution: The patient should seek medical advice before entering environments that are protected by a warning notice preventing entry by patients implanted with a cardiac pacemaker or defibrillator.

- **Extracorporeal shockwave lithotripsy** may damage the IPG. If therapeutic ultrasound is required, avoid positioning the area of the body where the IPG is implanted in the water bath or in any other position that would expose it to ultrasound therapy. If that positioning cannot be avoided, program the IPG output to 0 mA for the treatment, and then after therapy, reprogram the IPG to the original parameters.
- If the patient receives medical treatment for which electric current is passed through the body (such as from a TENS unit), either the IPG output should be set to 0 mA or function of the IPG should be monitored during initial stages of treatment.
- **Therapeutic ultrasound.** Routine therapeutic ultrasound could damage the IPG and may be inadvertently concentrated by the device, causing harm to the patient.

Magnetic resonance imaging (MRI) should not be performed.

Patients with an implanted device should not be exposed to the electromagnetic fields produced by magnetic resonance imaging (MRI). Use of MRI may potentially result in system failure or dislodgment, heating, or induced voltages in the IPG and/or lead. An induced voltage through the IPG or lead may cause uncomfortable, “jolting” or “shocking,” levels of stimulation.

5.4.2. Home occupational environments

Properly operating microwave ovens, electrical ignition systems, power transmission lines, theft-prevention devices, and metal detectors are not expected to affect the IPG. Similarly, most routine diagnostic procedures, such as fluoroscopy and radiography, are not expected to affect system operation. However, because of their higher energy levels, sources such as transmitting antennas may interfere with the Paired VNS Therapy Serenity System. It is suggested that the IPG be moved away from equipment—typically at least 1.8 meters (6 feet)—that may be causing interference.

5.4.3. Cellular phones

Cellular phones should have no effect on IPG operation. Unlike an implanted pacemaker or

defibrillator, the IPG does not sense physiologic signals.

5.4.4. Other environmental hazards

Strong magnets, hair clippers, vibrators, loudspeaker magnets, Electronic Article Surveillance (EAS) System tag deactivators, and other similar electrical or electro-mechanical devices, which may have a strong static or pulsing magnetic field, can cause accidental closure of the reed switch. Patients should be cautioned to keep such devices away from the IPG, typically at least 15 centimeters (6 inches) away.

5.4.5. Programming Software

The IPG can be programmed using TAPS. This software should be used on the provided laptop or computer dedicated only to programming the Paired VNS Therapy Serenity System.

5.4.6. Implantable Pulse Generator (IPG) and EMI effects on other devices

The IPG should be moved—typically at least 1.8 meters (6 feet)—away from equipment with which it may be interfering.

Programming or interrogating the IPG may momentarily interfere with other sensitive electronic equipment nearby. The IPG is not expected to trigger airport metal detectors or theft-protection devices that are further than about 1.8 meters (6 feet).

The IPG may affect the operation of **other implanted devices,** such as cardiac pacemakers and implantable defibrillators. Possible effects include sensing problems and inappropriate IPG responses.

The Magnet provided for activation or inhibition of the IPG may damage **televisions, computer disks, credit cards, and other items** affected by strong magnetic fields.

5.4.8. Implantable Pulse Generator (IPG) disposal

- Do not incinerate the IPG, because it can explode if subjected to incineration or cremation temperatures.
- Return all explanted IPGs to MicroTransponder for examination and safe disposal.
- Do not implant an explanted IPG in another patient, because sterility, functionality, and reliability cannot be ensured.

6.0 DETAILED DEVICE DESCRIPTION

6.1. Physical Characteristics

The titanium case of the Paired VNS Therapy® Serenity System® Model 1000 IPG is hermetically sealed and leak-rate tested. Specially designed feedthroughs using platinum conductors form the electrical connection from the connector blocks to the circuitry through the hermetically sealed enclosure. The Model 1000 IPG accepts the single-pin Model 3000 Lead.

6.2. Biological Compatibility

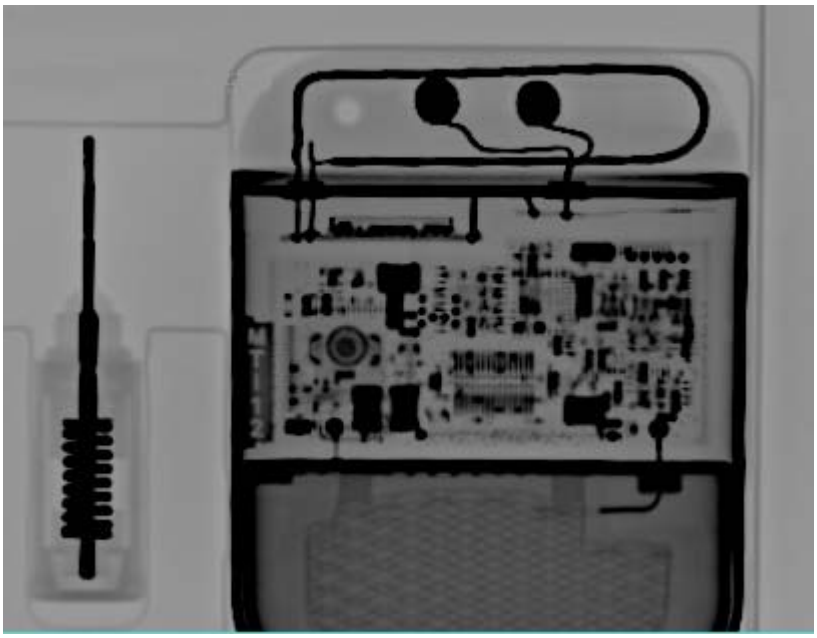
Materials exposed to the subcutaneous environment are biologically compatible. All of these materials have a long history in medical implants and have been found to be tissue compatible.

6.3. Power Source

The power source for the Model 1000 IPG is a Wilson Greatbatch Ltd, Model WG 9086, Li CfX - Lithium / Carbon Monofluoride with an open-circuit voltage of 3.3V. The battery's maximum available capacity is approximately 2.5 Amp-hours. The voltage in this battery gradually decreases as the battery nears its end of life (EOL).

The IPG can be identified on an x-ray film and will appear as shown in Figure 6.1. The serial number and model number of the IPG are marked on its titanium case, but do not appear on the x-ray film. The serial number and model number can be identified by interrogating the IPG with the Programming Software.

Figure 6.1 X-Ray IPG identification



The radiograph in Figure 6.1 shows a Model 1000 IPG (and the provided screwdriver to the left). The x-ray tag included uses the code MTI12, in which:

- MTI = MicroTransponder Model 1000
- 12 = The year of manufacture

7. DIRECTIONS FOR USE

7.1. IPG Specifications and Product Information

The Paired VNS Therapy Serenity System IPG is a neurostimulator device similar to other implanted neurostimulators such as the Cyberonics' NeuroCybernetic Prosthesis or the Medtronic's DBS System. The IPG has a metal Titanium case or "can" that is hermitically sealed and houses the electrical components of the device; a polyurethane header is attached to the can and has feedthrough connectors that pass the electrical signal from inside the can to the external lead connectors, while at the same time isolating the can from the stimulation electrodes and providing EMI filtering.

The IPG also has an internal battery (primary cell – Li/CFx, Lithium/Carbon MonoFluoride) that provides power to the electrical components. The IPG is programmable by the physician, and provides stimulation at amplitudes of up to 3.5 mA, frequencies up to 30 Hz., pulse widths up to 1000 uSec, and stimulation durations of up to one minute. The device characteristics for the

Paired VNS Therapy System Serenity IPGs are presented in Table 7.1 and the full range of settings is described in Table 7.2.

The IPG has been designed to accept the Cyberonics Model 304 Perennia lead

Table 7.1: Characteristics of the Single Use IPG

Size	48 mm wide x 62 mm tall x 11.5 mm thick
Shape	Rectangular with radius >= 2mm and no sharp corners/edges
Weight	70 g
Power Source	WG 9086, Li CfX - Lithium / Carbon Monofluoride
Housing (Can)	Titanium
Header Material	Epoxy Resin

Table 7.2: IPG: Electrical Characteristics

Parameter	Range / Tolerance
Output Current	0 to 3.5 mA in 0.1 mA steps; (+/- 0.1 mA <= 1 mA, +/-10% > 1 mA tolerance), with a maximum 12 volts
Frequency	1 to 30 Hz, with the following steps (1,2,5,10,15,20,25,30); +/-1% tolerance
Pulse Width	10 µs to 1000 µs with the following steps (10 us steps from 10 to 100, 25 µs steps from 100 to 500 µs, and 50 µs steps from 500 to 1000 µs) (+/- 2µS or 1% tolerance, whichever is greater)
Duration	0.5 seconds to 60 seconds, in 1 seconds steps, starting at 1 sec (e.g. 0.5, 1, 2, 3, etc.) (+/- 1% tolerance)
Identification	factory-only programmed Model Number and Unique Serial number that can be retrieved via the RF communications, X-RAY ID tag (MTI)
Lead Measure	report the lead impedance from 250 Ohms to 10 K ohms with 20% accuracy
Output	Bipolar output; electrically floating can with at least 10M ohm DC impedance to either + or –.
Upgradability	IPG firmware shall be wirelessly upgradeable

Note: See the Paired VNS Therapy Serenity Non-Implantable Physician's Manual for more information on TAPS, including a list of the requirements for the laptop to be used with this software.

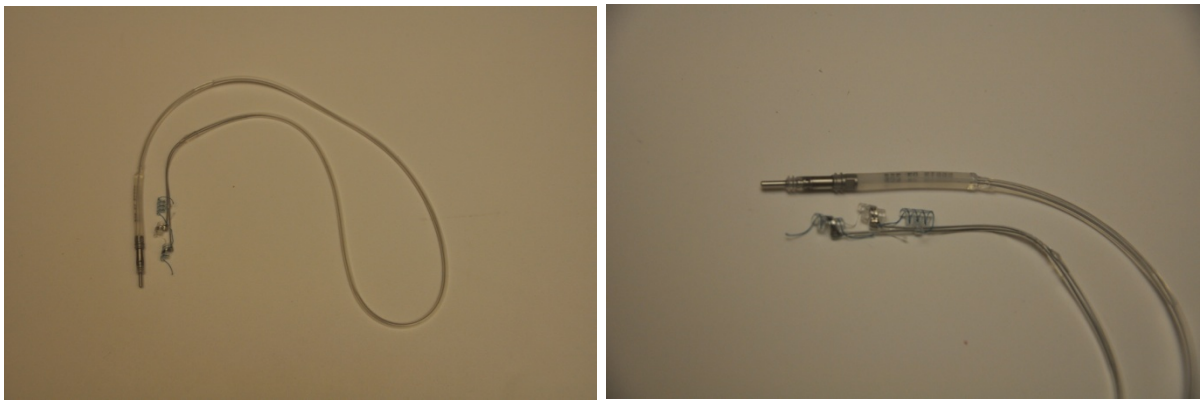
* Latex is not included in any component of the Paired VNS Therapy Serenity System.

7.2 Lead Specifications and Product Information

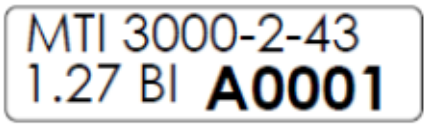
The Lead is similar to other vagus nerve leads such as the Cyberonics Model 304. The Lead delivers the electrical signal from the Serenity IPG to the vagus nerve, is insulated with silicone and is bifurcated at the nerve end to provide bipolar stimulation. It has two helical electrodes (nerve cuffs) and an anchor tether, which are coiled around the left vagus nerve. The connector end of the Lead is tunneled subcutaneously to the IPG pocket. The lead is available in both a 43 cm and 85 cm length. The lead length and serial number are indicated on the tag inside the connector of the lead.

The lead and identification tag are shown below in Figure 7.1 A, B and C; Table 7.3 shows lead characteristics.

Figure 7.1 A. VNS Lead **B. Close-up of both ends**



C. Lead Identification Tag



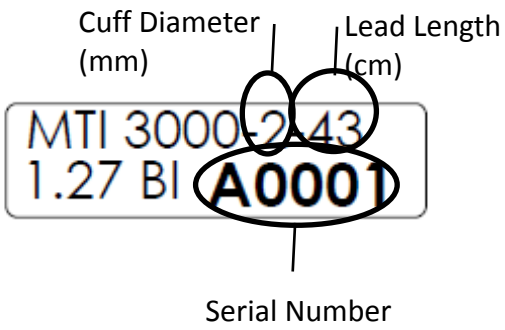

Cuff Diameter
(mm)
Lead Length
(cm)
MTI 3000-243
1.27 BI A0001
Serial Number

Table 7.3: Characteristics of VNS Lead

Total Length	43 cm or 86 cm
Outer Material (insulation)	Silicone
Lead body diameter	2 mm
Conductor coil	MP-35N Alloy, quadfilar
Connector – Outer Material	Silicone
Connector - Connector Pin	300 series stainless steel; 1.6 mm diameter
Connector - Connector Ring	300 series stainless steel; 2.67 mm diameter
Resistance	< 200 Ohms (43 cm), < 400 Ohms (86 cm)
Helical Cuff material	Pt/Ir alloy and silicone
Helical Coil Separation	8 mm center to center
Cuff Diameter	2 mm
Tie Downs	Four silicone tie downs

7.3. Operating Characteristics

7.3.1. Communicating with the Paired VNS Therapy Serenity System

7.3.1.1. TAPS

The IPG can be programmed with the Paired VNS Therapy System Serenity TAPS Software.

TAPS is used on a computer supplied by MicroTransponder that is dedicated only to programming the Paired VNS Therapy Serenity System. More information on TAPS can be found in the Paired VNS Therapy System Serenity Non-Implantable Physician's Manual.

7.3.1.2. Wireless Transmitter

A Wireless Transmitter connected to a compatible computer running the Programming Software is needed to communicate with the IPG (see the Paired VNS Therapy Serenity System Non-Implantable Physician's Manual for a list of compatible computers).

7.3.1.3. Prompts and messages

After the program has been initiated, the software screens display prompts and messages to aid in communicating with the IPG.

7.3.1.4. Communication

The IPG "listens" for a communication signal from the Wireless Transmitter. Communication usually takes less than two (2) seconds, but may be prolonged or interrupted in the presence of electromagnetic interference (EMI). The IPG listens for and implements interrogations, parameter programming instructions, requests for Device Diagnostics testing, and Device History inquiries.

In response, the IPG transmits information on the stimulation parameter settings, lead

impedance, and battery status information. Each time these data are transmitted by the IPG, they are saved by the Programming Software to a database.

In addition to the Programming Software and Wireless Transmitter combination, a Magnet can be used for one-way communication to the IPG by activating a reed switch in the electronic circuitry. The Magnet can be used to temporarily inhibit stimulation, depending on how the Magnet Mode is configured in TAPS.

7.3.1.5. Typical Parameters

After the IPG has been programmed, the stimulation will be initiated by the Programming Software in accordance with the programmed settings for the length of time designated by the physician. Typically, settings are 0.8 mA, 30 Hz, 100 µSec, ½ second ON, 30 Seconds OFF, and 2.5 hours total treatment time. An audio tone is synchronized with the VNS signal (so a ½ second tone is played while the ½ second VNS pulse occurs); this tone is played by the computer and the Programming Software through the headphones and delivered to the patient's ears. This treatment session is typically given once per day and typically lasts 2.5 hours (150 minutes). The specific settings are programmed by the physician or audiologist. The patient may then start a daily session from their own home, using their own patient programming system. Stimulation duty cycles greater than 50% shall be inhibited.

7.3.1.6. Stimulation Inhibition via Magnet Application

A magnet is provided to the patient to inhibit stimulation in the unlikely event that stimulation is too strong or becomes uncomfortable or there is some device malfunction while the patient is at home between sessions. The site will also have a magnet available during the rehabilitation session so that stimulation can be easily aborted. The user should place the magnet over their chest where the IPG is located and hold the magnet in place. The device should not stimulate while the magnet is in place. If at home, the patient should then contact their physician or audiologist for an immediate appointment so that the device can be further tested.

7.3.1.7. IPG interrogation

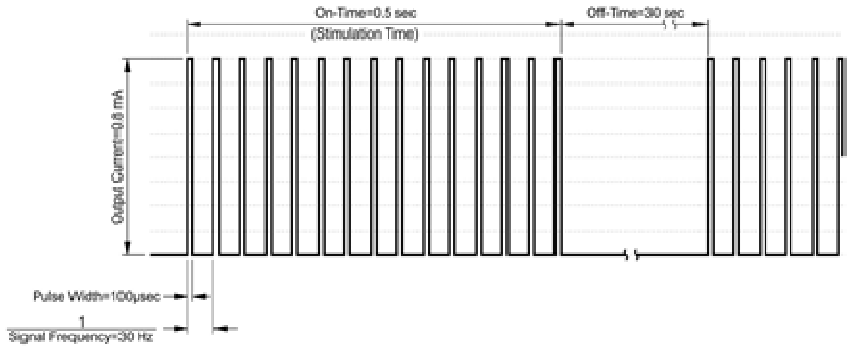
The IPG can be interrogated to determine the present settings of the stimulation parameters.

7.3.1.8. Programmable parameters

A graphic representation of VNS (Figure 7.2) depicts the relationship of the programmable parameters. Each parameter can be independently programmed, thereby offering multiple setting combinations from which the physician may select optimal stimulation for the patient.

Figure 7.2 shows that the output pulse can be varied both by amplitude (output current) and duration (pulse width). The number of output pulses delivered per second determines the frequency.

Figure 7.2 Stimulation Waveform



The typical VNS session for tinnitus rehabilitation will be 150 minutes.

7.3.1.9 Parameter settings and battery life

When selecting a combination of parameter settings for stimulation, the physician should also consider that some combinations, such as higher output currents and longer On-Times, would decrease battery life faster than others.

7.3.2. Paired VNS Therapy System Serenity Magnet

The main use of the magnet is to temporarily inhibit stimulation. This is done by placing the magnet over the chest where the IPG is implanted. Stimulation is inhibited for as long as the magnet is placed over the IPG.

7.3.3. Device History

The Device History consists of the IPG serial number, model number, the patient ID, tone therapy, and other information pertinent to diagnostic and programming events. Use the TAPS to access and view Device History information.

7.3.4. Check Impedance

In the ***Status*** portion of the ***Program Implant*** menu, the lead impedance can be checked by selecting the ***Check*** button. When the ***Check*** button is selected the IPG delivers a small current to assess Lead impedance. High lead impedance is defined as any value >= 10,000 ohms. Low lead impedance is defined as any value <= 600ohms.

Caution: Possible cases of high lead impedance readings are thought to include: fibrosis between the nerves and the electrode, Lead discontinuity, or Lead disconnection from the IPG.

Caution: possible causes of low lead impedance are thought to include: short circuit condition within the lead or a defective IPG.

7.3.4.1. High Lead impedance: possible implications

High Lead impedance (≥10,000 Ohms), in the absence of other device-related complications, is an indication that it is difficult for the IPG to deliver the programmed output current, and that the battery may therefore not last as long as typical. In conjunction with the patient's failure to feel stimulation, High Lead Impedance may indicate a Lead wire fracture or other type of electrical discontinuity in the Lead. Patients experiencing high Lead impedance, no sensation of stimulation, and an increase in tinnitus symptoms should be further evaluated for possible Lead replacement.

7.3.4.2. Low Lead Impedance: possible implications

Low Lead impedance (≤600 Ohms) likely indicates the existence of a short-circuit condition, although an impedance value of greater than 600 Ohms does not exclude the possibility. A sudden decrease in impedance value in combination with device-related complications (e.g., increase in tinnitus symptoms or painful stimulation; patient perception of feeling erratic, limited, or no stimulation) may also indicate a short-circuit condition in the Lead.

7.3.5. Implantable Pulse Generator (IPG) battery longevity

7.3.5.1. Battery longevity and programmed setting choices

The anticipated longevity of the IPG battery varies, depending on the choice of programmed settings. Higher output currents, frequencies, pulse widths, and duty cycles generally deplete the battery over a shorter period of time than lower settings. Generally, the increase in battery depletion rate is proportional to the increase in the programmed setting.

Other factors, such as the Lead impedance and, if applicable, magnet usage, also affect the anticipated longevity of the IPG battery. The anticipated battery longevity decreases as Lead impedance increases. Although 1.5 k to 3 kOhms may be typical Lead impedance at implantation, the impedance may increase to 3 k to 5 kOhms during the life of the implant.

The approximate battery longevity predicted is greater than 5 years at programmed settings of 1.5 mA in to 3K ohm load, 50 Hz, 500 µS PW, 0.5 S pulse train, and a separation of 15 S between pulse trains. Because of the number of possible parameter combinations, it is impractical to provide the projected life for all possible combinations. Increasing settings (output current, pulse width, duty cycle) will decrease battery life. As impedance increases battery life also decreases.

Caution: *Undeliverable output currents—*
Programming the IPG to a high output current that cannot be delivered due to a high Lead impedance may disproportionately increase the battery depletion rate and should be avoided.

Caution: *Battery evaluation at cold temperatures*—Low storage temperatures may affect the battery status indicators. In such cases, the battery status indicators should be re-evaluated

using the System Diagnostics or Generator Diagnostics after the IPG has been at room or body temperature for 30 minutes.

7.3.5.2. Battery status indicators

The Programming Software will display warning messages after an interrogation or programming of the IPG if the battery is nearing its depletion. The first indication is an Elective Replacement Indicator (ERI) flag, which indicates less than 15% of the battery life is left (likely nine [9] months or less). The final indication is an End of Life (EOL) flag, which indicates less than 5% of the battery life is left. It is recommended that IPG replacement start being considered at ERI. Please refer to the Paired VNS Therapy Serenity System Non-Implantable Physician's Manual for additional information in these indicators.

7.4 Implantable Pulse Generator (IPG) Replacement

All Paired VNS Therapy Serenity IPGs eventually require surgical replacement as a result of battery depletion. IPG replacement does not, of itself, require Lead replacement unless a Lead discontinuity is suspected. IPG replacement or removal requires dissection to the IPG's pocket, with care being taken not to damage or cut the Lead. Replacement of the IPG only typically requires 30 minutes or less; replacement of the entire system typically requires approximately 90 minutes.

7.5 Lead Lifetime and Replacement

A Lead requires replacement when a Lead discontinuity is suspected. An increase in clinical signs and symptoms may signal a need for Lead replacement. Events that can shorten the life expectancy of the Lead are as follows:

- Blunt trauma to the neck and/or any area of the body beneath which the Lead is implanted
- Twisting or picking (Twiddler's Syndrome) at either the implanted Lead or the IPG
- Improper surgical implantation of the Paired VNS Therapy Serenity System, including (but not limited to) providing an inadequate strain-relief loop, placing sutures directly on the Lead body rather than using the tie-downs, and suturing the Lead body to muscle.

Caution: *Lead replacement or removal*—Replacing or removing Leads **because of lack of efficacy** is a medical judgment that includes the patient's desires and health status, and must be carefully weighed against the known and unknown risks of surgery. At present, no known long-term hazards or risks are associated with leaving the Lead implanted, beyond those already mentioned in this multi-part physician's manual. All precautions and contraindications still should be observed (see "Troubleshooting", Section 8 below).

7.6 Signs of End of Life

The most common reason for the absence of stimulation is battery depletion, although there

may be other reasons. When end of life (EOL) occurs, the IPG will disable stimulation and no output will be delivered. If the IPG is not explanted or replaced at EOL, the battery voltage will continue to gradually decrease and communication with the IPG may not be possible.

7.7 Replacement Based on Battery Status Indicators

The TAPS battery status indicators provide warnings that an IPG battery should be monitored more frequently, is near EOL, or has reached EOL. Once these warning messages appear, see recommendations in the Paired VNS Therapy Serenity Non-Implantable Physician's Manual.

8. TROUBLESHOOTING

This section provides troubleshooting instructions in two parts: (1) in the Operating Room (OR) and (2) at patient follow-up visits.

A communication problem can cause an error message (such as "There is an error establishing communication with the device" or "Failed to retrieve diagnostic data") during:

- Interrogation
- Programming of parameters or implant date/patient code
- Diagnostic testing indicated by the message, Communication "FAULT"

Failure of the IPG and Wireless Transmitter to clearly communicate with each other to interrogate, program, or run diagnostic tests can be attributed to several factors:

Movement of the Wireless Transmitter away from the IPG during communication

Improper cable connection between the Wireless Transmitter and Programming Computer

Electromagnetic interference (EMI), i.e., OR lights, Programming Computer

IPG battery at end of life (EOL)

Defective Wireless Transmitter

Defective Programming Computer

Defective IPG

The most common cause of difficulties are connection issues. Verify that the Wireless Transmitter connector is correctly inserted into the computer's USB port. Refer to the Paired VNS Therapy Serenity Non-Implantable Physician's Manual for further details. Communication problems are often intermittent and are rarely related to the IPG. The surrounding environment can often cause these problems.

A communication problem causes an error message (such as "Data transmission error between programmer and device") during interrogation, when programming of parameters or implant date/patient code, or when receiving "FAULT" results on a diagnostic test. Performing these

steps may restore communication.

If communication was possible before the IPG was inserted into the chest pocket, but is not possible with the IPG inside the pocket, verify that the Wireless Transmitter is within 3-feet of the IPG.

- Programming, interrogating, or completing diagnostic tests in an area with EMI may be difficult or impossible. The problem can usually be resolved by repositioning the patient, the Wireless Transmitter, or source of EMI.

9. SAFETY INFORMATION (from VNS Studies of Depression)

Except where noted otherwise, the safety information presented in this section derives from the Cyberonics' pivotal (D-02) study of VNS for depression. Although from a different indication (depression), and using a different device (Cyberonics' VNS Therapy device), the information from this study is included here because it is thought to be representative of possible adverse events expected with paired VNS Therapy for tinnitus using the Serenity System. The information provided on VNS Therapy for depression consists of both an acute and a long-term phase showing adverse event and safety data when treating people with chronic or recurrent treatment-resistant depression.

9.1. Device Performance

The VNS Therapy System performed according to its specifications. Most device issues were communication difficulties resolved by repositioning the Programming Interface or replacing the Programming Interface batteries. One high Lead impedance occurred requiring replacement; a Lead break due to fatigue at the electrode bifurcation was noted. Most device complaints were resolved on the day of initial complaint.

9.2. Adverse Events

The number (and percentage) of subjects reporting an adverse event during the 0-3 month period and during the 9-12 month period of the pivotal (D-02) study is depicted in Table 9.1 for the most commonly reported adverse events. Adverse events were coded using the COSTART 5 dictionary. Note that some subjects may have reported multiple events.

Table 9.1 D-02 Adverse Events

Adverse Event		0-3 Months (N=232)	9-12 Months (N=209)
Voice Alteration		135 (58.2%)	113 (54.1%)
Increased Cough		55 (23.7%)	13 (6.2%)
Neck Pain		38 (16.4%)	27 (12.9%)
Dyspnea		33 (14.2%)	34 (16.3%)
Dysphagia		31 (13.4%)	9 (4.3%)

Paresthesia		26 (11.2%)	9 (4.3%)
Laryngismus		23 (9.9%)	10 (4.8%)
Pharyngitis		14 (6.0%)	11 (5.3%)
Nausea		13 (5.6%)	4 (1.9%)
Pain		13 (5.6%)	13 (6.2%)
Headache		12 (5.2%)	8 (3.8%)
Insomnia		10 (4.3%)	2 (1.0%)
Palpitation		9 (3.9%)	6 (2.9%)
Chest Pain		9 (3.9%)	4 (1.9%)
Dyspepsia		8 (3.4%)	4 (1.9%)
Hypertonia		6 (2.6%)	10 (4.8%)
Hypesthesia		6 (2.6%)	2 (1.0%)
Anxiety		5 (2.2%)	6 (2.9%)
Ear Pain		5 (2.2%)	6 (2.9%)
Eructation		4 (1.7%)	0
Diarrhea		4 (1.7%)	2 (1.0%)
Dizziness		4 (1.7%)	3 (1.4%)
Incision Site Reaction		4 (1.7%)	2 (1.0%)
Asthma		4 (1.7%)	3 (1.4%)
Device site reaction		4 (1.7%)	0
Device Site Pain		4 (1.7%)	2 (1.0%)
Migraine Headache		4 (1.7%)	2 (1.0%)

It is important to note that subjects often had comorbid illnesses and almost all study subjects were also receiving antidepressant and other drugs that could have contributed to these events.

9.2.1. Discontinuation due to adverse events

By the time all continuing subjects in the pivotal (D-02) study had at least 1 year of VNS Therapy, 3% (8/235) of the subjects had discontinued VNS Therapy for an adverse event-related reason. The reasons for these eight discontinuations included one case each of suicide, implant-related infection necessitating device removal, hoarseness, lightheadedness, post-operative pain, chest and arm pain, sudden death (of unknown cause), and worsening depression (reported by the investigator as an adverse event rather than as lack of efficacy).

9.3. Serious Adverse Events (SAEs)

9.3.1. SAEs

The SAEs described in this section are based on investigator reports from the pivotal (D-02) study from study initiation through the data cutoff date for submission; the data cutoff date included the entire period of evaluation for subjects who did not complete 12 months of VNS Therapy and included a minimum of 12 months of evaluation during VNS Therapy for all subjects who continued the study for 12 months or longer.

During the pivotal (D-02) study, 12 SAEs were considered related to the implant procedure (wound infection, asystole, bradycardia, syncope, abnormal thinking, vocal cord paralysis, aspiration pneumonia, voice alteration, device site reaction [two reports], acute renal failure, and urinary retention). During the acute phase of the D-02 study, investigators did not report any

SAE to be related to stimulation. During the long-term phase of the D-02 study, eight SAEs were considered at least possibly related to stimulation (sudden death of unknown cause, syncope (two reports), dizziness, a manic depressive reaction in a subject with bipolar disorder, hemorrhage GI, paresthesia, and an incident of worsening depression. Table 9.2 displays all the SAEs reported during the D-02 study prior to the data cutoff date, regardless of relationship to implantation or stimulation.

Table 9.2 Serious Adverse Events (SAEs)

Event	**Acute (N=235)**		**Long Term (N=233)**	
	No. of Events VNS(N=119)/Sham(N=116)	No. of Subjects	No. of Events	No. of Subjects
Worsening Depression	5/7	11	62	31
Suicide Attempt	0	0	7	6
Syncope	0	0	4	3
Dehydration	1/1	2	1	1
Wound Infection	1/0	1	1	1
Cholecystitis	0/1	1	1	1
Gastro Disorder	0	0	2	2
Abnormal Thinking	1/0	1	1	1
Convulsion	0	0	2	2
Device Site Reaction	2/0	2	0	0
Pneumonia	0/1	1	0	0
Abdominal Pain	0	0	1	1
Accidental Injury	0	0	1	1
Chest Pain	0	0	1	1
Overdose	0	0	1	1
Peritonitis	0	0	1	1
Sudden Unexplained	0	0	1	1

Death				
Suicide	1/0	1	0	0
Surgical Procedure	1/0	1	0	0
Asystole	1/0	1	0	0
Bradycardia	1/0	1	0	0
Cholelithiasis	0	0	1	1
Constipation	0	0	1	1
Myasthenia	0/1	1	0	0
Confusion	1/0	1	0	0
Dizziness	0	0	1	1
Drug Dependence	0	0	1	1
Manic Depression	0	0	1	1
Somnolence	0	0	1	1
Vocal Cord Paralysis	0/1	1	0	0
Breast Cancer	0	0	1	1
Aspiration Pneumonia	1/0	1	0	0
Voice Alteration	0/1	1	0	0
Acute Renal Failure	0/1	1	0	0
Enlarged Uterine Fibroid	0	0	1	1
Urinary Retention	1/0	1	0	0

9.3.2. Deaths

Four deaths occurred during the pivotal (D-02) study: one after the subject had given consent, but before the subject was implanted; the second, a suicide; the third, a death of unknown cause; and the fourth, a subject who developed multi-organ failure.

9.3.3. Unanticipated adverse device effects

Two events in the pivotal (D-02) study met criteria for an unanticipated adverse device effect (UADE)—see *Glossary* for definition. Both these events were non-specific complications of surgery related to the implant procedure and occurred before stimulation began. One UADE was an episode of acute renal failure thought to be secondary to antibiotic administration, and the other was an episode of altered mental status thought to be due to perioperative narcotic administration.

9.4. Safety Considerations Specific to Depressed Patients

Two specific safety concerns in the use of all antidepressant therapies are the precipitation of manic or hypomanic episodes and the possible effect of antidepressant therapy on suicidal ideation and behavior.

9.4.1. Antidepressant treatments and manic or hypomanic reaction

Although patients with bipolar disorder experience manic episodes as the cardinal feature of their disorder, effective antidepressant therapies themselves can occasionally precipitate a manic or hypomanic episode. Antidepressant therapies can also occasionally precipitate a manic or hypomanic episode in patients without a prior history of mania who are being treated for a major depressive episode.

9.4.1.1. Manic reactions

In the pivotal (D-02) study, six hypomanic or manic reactions were identified according to DSM IV criteria or the Young Mania Rating Scale (YMRS). Five were observed in subjects with a known history of prior hypomanic or manic episodes. One of the events was considered serious and the subject was hospitalized.

9.4.2. Suicidal ideation, suicide attempts, suicide, and worsened depression

Suicidal ideation was analyzed by examining the HRSD24 Item 3 scores. At 12 months of VNS Therapy, 90% of the subjects in the pivotal (D-02) study showed either improvement (56%) or no change (34%) in their Item 3 scores. During the acute D-02 study, 2.6% of the sham subjects and 1.7% of the stimulation subjects increased their Item 3 score by 2 or more points, indicative of an increase in suicidal ideation. During the long-term D-02 phase, 2.8% of the subjects had an increase in their Item 3 score by at least 2 points at 12 months compared to baseline. In a non-randomized control group of subjects treated with standard antidepressant therapies without VNS Therapy (the D-04 study population), 1.9% of the subjects had an increase of at least 2 points. Based on the occurrence of any increase in Item 3 score from baseline to 12 months, 10% of the D-02 subjects had an increase compared to 11% of the D-04 population. Conversely, 27% of the D-02 subjects decreased their score by at least 2 points at 12 months compared to baseline, whereas only 9% of the D-04 subjects did.

Suicide attempts and completed suicides in the D-02 and D-04 studies indicate that suicide attempts in the VNS population (D-02) were similar to rates in a similarly depressed population that did not receive VNS Therapy (D-04), with 2.4% and 2.5% attempts per patient years, respectively.

In the acute phase of the D-02 study, there were 12 reports of worsening depression, 5 in the stimulation group (5 of 119 subjects) and 7 in the sham group (7 of 116 subjects). One of the treatment-group reports occurred prior to stimulation initiation. Following acute phase exit and during the long-term phase of stimulation, 62 events were reported in 31 subjects. The number of episodes of worsening depression per subject ranged from 1 to 6. Although specific rates of worsening depression (and other safety endpoints) were not collected during the D-04 study, "hospitalizations for psychiatric illness," which might be a reasonable surrogate for worsening depression, were recorded. The rate of this event was 0.237 events per patient-year in the D-04 group compared to 0.293 events of worsening depression per patient-year in the D-02 group.

9.5. Adverse Event (AE) Relationship to VNS Therapy and Duration of Events

The pivotal (D-02) study investigators determined whether an adverse event (AE) was possibly, probably, or definitely related to implantation of, or stimulation by, the VNS Therapy IPG and Lead.

9.5.1 AE related to implantation

Because all eligible study subjects in the pivotal (D-02) study were implanted with the VNS Therapy™ System device, no control was available to assess whether an adverse event was related to the surgery. Investigators, therefore, determined which adverse events were related to implantation. The events reported as related to implantation and occurring in at least 10% of the subjects who received VNS Therapy System implants in the pivotal (D-02) study were device site pain (23%), device site reaction (14%), incision pain (36%), dysphagia (11%), hypesthesia (11%), pharyngitis (13%), voice alteration (33%), and incision site reaction (29%).

9.5.2. Duration of implant-related adverse events

Many of the individual incidences of the most common implantation-related AEs resolved within 30 days. Hypesthesia (generally described as a localized numbness) and voice alteration, however, tended to be more persistent in some individuals. For example, in 17 of 24 reports of implantation-related hypesthesia, the event continued beyond 3 months. Hypesthesia would be an expected side effect of nerve injury during surgery. The persistence of voice alteration in some subjects is difficult to assess because it could represent surgical injury to the innervation of the larynx, but vagus nerve stimulation itself can cause voice alteration.

9.5.3. Stimulation-related adverse events

Among AEs judged by investigators to be stimulation-related in the D-02 study acute phase treatment group, seven events occurred at a frequency of 10% or greater: voice alteration (55%), cough increased (24%), dyspnea (19%), neck pain (16%), dysphagia (13%), laryngismus (11%), and paresthesia (10%).

9.6. Severity of Adverse Events

Investigators rated adverse events as mild, moderate, or severe according to the protocol definitions: mild events were transient and easily tolerated by the subject; moderate events caused discomfort and interrupted usual activities; severe events caused considerable interference with the subject's usual activities.

Most adverse events for the feasibility (D-01) study and pivotal (D-02) study were mild or moderate. Because the pivotal (D-02) study included a sham-control group, further analysis of severity rating was performed. After 3 months of treatment, there were 280 (43%) adverse events that were categorized as mild, 293 (45%) as moderate, and 73 (11%) as severe in the sham-control group. The active VNS Therapy group had 360 (47%) adverse events categorized

as mild, 349 (45%) as moderate, and 61 (8%) as severe.

9.7. VNS Therapy Continuation Rates

Of the 295 subjects implanted during both the feasibility (D-01) and pivotal studies (D-02), 270 subjects (92%) were still receiving VNS Therapy at 12 months and 242 subjects (82%) were still receiving VNS Therapy at 24 months. This is similar to the epilepsy continuation rates; 12- and 24-month continuation rates of 95% and 83% were seen, respectively, for the subjects implanted in the epilepsy preapproval trials.

10.0 SAFETY INFORMATION (from VNS Studies of Epilepsy)

The Cyberonics' VNS Therapy™ System for refractory epilepsy was implanted in 454 patients in five clinical studies involving 611 devices (some patients had IPG replacements). As of August 1996, total VNS Therapy exposure in these 454 patients was 901 device-years. Individual patient exposure averaged 24 months, with a range of eight days to 7.4 years.

A total of nine patients died during these five studies. One patient died from each of the following: thrombotic thrombocytopenic purpura, drowning, aspiration pneumonia, pneumonia, and renal failure associated with drug and alcohol ingestion. No cause of death was apparent for the other four deaths, which may be classified as sudden unexpected death in epilepsy (SUDEP). None of these deaths were attributed by the investigators to the VNS Therapy System.

10.1. Device Performance

The VNS Therapy System performed according to its specifications. Most device issues were communication difficulties resolved by repositioning the Programming Interface or replacing the Programming Interface batteries. One high Lead impedance occurred requiring replacement; a lead break due to fatigue at the electrode bifurcation was noted. Most device complaints were resolved on the day of initial complaint.

10.2. Adverse Events Observed in Studies

Included among the five clinical trials were two randomized, blinded, active control trials (Study E03 and E05), which involved 314 patients and the implantation of 413 devices, yielding a total VNS Therapy System exposure (inclusive of long-term follow up) of 591 device years. These trials form the basis of the rates of observed adverse events. Table 1 contains only a partial list of the more common and expected observed adverse events associated with the VNS Therapy System. A comprehensive listing of adverse events observed in studies is available by study from the Clinical Research department at MicroTransponder®.

Table 10.1 reports the adverse events from these studies during the randomized phase (approximately a 14-week observation period) and randomized phase plus long-term follow up (> 3 months) through August 1996. The most common side effect associated with stimulation was hoarseness (voice alteration), which, depending on device settings, can be severe to barely perceptible. Hoarseness is reported to occur primarily during the ON period of stimulation.

Table 10.1 Epilepsy Study Adverse Events

Randomized + Long-term Follow-up (>3 months) N=314 Patients, 591 Device Years					Randomized Phase, HIGH only, 152 Patients	
Adverse Events	No. of Patients[1]	% of Patients[2]	Number of Events	Events/Device-Year	Number of Patients	% of Patients
Serious AEs[3]						
Surgery Related	13	4.1	13	0.0222	N/A	N/A
Stimulation Related	4	1.2	4	0.007	1	0.7
Non-serious AEs						
Voice Alteration	156	50	720	1.228	91	60
Increased Coughing	129	41	456	0.772	57	38
Pharyngitis	84	27	182	0.308	36	24
Paresthesia	87	28	377	0.638	32	21
Dyspnea	55	18	55	0.093	32	21
Dyspepsia	36	12	98	0.166	22	15
Nausea	59	19	154	0.261	21	14
Laryngismus	10	3.2	30	0.051	9	5.9

1 – Number of patients reporting the event at least once.
2 – Percentage of patients reporting the event at least once.
3 – Included infection, nerve paralysis, hypesthesia, facial paresis, left vocal cord paralysis, left facial paralysis, left hemidiaphragm paralysis, left recurrent laryngeal nerve injury, urinary retention, and low-grade fever.

10.3 Potential AEs

Adverse events reported during clinical studies as statistically significant are listed below in alphabetical order:

Ataxia (Loss of the ability to coordinate muscular movement), Dyspepsia (indigestion), Dyspnea (difficulty breathing, shortness of breath), Hypesthesia (impaired sense of touch), Increased coughing, Infection, Insomnia (inability to sleep), Laryngismus (throat, larynx spasms), Muscle movement or twitching generally associated with stimulation, Nausea, Pain, Paresthesia (prickling of the skin), Pharyngitis (inflammation of the pharynx, throat), Voice alteration (hoarseness), Vomiting

Other potential adverse events possibly associated with surgery or stimulation include, but are not limited to, the following:

Aspiration (fluid in the lungs), Blood clotting, Choking sensation, Damage to nerves or vasculature in the surgical area, including the carotid artery and jugular vein, Device (IPG and/or Lead) migration or extrusion, Dizziness, Dysphagia (Difficulty Swallowing), Duodenal ulcer, gastric ulcer, Ear pain, Facial flushing, Facial paralysis, paresis, Foreign body reaction to implants, including possible tumor formation, Formation of fibrous tissue, pockets of fluid, Heart rate and rhythm changes, Hiccuping, Incision site pain, Irritability, Laryngeal irritation (sore, painful throat), Left hemidiaphragm paralysis, Left recurrent laryngeal nerve injury, Left vocal cord paralysis, Low-grade fever, Muscle pain, Neck pain,

Nerve injury, Painful or irregular stimulation, Seroma, Skin, tissue reaction, Stomach discomfort, Tinnitus (ringing in the ears), Tooth pain, Unusual scarring at the incision site, Urinary retention, Vagus nerve paralysis, Weight change, Worsening of asthma and bronchitis.

Although the pilot study of VNS for tinnitus did not show any worsened tinnitus, in the absence of any definitive data, it is possible that device use could worsen tinnitus, or that worsening of tinnitus could occur if the device stops.

11. BIBLIOGRAPHY

A bibliography of animal, clinical, and mechanism of action studies is available from MicroTransponder® on request.

12. GUIDELINES FOR PATIENT FOLLOW UP

During the first few weeks after implantation, the patient should be seen to confirm wound healing and proper Serenity System operation. During initial programming, the output current should be programmed to start at nominal parameters (0 mA) and then be slowly increased in 0.10 mA increments until the patient feels the stimulation at a comfortable level. The target output current is 0.8 mA, however patients who cannot tolerate this level should have the highest tolerable level below this amount. Patients who are receiving replacement IPGs should also be started at nominal parameters, with 0.1 mA-step increases to allow re- accommodation. After proper training, the patient may return frequently during the first week or two of device use, so that the physician/audiologist may review the patient's computer records and verify proper device use; retraining and further follow-up should occur if indicated.

At each patient visit, the IPG should be checked, using the appropriate version of the TAPS. After reprogramming and/or diagnostics testing, data can be printed out and filed. These data can be used for comparison with a patient's own records to evaluate the Paired VNS Therapy Serenity System, to confirm proper Paired VNS Therapy Serenity System functioning, and to assess the need for reprogramming. However, all information is also kept in the TAPS database, and can be reviewed within the TAPS program.

Paired VNS Therapy Serenity System treatment should not be uncomfortable, nor should it cause bothersome side effects. Patients should be observed for the first stimulation period or after any stimulation setting adjustment to make certain that they are comfortable with the programmed stimulation.

The subsequent follow-up schedule and the nature of each examination should be determined by the physician on the basis of patient response to and tolerance of the implant. In all other respects, follow-ups should be performed in accordance with the standard medical practice for patients with tinnitus.

In the event intolerable adverse events are reported, physicians should always try reducing the output current (mA) as a means of eliminating or reducing the severity of an event. Additionally, physicians should instruct patients or caregivers on the application of the Magnet to turn the IPG off (output current 0 mA) if an adverse event becomes intolerable.

MicroTransponder strongly encourages physicians **to keep all medications stable for the first**

three months of stimulation before attempting to reduce or change a patient's medication.

Paired VNS Therapy System treatment should not be uncomfortable, nor should it cause bothersome side effects. Patients should be instructed and shown how to place the magnet over their device in order to stop stimulation. It should be verified that the patient can do this during the first session when stimulation is started; it should also be verified that the patient is given a magnet to take home with them for this use.

13. PATIENT COUNSELING INFORMATION

In the unlikely event of uncomfortable adverse events, continuous stimulation, or other malfunction, the patient must be advised to hold or tape the Magnet directly over the implanted IPG to prevent additional stimulation. If patients or caregivers find this procedure necessary, they should immediately notify the patient's physician.

Patients should also be instructed that they should not manipulate the device or lead through their skin, as this could damage the device. Pulling on the lead may move the electrode on the nerve, and cause possible nerve damage. Additionally, patients should not pick at their surgical scars.

14. MECHANISM OF ACTION

The precise mechanism(s) by which Paired VNS Therapy exerts its tinnitus action is unknown.

Previous animal studies of VNS enhanced learning demonstrated the principle that one can open a window of enhanced learning by VNS. The use of VNS therapy is based on animal and clinical observations that VNS can indeed improve learning and memory in normal animals and humans (Clark et al., 1995). Importantly, the VNS parameters that have been found to be most effective in rats are also the most effective parameters to use in humans (Clark et al., 1999). VNS has also been shown to improve motor performance in rat models of percussion brain injury (Smith et al., 2005; Clough et al., 2007).

These studies did not pair the stimulation specifically with desired learning tasks. The current approach takes advantage of this window by specifically pairing tones with very short periods (such as 0.5 seconds) of VNS.

It is generally accepted that tinnitus arises from hyperactivity of neurons in the central auditory system subsequent to central or peripheral auditory system damage (Norena and Eggermont, 2003; Rajan and Irvine, 1998; Seki and Eggermont, 2003; Kaltenbach et al., 2007; Bauer et al., 2008). Human and animal studies have shown that neurons deprived of auditory input begin to respond to the same frequencies as neighboring neurons that receive input from undamaged parts of the cochlear (Rajan et al., 1993; Dietrich et al., 2001; Syka, 2002). This change in neuronal behavior results in a dramatic increase in the number of neurons that respond to a narrow range of frequencies. When the number of neurons that respond to a given frequency increases beyond some critical level, synchronous spontaneous activity sets in, which is thought to account for tinnitus (Eggermont and Roberts, 2004; Muhlnickel et al., 1998; Møller, 2006).

Current treatments for tinnitus are not very effective and no current treatment has been shown to reverse the pathological plasticity that gives rise to tinnitus (Flor et al., 2004; Tyler et al., 1984; Searchfield et al., 2007; Szczepaniak and Møller, 1995; Darlington and Smith, 2007; Tyler et al., 2007; Miyamoto and Bichey, 2003; Steenerson and Cronin, 2003; Kleinjung et al., 2007). A treatment that reversed the underlying pathology would be expected to be very effective. Our studies suggest that targeted manipulation of neural plasticity can reverse the pathological plasticity and decrease the symptoms of tinnitus (Engineer et al., 2011). Our approach is to greatly speed up the rehabilitation process by using VNS to briefly put the brain into a receptive state during which associated stimuli can drive therapeutic neural plasticity.

15. PHYSICIAN TRAINING / INFORMATION

All Paired VNS Therapy Serenity System programming should be performed by or under the supervision of a physician familiar with the use and operation of the Programming Software.

Training Materials
Physicians implanting the Paired VNS Therapy Serenity System should be thoroughly familiar with all associated training materials, including:
o Product labeling for the IPG, Lead, and accessories, including physician and patient manuals and directions for use
o *"Implant Guide for the Paired VNS Therapy Serenity System"* training manual and other brochures

16. PAIRED VNS THERAPY SERENITY SYSTEM DEVICES

16.1 IPG Package Contents

The IPG package contains the following:
o 1 MicroTransponder ® Paired VNS Therapy Serenity Implantable Pulse Generator (IPG)
o 1 hex screwdriver
o Documentation

- **Note**: Ensure that at least one back-up IPG is available before starting the procedure.

16.2 Lead Package Contents

The Lead package contains the following:

- 1 VNS Therapy Lead
- 4 (or more) silicone tie-downs
- Documentation

Note: Ensure that at least one back-up Lead is available before starting the procedure.

16.3 Other MicroTransponder Products

- 1 Paired VNS Therapy Serenity System Wireless Transmitter (non-sterile)
- 1 Laptop preloaded with TAPS.
- MTI-approved Headphones

16.4 Surgical Materials

The following is a list of additional materials typically used during the

VNS Therapy implantation procedure:

- Sterile Laser Arm Bag or equivalent (optional, Programming System typical distance of 3 meters may preclude need for the sterile bag)
- Vessel loops and/or silicone sheet for manipulation of the vagus nerve (suggested but optional)
- Blunt dissection tool (such as blunt forceps, blunt scissors – surgeons decision)
- Sterile tube for ease of moving the connector end of the leads from the neck incision to the chest incision (optional; surgeon may prefer other tool or method)

16.5 To Open the Sterile Package

Before the package is opened, it should be examined carefully for evidence of damage or compromised sterility. If the outer or inner package has been opened or damaged, MicroTransponder cannot guarantee sterility of the IPG or Lead, and it should not be used if the sterile package has been opened or damaged. An opened or damaged product should be returned to MicroTransponder.

To open the package, do the following:

1. Grasp the tab, and peel back the outer cover.

2. Observing sterile technique, lift out the sterile inner tray.

3. Grasp the inner tray's tab, and carefully peel off the inner cover to expose the contents without dropping them.

- The sterile Lead package should only be opened after exposing the vagus nerve and selecting the MicroTransponder Lead that best fits.

- Tie downs could potentially fall out of package, carefully remove the lead to maintain control of these.

- Caution: Do not use the package if it has been exposed to extreme temperatures or if there is any indication of external damage or damage to the package seal. Instead, return it unopened to MicroTransponder.

17. RECOMMENDATIONS FOR IMPLANTATION

In general, implantation of the Paired VNS Therapy Serenity System is similar to accepted practice for implantation of other implantable devices. The most novel portion of the surgery is the placement of the electrodes and the subcutaneous routing of the Lead connector and body over the clavicle. Although the surgical approach and techniques will vary with the preference of the implanting physician this part of the physician's manual provides recommendations for implantation, along with a detailed description of the order of placement of the helical electrodes and the anchor tether and other essential steps.

Critical to the long-term success of the implant are proper techniques both for the attachment of the electrodes and the anchor tether to the left vagus nerve, and for the provision of adequate strain relief below and above the sternocleidomastoid muscle.

It is recommended that the Lead body be coiled and placed in the chest pocket underneath or to the side of the IPG; placement above the generator may cause damage to the lead body during generator replacement, and is therefore not recommended.

Adequate exposure of the vagus nerve (>3 cm) facilitates placement of the electrodes on the nerve. Stretching the nerve or allowing it to dry during implantation may result in temporary swelling of the nerve. Constriction of the nerve or other nerve damage may result in vocal cord dysfunction.

After the electrodes are placed on the nerve, the electrode-nerve interface impedance is tested by connecting the Lead directly to the IPG and performing a Lead Impedance Check.

17.1. Check the device and Input Patient Data

To ensure proper device communication, using TAPS, check the IPG by communicating with it while still in the sterile package. [See the Paired VNS Therapy Serenity Non-Implantable Physician's Manual for a detailed explanation or the Programming Software instruction card (handheld) for a quick reference.]

Using TAPS, input the patient identification into the IPG. [See the Paired VNS Therapy Serenity Non-Implantable Physician's Manual for a detailed explanation.]

17.2. Procedure Overview

The following overview summarizes the recommended sequence for implanting the Lead:

1. Expose the left carotid sheath and left vagus nerve.

2. Create a pocket in the chest for the IPG.

3. Tunnel the Lead connector and body subcutaneously from the neck to the IPG pocket in the chest.

4. Attach the electrodes and anchor tether to the left vagus nerve.

5. Secure the Lead parallel to the nerve using the provided tie-downs, do not suture around or on the lead body itself as it may damage it.

6. Form the strain relief bend and strain relief loop and secure using the provided tie-downs.

7. Attach the Lead connector to the IPG.

8. Visually verify that the connector pin is fully inserted, tighten the setscrews.

9. Perform Lead Impedance Check

10. Place the IPG in the chest pocket, with the extra coiled lead body underneath or to the side of the IPG, not above it.

11. Secure the IPG to fascia; do not place sutures directly around or on the Lead.

12. Perform the second Lead Impedance Check.

13. Check the IPG to verify current is 0.0 mA.

14. Irrigate the incision site with bacitracin or other solution.

15. Close the incisions.

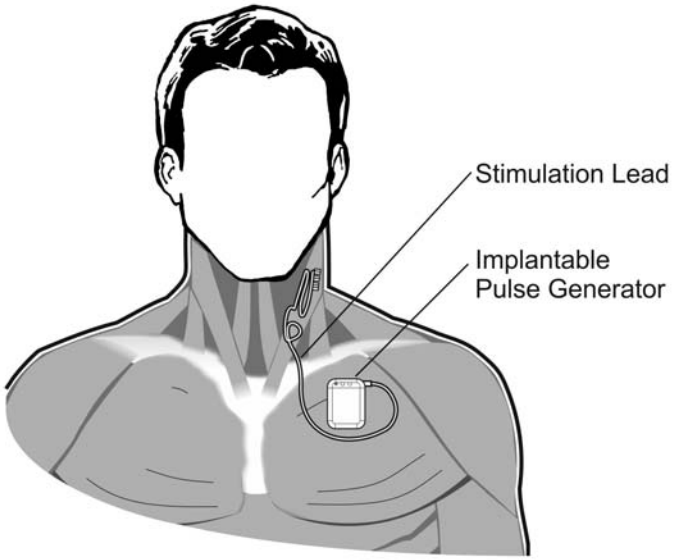
17.3 Prepare for Surgery

The surgeon should verify that the IPG and lead are compatible. MicroTransponder recommends that the patient be given antibiotics preoperatively and that both incision sites be irrigated frequently with generous amounts of bacitracin or equivalent solution prior to closure. (These incisions should be closed with cosmetic closure techniques to minimize scarring.) Also, antibiotics should be administered postoperatively at the discretion of the physician.

17.4 Lead and Pocket Location

The IPG is usually implanted just below the clavicle in a subcutaneous pocket in the left upper chest. Suggested placement for the Lead is the area of the left vagus nerve half-way between the clavicle and the mastoid process, with the Lead subcutaneously tunneled between the incision site in the neck and the pocket formed in the upper chest (see Figure 17.1). It is recommended that both the Lead body and the IPG be positioned on the left side of the body.

Figure 17.1 Placement of IPG and Lead



17.5 Begin the Procedure

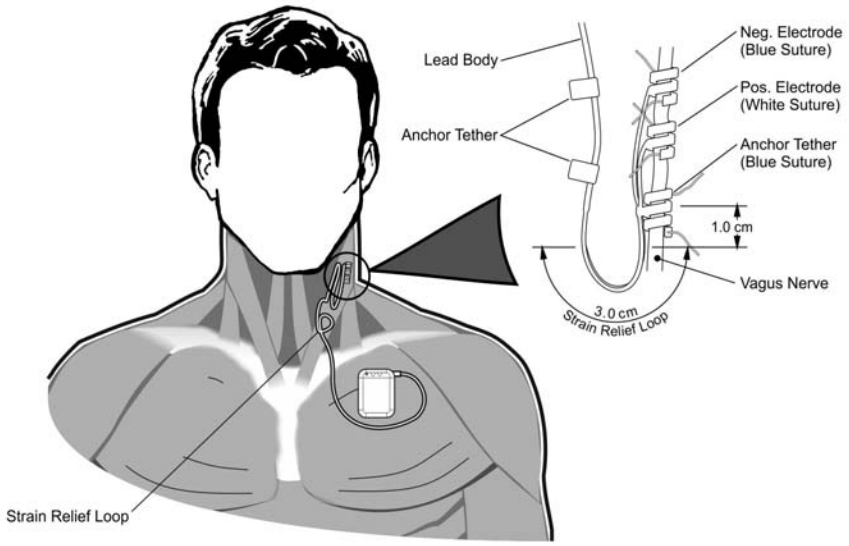
While the specific surgical approach and techniques for implanting the Lead will vary with the physician performing the implant, the following detailed instructions are provided for guidance:

1. After administering appropriate anesthesia to the patient, expose the left carotid sheath as it extends along the anterior border of the sternocleidomastoid muscle.

2. Locate and expose *at least 3 centimeters (1.18 inches)* of the left vagus nerve. The recommended stimulation site is a 3-cm section of the vagus nerve, approximately half-way up between the clavicle and the mastoid process, where it is clear of branches (below where the superior and inferior cervical cardiac branches separate from the vagus nerve—see Figure 17.2

and Figure 17.4). The nerve usually lies in a posterior groove between the carotid artery and internal jugular vein.

Figure 17.2 Electrode Placement



3. Create a subcutaneous pocket in the chest below the clavicle for the IPG.

17.6 Implant the lead

Caution: Do not expose the Lead to dust or other similar particulates, because its silicone insulation can attract particulate matter.

Caution: Do not soak the Lead in saline or similar solution before implanting it, because this may cause the insulated portions of the connector pin to swell and become difficult to insert into the IPG.

17.7 Make a tunnel and pass the Lead

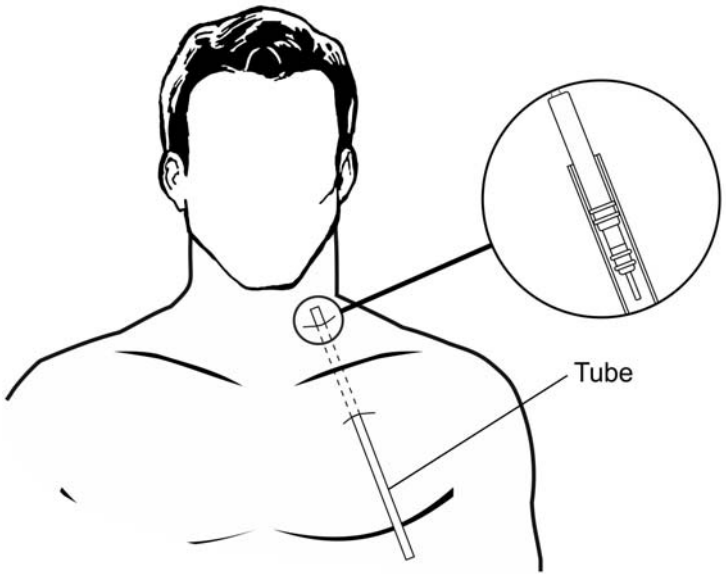
The surgeon should use blunt dissection to create a subcutaneous tunnel or pathway from the neck incision to the chest incision. The lead connector end can then be passed from the neck to chest incision using a sterile bag or sterile tube. Although the connector can be passed after the electrode has been placed on the nerve and secured, MicroTransponder recommends that the connector be passed first, in order to avoid the possibility of accidentally putting tension on the electrodes or nerve while passing the lead connectors.

Caution: To maximize system performance and minimize possible mechanical damage to the nerve or Lead, pay careful attention to Lead routing, Lead stabilization, and electrode placement.

Caution: Never route the Lead through muscle.
Caution: Never suture the Lead or Lead body to muscle tissue.
Caution: Always use the tie-downs.
Caution: Do not place sutures directly on the Lead body. Doing so may result in insulation damage or wire failure, causing premature failure of the Lead.

To pass the tube, do the following:

Figure 17.3 Position of Tube and Lead Connector(s) (Example is shown with a tube, although a sterile bag could be used instead).



1. With the tube or bag in place between the two incisions, carefully insert the Lead connector(s) inside the end of the tube or bag at the neck incision.
2. Carefully pull the tube or bag and Lead connector(s), from the neck incision end until the lead connector(s) completely exit(s) the chest incision.
3. Remove the Lead connector(s) from the sleeve, leaving the electrode array at the neck incision site.
4. Discard the tube or bag after use.

17.8 Place the Electrodes

It is very important that the surgeon implanting the Paired VNS Therapy Serenity System be familiar with vagus nerve anatomy, particularly the cardiac branches. The Lead electrodes must not be placed on either the superior or the inferior cervical cardiac branches. **Place the Lead below where the superior and inferior cardiac branches separate from the vagus nerve.** Stimulation of either of these two branches during the Lead Impedance Check may cause **bradycardia and/or asystole.** Careful dissection laterally on the vagus nerve should aid the

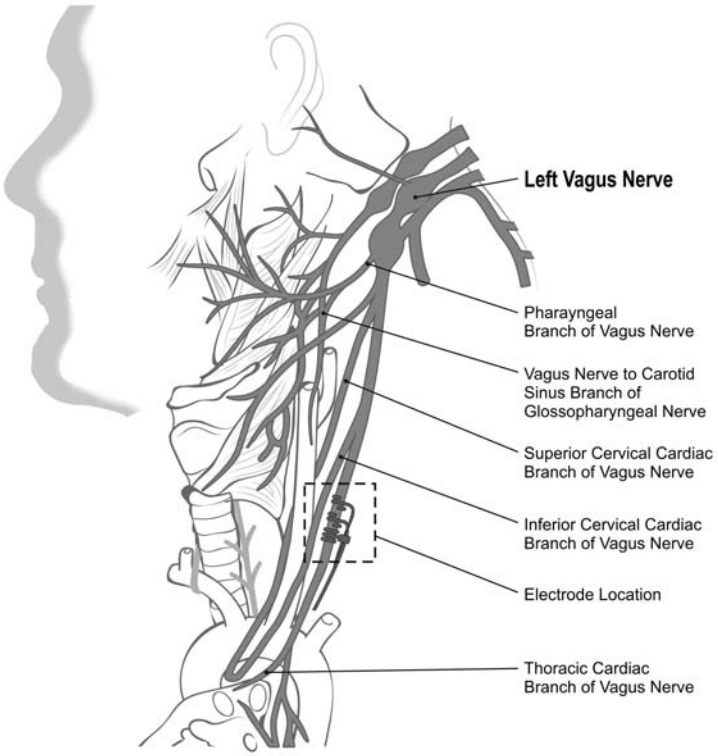
physician in determining proper electrode placement. In most but not all patients, the main vagus nerve is the largest of the three nerves. Figure 17.4 shows the correct anatomical placement of the helices.

Caution: Attachment of Lead electrodes must not involve the superior cervical cardiac branch or the inferior cervical cardiac branch of the vagus nerve. Place the electrodes *below* where these two branches separate from the vagus nerve.

Caution: When flushing the nerve and neck incision site, be careful not to use a cold solution. Solutions not at body temperature may cause temporary bradycardia or other cardiac effects.

Caution: Excessive manipulation of the vagus nerve during placement of the Lead can result in noticeable post-operative hoarseness. Under most circumstances, this condition will resolve without additional medical intervention within three to four weeks, depending on the degree of stress applied to the nerve during surgery. MicroTransponder does not recommend that stimulation treatment be initiated until this condition has resolved, since it could aggravate the condition.

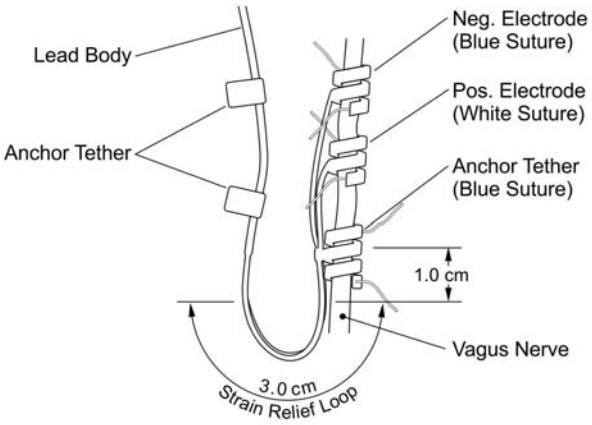
Figure 17.4 Vagus Nerve Anatomy and Placement of the Lead



The helical electrodes and anchor tether are coiled around the nerve, beginning with the electrode that is farthest from the Lead bifurcation (with a blue suture embedded in the helical material). This electrode should be nearest (proximal to) the patient's head.

Depending on the surgeon's preference, the helices can alternately be placed by putting the anchor tether on first (distal to head), next placing the electrode closest to the Lead bifurcation (with white suture), and then placing the electrode farthest from the Lead bifurcation (with blue suture). The polarity of stimulation does not change (see Figure 17.5). The following instructions show placement beginning with the electrode farthest from the Lead bifurcation (blue suture).

Figure 17.5 Electrode Polarity



The helical electrodes can be placed on the nerve as described below. As an alternative, each helical electrode can be placed underneath the nerve before it is spread. A silicone sheet may be useful to separate the nerve from tissue during the procedure.

1. Place the first helical electrode (negative electrode with the green suture, which will be the closest to the head) in the following manner:

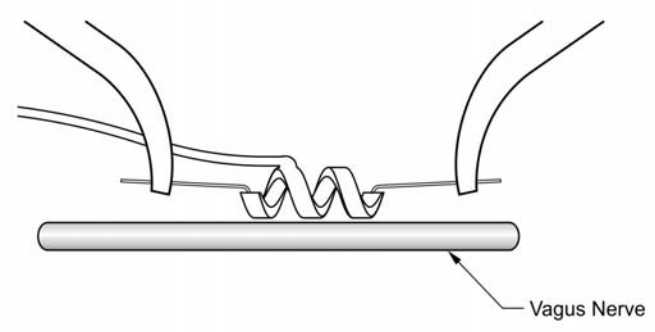
a. With forceps, gently pull each end of the helix, using the attached sutures to spread the helix (see Figure 17.6).

Caution: The suture may become dislodged from the helical electrode if product labeling is not followed, i.e., grasping the elastomer and suture to manipulate the helical electrode onto the nerve.

Caution: The Lead and helical electrodes are very delicate. Take care not to stretch, pinch, or crush the helical electrodes when using forceps. Take care to not over-straighten or stretch the

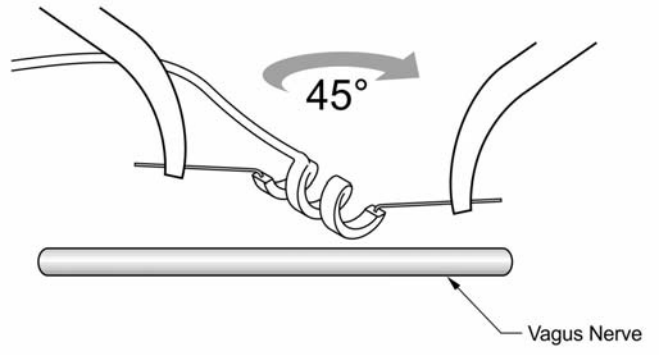
helices when coiling them around the nerve, because doing so may damage the electrode or tether. Use soft rubber vessel loops or equivalent to raise, or lift the nerve, if necessary.

Figure 17.6 Spread the Helical Electrode



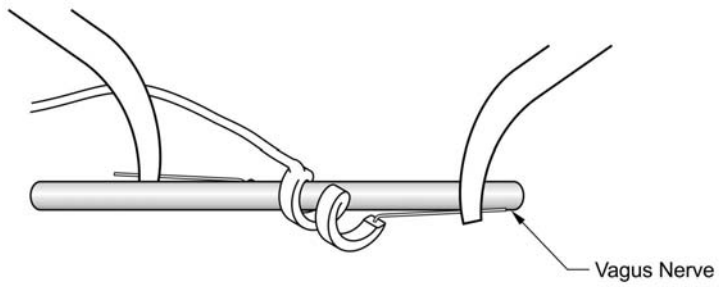
b. Starting with the opened helical electrode spread directly above and parallel to the exposed nerve, turn the helical electrode clockwise at a 45 degree angle to the nerve (see Figure 17.7).

Fig. 17.7 Turn the Helical Electrode



c. Place the turn of the helical electrode where the Lead wire connects to the helical electrode (the section with the metal ribbon) onto the nerve (see Figure 17.8).

Fig. 17.8 Placement of the Turn



d. Pass the *distal* suture portion of the helical electrode under the nerve and back around so that it encircles the nerve (see Figure 17.9 and Figure 17.10).

Figure 17.9 Starting to Wrap the Electrode

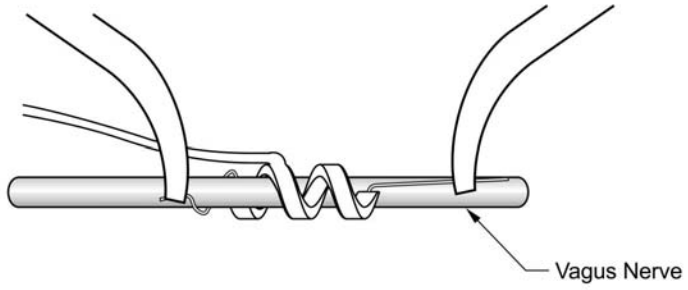
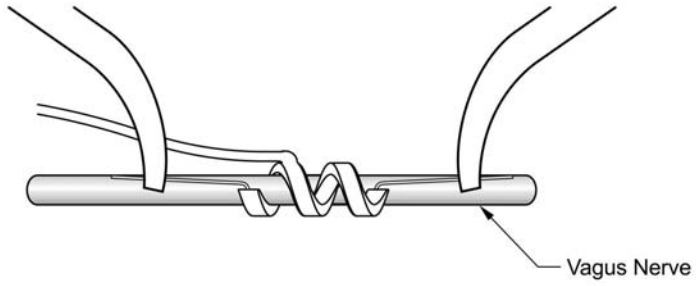
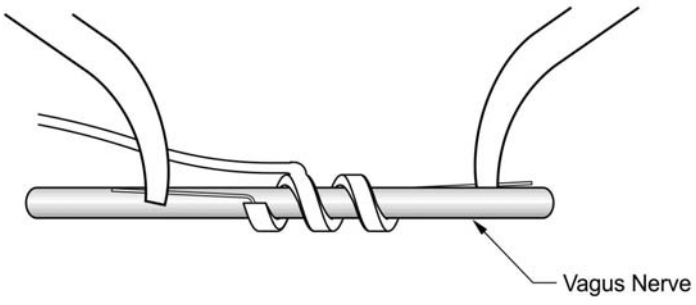


Figure 17.10 Partial Wrap of the Electrode around Nerve



e. Pass the *proximal* suture portion of the helical electrode under the nerve and back around so that it encircles the nerve (see Figure 17.11).

Figure 17.11 Placement of the Proximal Portion of the Helical Electrode

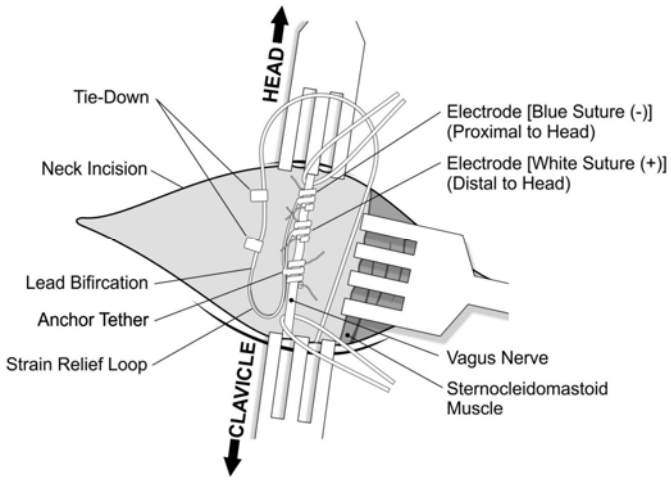


2. Repeat steps 1a through 1e for the middle helical electrode (the positive electrode with the white suture).

3. Next, place the third helical electrode (with blue suture but without any electrode portion) around the nerve, following the same general steps as for the other two helices.

4. After all three helices have been coiled around the nerve, verify that the Lead body exits each helical electrode in the same direction and that the Lead bodies are aligned parallel to each other and to the nerve. The correct placement of the two helical electrodes and anchor tether is shown in Figure 17.12.

Figure 17.12 Placement of Electrodes and Anchor Tether



Caution: Sutures that are part of the Lead (embedded in the helices of the electrodes and anchor tether) are meant to assist in helical electrode placement around the vagus nerve. These sutures should not be tied to each other or around the nerve, since this may cause nerve damage.

Caution: Proper **techniques** for attaching the electrodes and the anchor tether to the left vagus nerve are critical to the long-term success of the implant

NOTE: Provide Proper Strain Relief

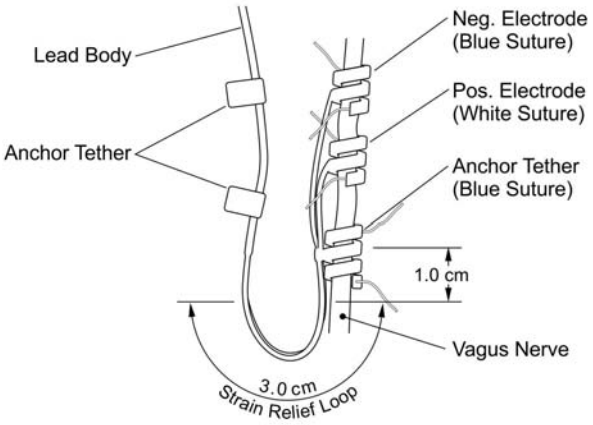
After attaching the two electrodes and the anchor tether, form a strain relief bend and a strain relief loop in the Lead to provide adequate slack and allow for neck movement.

1. To form the *strain relief bend* [see Figure 17. 12 above], do the following:
   a. Form the Lead body into a 3-cm (1.18 in) strain relief bend with at least an additional 1 cm (.39 in) of Lead routed parallel to the nerve. The parallel portion can be placed in a pocket formed adjacent to the anchor tether.
   b. Loosely attach the 3-cm strain relief bend to the adjacent fascia with tie-downs and then route the Lead over the muscle. The first tie-down should be positioned laterally to the anchor tether (see Figure 17.13). Five tie-downs are provided in the Lead package.

Caution: Proper techniques for providing adequate strain relief below and above the sternocleidomastoid muscle are critical to the long-term success of the implant.

Caution: The Lead and Lead **wire may fracture** if the recommended strain relief is not provided.

Figure 17.13 Use of Tie-Downs in Electrode Placement



Caution: Sutures that are part of the Lead coil are meant to assist in electrode placement around the left vagus nerve. These sutures should *not* be tied to each other since this may cause nerve damage.

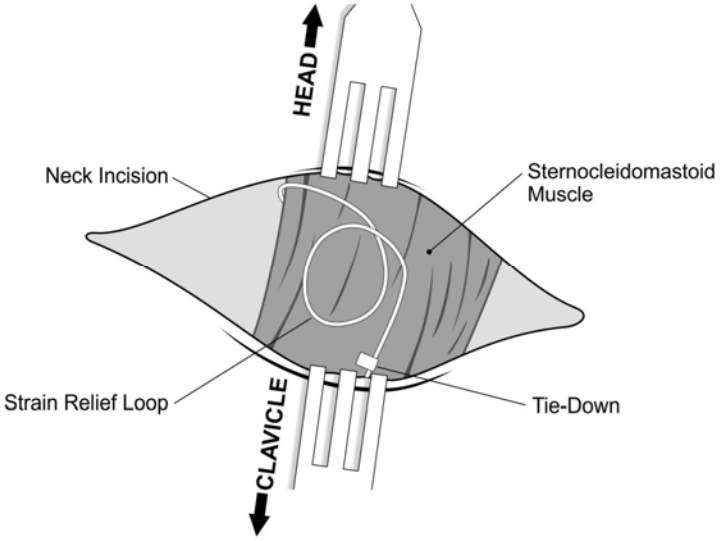
Caution: The Lead and its electrodes are very delicate, and care should be taken not to over stretch or crush the helices.

2. To form the *strain relief loop* (see Figure 17.14), do the following above the sternocleidomastoid muscle:

a. In the neck, form the Lead into a large subcutaneous loop.

b. Loosely attach it to fascia with a tie-down before routing the Lead over the clavicle. This strain relief loop should be large enough to provide several inches/centimeters of Lead extension when the neck is turned to its maximum stretched positions.

Figure 17.14 Strain Relief Loop



Caution: Leave enough extra Lead on both sides of the clavicle to prevent the tension over the clavicle from damaging the Lead.

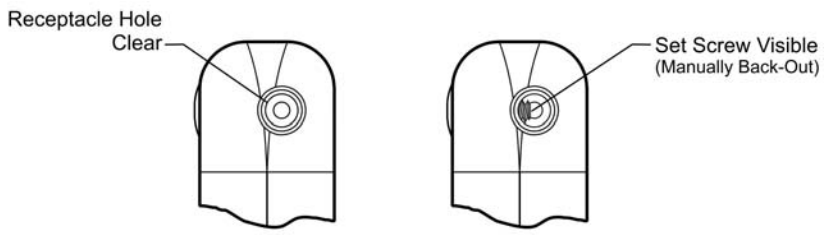
Caution: Placing the sutures directly on the Lead body may result in insulation damage or wire failure, causing premature failure of the Lead. Use only supplied tie-downs to secure the Lead.

17.9 Connect the Lead

To connect the Lead directly to the IPG:

1. Look inside the IPG Lead receptacle(s) to verify that no obstruction exists and that the setscrew(s) has been backed out adequately to allow full insertion of the connector pin(s). Avoid backing the setscrew(s) out further than needed for Lead insertion (see Figure 17.15). The figure is intended to show the contrast between a blocked and a clear receptacle, and applies to single or dual pin headers.

Figure 17.15 IPG Receptacle and Setscrew



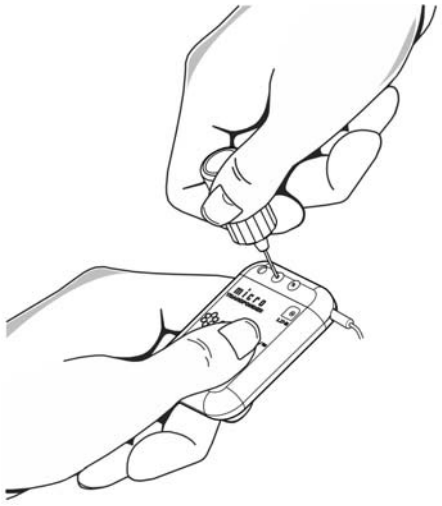
2. Keep the hex screwdriver perpendicular to the IPG while inserting the hex screwdriver through the center of the setscrew plug to vent back pressure accumulated during Lead insertion.

Caution: In the steps below, **always push down on the hex screwdriver while turning it clockwise until it clicks** (begins ratcheting) while ensuring that it is fully inserted in the setscrew. Also, the hex screwdriver must be inserted into the center of the silicone rubber setscrew plug and kept perpendicular to the IPG to avoid stripping the setscrew and/or dislodging the setscrew plug.

Caution: When using the hex screwdriver, grasp it by the handle only, as shown in Figure 17.16. Do not grasp any other portion of the hex screwdriver during use, as this may affect its proper function. Touching the metal shaft while the hex screwdriver is engaged with the setscrew can conduct an electrostatic discharge into the device circuitry and may damage the IPG.

Caution: Do not use electrosurgical equipment after the IPG has been introduced to the sterile field. Exposure to this equipment may damage the IPG.

Figure 17.16 Hex Screwdriver Position



3 When using the **single-receptacle MicroTransponder** IPG and MicroTransponder single-pin Lead, insert the Lead connector pin fully into the IPG header (Fig. 17.17, three images). To allow escape of the back pressure created by insertion, leave the tip of the hex screwdriver in the slit in the setscrew plug.

Caution: To avoid backing the setscrew out completely when loosening during surgery, use no more than two counterclockwise turns

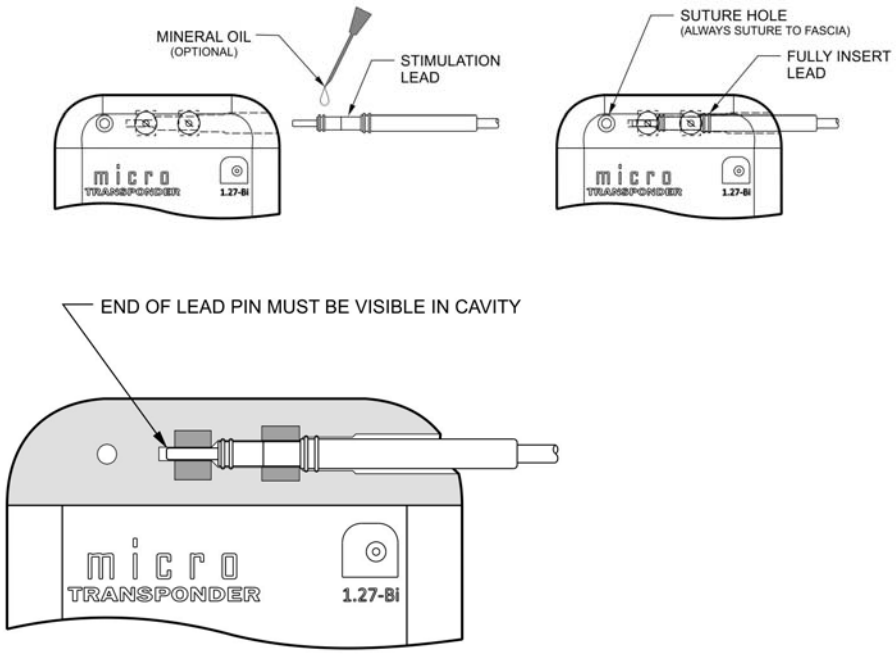


Figure 17.17 Lead Connector(s) Prior to Insertion and Fully Inserted

4. With the hex screwdriver still inserted through the setscrew plug, verify that the connector pin is fully inserted. The pin should be visible in the area at the back end of the setscrew connector block. If it is not, remove the pin. To loosen the setscrew, engage the hex screwdriver into the setscrew, and turn it counterclockwise until the connector pin can be fully inserted. Avoid backing the setscrew out further than needed for Lead insertion.

5. After verifying that the connector pin has been fully inserted, tighten the setscrew by engaging it with the hex screwdriver and turning the hex screwdriver clockwise until it begins to click. Always push in on the hex screwdriver while turning it to ensure that the hex screwdriver is fully inserted in the setscrew.

Caution: It is important to do the following:

- Ensure that the Lead receptacle(s) is clean and free of obstruction.
- Carefully insert the Lead connector pin(s) into the Lead receptacle(s) without bending the Lead connector(s).
- Visually inspect that the connector pin(s) is clean and completely inserted.
- **Electrical connection to the IPG is not established until the setscrew is completely tightened with the hex screwdriver.** Failure to make a good connection can result in HIGH impedance during a Lead Impedance Check or erratic stimulation at varying intensity due to rapid, unpredictable changes in Lead impedance, which is expected to adversely affect device effectiveness and may have serious safety consequences.

- Gently grasp and pull on Lead connector boot (the thick section of the Lead) to verify the Lead is properly secured inside the Lead receptacle. Do not pull on Lead body (thin section) or use excessive pull force, because doing so may cause Lead damage.

17.10 Test the Serenity System

The Lead Impedance Check, which should be conducted first, is performed with the Lead and the IPG connected. Thus, if the Lead Impedance Check is successful, both components are working properly. However, if the Lead Impedance Check fails, either of the two components could be defective, or there may not be a good electrical connection between the IPG and the Lead connector pin(s). If a defective component is suspected in the IPG, disconnect the Lead, reconnect to another IPG, and then retest the system again using the Lead Impedance Check.

Caution: During the intraoperative Lead Impedance Check, infrequent incidents of bradycardia and/or asystole may occur. If asystole, severe bradycardia (heart rate <40 bpm), or a clinically significant change in heart rate is encountered during a Lead Impedance Check or during initiation of stimulation, physicians should be prepared to follow guidelines consistent with Advanced Cardiac Life Support (ACLS).

Additionally, postoperative bradycardia can occur among patients with certain underlying cardiac arrhythmias. If a patient has experienced asystole, severe bradycardia (heart rate <40 bpm), or a clinically significant change in heart rate during a Lead Impedance Check at the time of initial device implantation, the patient should be placed on a cardiac monitor during initiation of stimulation.

The safety of this therapy has not been systematically established for patients experiencing bradycardia or asystole during VNS Therapy System implantation.

18. INFORMATION AND SUPPORT

If there are questions regarding use of the Paired VNS Therapy Serenity System or any of its accessories, contact MicroTransponder:

MicroTransponder, Inc.

2802 Flintrock Trace, Suite 226
Austin, TX 78738

Phone: 512-371-4160
Fax: 888-822-5206 or 214-299-8660.

For 24-hour Clinical and Technical Support, call:

Telephone: 512-371-4160

Internet
www.microtransponder.com

19. GLOSSARY

AE (adverse event) - Any symptom, sign, illness, or experience that develops or worsens in severity and/or frequency during the course of the study (i.e., any changes from baseline)

D-01, D-02, D-04 clinical studies *(depression studies)-* Clinical trials conducted by Cyberonics. The D-01 and D-02 studies used VNS Therapy in patients with chronic or recurrent treatment-resistant depression. The D-04 study was a long-term, prospective, observational study of patients with chronic or recurrent treatment-resistant depression who were being treated with standard antidepressant treatments, but not VNS Therapy.

Electrode – The mechanical and electrical interface of the Paired VNS Therapy Serenity System to the vagus nerve. The electrode is part of the Lead.

EMI - Electromagnetic interference

EOL – End of Life – The TAPS software displays an EOL indicator when there is less than 5% of the battery remaining. EOL indicates that the IPG will cease to function in the very near future.

ERI – Elective Replacement Indicator – The TAPS software displays an ERI indicator when there is less than 15% of the battery remaining. This is a warning to the user that the IPG is quickly approaching EOL and may stop functioning in the near future.

FDA – US Food and Drug Administration

High Lead impedance - Resistance to the flow of output current produced by the IPG, caused by any of the following: possible fibrosis between the nerve and electrode, dry nerve (during surgery), Lead fracture, Lead disconnection from the Pulse Generator, or high battery impedance approaching end of service.

IPG – Implantable Pulse Generator – The stimulator portion of the Paired VNS Therapy Serenity system, typically implanted in the chest below the clavicle. The IPG provides stimulation to the vagus nerve through a connected Lead and Lead electrode.

Lead - An implantable part of the VNS Therapy System; delivers electrical impulses from the IPG to the electrodes attached to the vagus nerve; contains flexible conductive wires within a bio-compatible insulating sheath.

LIMIT output current - Output current other than that which was programmed; not a sole indicator of a device malfunction.

Low Lead impedance - Lower than expected resistance to the flow of output current produced by the IPG potentially caused by a short-circuit condition resulting from a break within the Lead body or connector boot.

MRI - Magnetic resonance imaging

MR Unsafe - An item that poses hazards in all MRI environments

Output current - Amount of electrical current delivered in a single pulse of a stimulation, measured in mA.

Paired VNS Therapy® - VNS delivered by MicroTransponder's Paired VNS Therapy Serenity System. The Serenity system pairs VNS with tone therapy.

Pulse width - Duration of a single pulse within a stimulation, measured in µsec.

SAE (serious adverse event) - Any adverse event that resulted in any of the following outcomes: death, a life threatening adverse experience, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or any medical intervention that prevents one of the above.

Serenity – Trade name of the Paired VNS for tinnitus system

Signal frequency - Repetition rate of pulses in a stimulation; measured in number of pulses per second (Hz).

Signal OFF time - Interval between stimulations when there is no stimulation; measured in minutes.

Signal ON time - Length of time the programmed output current is delivered (not including ramp-up and ramp-down times); measured in seconds.

TAPS (tinnitus application & programming software) – Software that allows the physician or healthcare worker to set the VNS setting and initiate stimulation paired with tones.

UADE (unanticipated adverse device effect) - Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application); also, any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.

Vagus nerve - Either of the pair of tenth cranial nerves arising from the medulla and supplying mainly the viscera, especially with autonomic sensory and motor fibers

VNS - Vagus Nerve Stimulation

VNS Therapy® - VNS delivered by Cyberonics' VNS Therapy System. Paired VNS Therapy is delivered by the MicroTransponder Serenity System.

WT – Wireless Transmitter – A radio frequency device that connects via a USB plug to the computers USB port and provides communication with the IPG, used in conjunction with TAPS.