Depression Patient's Manual

For Vagus Nerve Stimulation with the VNS Therapy™ System

June 2005

This Patient's Manual is a supplement to the physician's manuals. It is not meant to take the place of advice from your doctor. For a complete discussion of indications for use, contraindications, precautions, warnings, and potential side effects, please talk to your doctor.

Please talk with your doctor about

- how this device is used
- how it should not be used
- safety measures
- warnings
- side effects

Your doctor's phone number:

_____

REF 26-0005-6000/4

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Useful Terms

These terms are used in this manual.

Adjunctive Therapy — Additional, add-on; VNS is adjunctive therapy, it is added on to other antidepressant treatments

Adverse events — Complications and side effects

Clinical benefit — Categories assigned to describe change in depressive symptoms on Hamilton Rating Scale for Depression-24 Item after VNS Therapy

> **Meaningful clinical benefit** – 25% to 49% improvement in depressive symptoms
>
> **Highly meaningful clinical benefit** – 50% to 74% improvement in depressive symptoms
>
> **Extraordinary clinical benefit** – over 75% improvement in depressive symptoms

Clinical studies — Tests of the effectiveness and safety of a therapy on humans

Cyberonics — Company that makes the VNS Therapy System

Electrodes — Part of the VNS Therapy Lead that connects to the vagus nerve

$HSRD_{24}$ — Standardized test to measure depressive symptoms as reported by the doctor; Hamilton Rating Scale for Depression-24 Item

ISD-SR — Standardized test to measure depressive symptoms as reported by the patient, Inventory of Depressive Symptomatology Self-Report

Lead — VNS Therapy Lead; small wire that connects the VNS Therapy Pulse Generator to the vagus nerve

MADRS — Standardized test to measure depressive symptoms as reported by the doctor, Montgomery-Asberg Depression Rating Scale; commonly used in Europe

Programming Wand — VNS Therapy instrument used to check or change VNS Therapy device and settings

Pulse Generator — VNS Therapy device implanted in the patient's chest; holds the battery and delivers stimulation to the vagus nerve through the VNS Therapy Lead

Reed Switch — This mechanism works like a gate. When the Magnet closes it, the signal (stimulation) cannot pass. The Pulse Generator is temporarily turned OFF.

Remitter —Study participant who was essentially free of depressive symptoms after receiving VNS Therapy; determined by scores of standardized tests; also called complete responder

Responder — Study participant whose depressive symptoms were reduced by 50% or more after receiving VNS Therapy; determined by scores of standardized tests

Stimulate — Send electrical signal; with VNS Therapy, the Pulse Generator sends an electrical signal through the Lead to the vagus nerve, which carries the signal to the brain

Stimulation — The electrical signal that is sent from the Pulse Generator to the brain

Treatment-resistant Depression (TRD) — Depression that has not responded to four or more antidepressant treatments

Vagus nerve — A nerve that extends from the brain through the neck to the major organs (heart, lungs, stomach, etc.) in the torso

Vagus Nerve Stimulation — (VNS) periodic electrical signals sent from the Pulse Generator to the vagus nerve

VNS Therapy — Treatment received from vagus nerve stimulation

VNS Therapy System — All of the parts that provide VNS Therapy: Pulse Generator, Lead, Programming Wand, Computer, Software, and Magnets

1. INTRODUCTION TO VNS THERAPY

Many people have depression. Through the years, doctors and scientists have learned much about depression. They have developed drugs and other treatments. Despite these efforts, some people still have depression. Your doctor has proposed the VNS Therapy™ System for you to reduce the symptoms of your depression because drugs have failed to control them adequately.

The VNS Therapy System sends a mild electrical impulse to a nerve that goes to the brain. This nerve is called the vagus nerve. The treatment is Vagus Nerve Stimulation (VNS) Therapy (VNS Therapy™).

2. THE VNS THERAPY SYSTEM

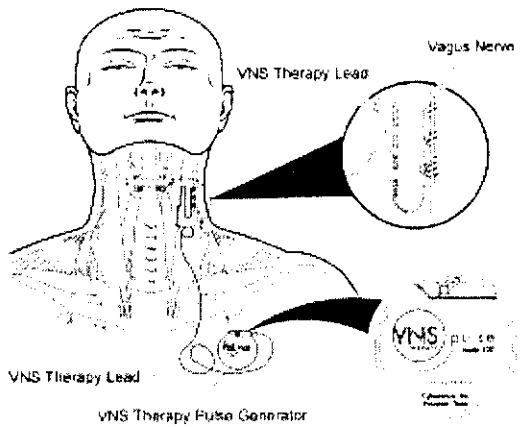
2.1. Parts of the VNS Therapy System

The VNS System has several implantable and nonimplantable parts (see Figure 1 and Figure 2).

2.1.1. Implantable parts

- VNS Therapy Pulse Generator
- VNS Therapy Lead

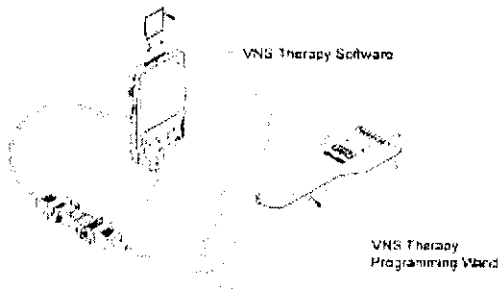
Figure 1. Implantable parts of the VNS Therapy System



2.1.2. Nonimplantable parts

- VNS Therapy Computer
- VNS Therapy Programming Software
- VNS Therapy Programming Wand
- VNS Therapy Magnets

Figure 2. Nonimplantable parts of the VNS Therapy System



2.1.3. Pulse Generator

The main part is the Pulse Generator, sometimes called a stimulator. Similar to cardiac pacemakers, which have been used since 1958 to control heart problems, the Pulse Generator is computer controlled and battery powered. It sends signals through the electrodes of the Lead to the brain by way of the left vagus nerve.

2.1.4. Placement of the Pulse Generator and Lead

The Pulse Generator is placed under the skin of the upper chest. The Lead connects the Pulse Generator to the vagus nerve. It is surgically attached to the left vagus nerve in the neck. A surgeon implants the Pulse Generator and Lead during an operation that typically lasts about 1 to 2 hours. Later, your doctor sets the Pulse Generator to deliver periodic stimulation 24 hours a day (for example, 30 minutes ON and 5 minutes OFF). At the office, your doctor can read and change stimulation settings with the Computer, Software, and Programming Wand.

2.1.5. Cyberonics Magnet

Cyberonics provides a Magnet for you to stop stimulation if and when you need to (see the "Using Your Cyberonics Magnets" section of this manual).

2.1.6. Stimulation settings

The Pulse Generator has many settings. Your doctor will choose the settings. He or she can change (reprogram) the periodic stimulation at any time with the Programming Wand, Software, and Computer. Most of the time, changing the VNS Therapy System settings is a painless procedure, takes only a few minutes, and can be done in the doctor's office.

2.1.7. Pulse Generator life

The battery in the Pulse Generator can last from 1 to 16 years.

The lifespan depends on these factors:

- Pulse Generator model

- Settings your doctor chooses
- Interaction of the Lead and vagus nerve over time

When the battery in your Pulse Generator runs out, the Pulse Generator must be replaced in order for you to continue to receive VNS Therapy. This requires an additional surgical procedure. The operation involves anesthesia and generally takes less than an hour to complete. Please refer to the "Battery depletion (running out)" section of this manual for additional information about battery depletion.

3. QUICK REFERENCE GUIDE

This quick guide provides important information about the VNS Therapy System. It will be most useful after you have read the whole manual. A list of frequently asked questions is included at the end of this manual.

When you see this symbol ⚠, pay special attention to the important information after it.

After you receive your VNS Therapy System, keep this important information in mind.

- You should not receive a VNS Therapy System implant if your left vagus nerve has previously been cut.
- You CANNOT have any short-wave diathermy, microwave diathermy, or therapeutic ultrasound diathermy anywhere on your body if you have an implanted VNS Therapy System.
- **Use the Cyberonics Magnet to stop the stimulation** if it becomes painful or irregular (see the "Using Your Cyberonics Magnets" section of this manual).
- **Call your doctor right away** if any of the following occur:
  - Your voice is constantly hoarse.
  - Stimulation becomes painful or irregular.
  - Stimulation causes any choking, trouble with breathing, trouble with swallowing, or change in heart rate.
  - You or someone else notices changes in your level of consciousness (for example, you become constantly drowsy).

- You think that the Pulse Generator may not be stimulating properly or that the VNS Therapy System battery is depleted (stops stimulating).
- You notice anything new or unusual that you relate to the stimulation.
- The feeling that you usually have during stimulation becomes stronger or weaker (see the "Complications" section of this manual).
- Your depressive symptoms increase or suicidality (suicidal thoughts or behavior) increases. See the "Additional Safety Considerations" section of this manual for details.

- Call your doctor before you have **any medical tests** that might affect, or be affected by, the VNS Therapy System, such as magnetic resonance imaging (MRI) scans (see the "Medical Hazards" section of this manual).
- Call your doctor before you have **any other medical devices implanted** (see the "Medical Hazards" section of this manual).
- Tell your doctor at your next visit if you no longer feel the routine stimulation. Your doctor may decide to change your settings.

Cyberonics *cannot* provide health care advice or services. Your source for health questions must always be your doctor.

4. WHO USES VNS THERAPY?

VNS Therapy has been approved for people with chronic or recurrent treatment resistant depression who have failed to respond to four or more adequate treatments. It is *not* right for everyone who has depression. You and your doctor will decide if VNS Therapy is right for you. Your doctor will also decide if you have any other medical conditions that might be affected by VNS Therapy.

4.1. Indications for Use

The VNS Therapy System is indicated for the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments.

4.2. Contraindications (When VNS Therapy Should Not Be Used)

⚠ CONTRAINDICATION: The VNS Therapy System should not be used (is contraindicated) in people who have had the left vagus nerve cut to treat another disorder (a left vagotomy).

⚠ CONTRAINDICATION: Inform anyone treating you that you CANNOT have any short-wave diathermy, microwave diathermy, or therapeutic ultrasound diathermy (hereafter referred to as "diathermy") anywhere on your body because you have an implanted VNS Therapy System (sometimes referred to as a "Vagus Nerve Stimulator" or "Vagus Nerve

Stimulation"). **Diagnostic ultrasound is not included in this contraindication.**

Diathermy is a treatment to promote healing or relieve pain. It is provided by special medical equipment (diathermy equipment) in a doctor's office, dentist's office, or other healthcare setting.

Energy from diathermy therapy may cause heating of the VNS Therapy System. The heating of the VNS Therapy System resulting from diathermy can cause temporary or permanent nerve or 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.

Diathermy may also damage parts of your VNS Therapy System. This damage can result in loss of therapy from your VNS Therapy System. More surgery may be required to remove or replace parts of your implanted device.

Injury or damage can occur during diathermy treatment whether your VNS Therapy System is turned "ON" or "OFF."

5. WARNINGS AND PRECAUTIONS

As with all types of treatment for depression, VNS Therapy carries some risks. Talk to your physician about other risks not covered in this manual that you should know about. Also be sure to ask any questions that you have about any of the following warnings, precautions, side effects, and possible hazards.

5.1. Warnings

⚠ **Worsening Depression/Suicidality**

You will need to be observed closely for clinical worsening and suicidality (suicidal thoughts or behavior), especially at the time of drug or drug dose changes, or VNS Therapy stimulation parameter changes.

⚠ **Unapproved uses**

The safety and efficacy of the VNS Therapy System have not been established for uses outside its approved indications for use. The safety and efficacy of VNS Therapy have *not* been shown for people with these conditions:

- 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 brain injury
- Progressive neurological diseases other than epilepsy

- Heart arrhythmias (irregular heart beats) or other heart abnormalities
- History of dysautonomias
- History of lung diseases or disorders, including shortness of breath and asthma
- History of ulcers (gastric, duodenal, or other)
- History of vasovagal syncope (fainting)
- Only one vagus nerve
- Other concurrent forms of brain stimulation
- Preexisting hoarseness

⚠ **Swallowing difficulties**
Difficulty swallowing may occur with active stimulation, and aspiration may result from the increased swallowing difficulties.

⚠ **Shortness of breath**
Shortness of breath may occur with active VNS Therapy, especially if you have chronic obstructive pulmonary disease or asthma.

⚠ **Obstructive sleep apnea**
Use of the VNS Therapy device can cause or worsen pre-existing obstructive sleep apnea (episodes where breathing stops for short periods of time while sleeping).

⚠ **Device malfunction**
Device malfunction could cause painful stimulation or direct

current stimulation. Either event could cause nerve damage and other associated problems.

⚠ **Magnetic resonance imaging (MRI)**
You should not have a full body MRI while the VNS Therapy device is in place. Additional surgery may be required to remove the system if full body MRI is required. You should contact your physician before undergoing MRI.

⚠ **Device removal**
Device removal requires an additional surgical procedure. When removing a device, the surgeon may leave part of the Lead behind. This may pose certain risks **(see the "Medical Hazards" section in this manual)**.

⚠ **Device manipulation**
Do not manipulate the Pulse Generator and Lead through the skin as this may damage or disconnect the Lead from the Pulse Generator and/or possibly cause damage to the vagus nerve.

5.2. Precautions

⚠ **Use during pregnancy**
The safety and effectiveness of the VNS Therapy System have not been established for use during pregnancy.

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

5.3. Environmental Hazards

Being close to certain types of equipment can affect the Pulse Generator. Move away from or avoid equipment such as transmitting antennas.

5.3.1. Pacemaker Warning signs

Talk to your doctor before going into places with Pacemaker Warning signs.

5.3.2. Small appliances

Properly operating microwave ovens and other small electrical appliances, such as toasters, hair dryers, and electric shavers, should *not* affect the Pulse Generator.

5.3.3. Cellular phones

Cellular phones can affect some implanted cardiac defibrillators and pacemakers. But tests to date show that they do *not* affect the Pulse Generator.

5.3.4. Transmitting devices

Properly operating electrical ignition systems and power transmission lines should *not* affect the Pulse Generator. Sources with high energy levels, such as transmitting antennas, *may interfere* with the device. Move at least 2 meters (6 feet) away from any equipment that interferes with your device.

5.3.5. Antitheft devices, airport security systems, and other metal detectors

Antitheft devices and metal detectors should *not* affect the Pulse Generator or be affected by it. As a precaution, however, move through them at a steady pace; do not linger in the area.

5.3.6. Devices with strong electromagnetic fields

Electrical or electromechanical devices with a strong static or pulsing magnetic field can cause the Pulse Generator to start suddenly. Such devices may include strong magnets, hair clippers, vibrators, and loudspeakers. Keep this type of equipment at least 15 centimeters (6 inches) away from your chest.

If your Pulse Generator stops while you are in a strong electromagnetic field, move away from the source so that the device may return to regular operation.

5.4. Medical Hazards

Medical equipment, procedures, and surgery using certain electrical instruments can affect the VNS Therapy System's operation and sometimes damage the Pulse Generator or Lead.

⚠ Make sure that medical personnel know you have a device implanted in your chest.

⚠ Always call your doctor before you have any medical tests that may affect, or be affected by, the VNS Therapy System as described below. Precautions may be needed.

5.4.1. Routine diagnostic procedures

Most routine diagnostic procedures, such as diagnostic ultrasound and radiography (x-rays), should *not* affect the VNS Therapy System.

5.4.2. Mammography

Because the Pulse Generator is in your chest, you may need to be specially positioned for a mammogram. Otherwise, the device may be seen as a shadow on the mammogram. It could make a lesion or lump in that area hard or even impossible to detect. Make sure that your doctor and the mammography technician are aware of the implanted device.

5.4.3. Radiation treatment

Treatment with radiation, cobalt machines, and linear accelerators *may* damage the Pulse Generator. Note that no testing has been done to date. The effect of radiation on the device is not known. Talk with your doctor if you plan to have radiation treatment.

5.4.4. Magnetic resonance imaging

If you plan to have **magnetic resonance imaging** (MRI), make sure your doctor has the following information.

⚠ Magnetic resonance imaging (MRI) should not be performed with a magnetic resonance body coil in the Transmit Mode. The heat induced in the Lead by an MRI body scan can cause injury.

MRI using the whole body coil is not recommended because it can damage the vagus nerve. Contact your physician before having any MRI performed so that it can be discussed with the MRI personnel.

5.4.5. Other procedures

External cardiac defibrillation and other procedures for heart problems, as well as extracorporeal shockwave lithotripsy, diathermy, and electrocautery, *may damage* the Pulse Generator. If you had any of these procedures and your doctor did not know about it, have the Pulse Generator checked.

While *diagnostic* ultrasound should *not* affect the VNS Therapy System, *therapeutic* ultrasound therapy *could* damage the Pulse Generator or inadvertently harm you.

5.5. Interference with Other Devices

While the Pulse Generator is stimulating or being set or tested, it may briefly interfere with nearby equipment. If this happens, move at least 2 meters (6 feet) away from such equipment.

5.5.1. Radios and hearing aids

The Pulse Generator can interfere with devices operating in the 40 kHz to 100 kHz range. Hearing aids and transistor radios operate in this range. In theory, the Pulse Generator could affect them, but no effects have yet been reported. No detailed testing has been done, so the effects are unknown.

5.5.2. Implanted devices

The Pulse Generator may affect other implanted medical devices, such as cardiac pacemakers and implantable defibrillators. Possible effects include sensing problems. These could lead to inappropriate responses from the Pulse Generator.

5.5.3. Credit cards and computer discs

The VNS Therapy Magnets are very strong. They *can* damage televisions, computer disks, credit cards, and other items that are affected by strong magnetic fields. Keep your Magnet at least 25 centimeters (10 inches) away from any of these items. **Do not carry or store the Magnets near them.**

6. SIDE EFFECT AND SAFETY PROFILE OF VNS THERAPY OBSERVED IN CLINICAL STUDIES IN DEPRESSED PATIENTS

This section describes the side effects and safety concerns that were observed in the clinical studies that led to the approval of VNS Therapy as an treatment for patients with treatment-resistant depression. The side effects and safety concerns associated both with the surgical implantation procedure for the VNS Therapy System and those related to stimulation of the vagus nerve are discussed. In addition, this section discusses some specific safety considerations for the treatment of patients with depression.

6.1. Overview of Clinical Studies

Safety and effectiveness studies involved a total of 295 men and women who received VNS Therapy along with their usual antidepressant treatments. Sixty of them participated in a pilot study that compared depressive symptoms before and after VNS Therapy. The favorable results from that study prompted a second study. The second study (sometimes referred to as "D-02") consisted of two "phases" and included people with treatment-resistant depression. In the first phase, which lasted 3 months, half of the 235 patients who were implanted with the device had it turned on while the other half did not. Patients did not know whether the device was on or not. In the second phase of the study (referred to as the "long-term phase of D-02"), all patients had the device turned on after the first 3 months and were followed for at least a full year. Patients in the long-term phase of the study were allowed to have adjustments in the doses of depression medications prescribed and were also allowed to have new medications or ECT prescribed during this time. These

patients were compared to a separate group of 124 people with treatment resistant depression who received antidepressant treatments, but who did not have the device implanted.

6.2. Surgical Implantation Procedure

6.2.1. Side effects that may occur from implantation of the VNS Therapy System

The following is a list of the side effects that were most commonly reported as being related to the surgical implantation of the VNS Therapy System during the D-02 study. The side effects that occurred in at least 3% of the patients in the D-02 study and the percentage of patients who experienced them were as follows:

- Incision pain (36%)
- Voice alteration (33%)
- Incision site reaction (for example, redness, itching, soreness) (29%)
- Pain around the device generator or leads (23%)
- Other reactions around the device generator or leads (for example, swelling, tendernous) (14%)
- Pharyngitis (inflammation of the throat) (13%)
- Difficulty swallowing (11%)
- Numbness (11%)
- Nausea (9%)

- Shortness of breath (9%)
- Headache (8%)
- Neck pain (7%)
- Pain elsewhere (7%)
- Increased cough (6%)
- Paresthesia (tingling sensation) (6%)
- Infection at the surgical site (4%)
- Chest pain (3%)
- Dizziness (3%)
- Increased tension of the muscles (3%)
- Vocal cord paralysis (3%)
- Skin rash (3%)
- Inability to pass urine (urinary retention) (3%)

Many of these side effects resolved within 30 days, but in some cases the side effects persisted beyond 90 days. Voice alteration was particularly likely to persist for longer than 90 days.

⚠ Implantation of the Lead may cause nerve constriction (squeezing of the nerve). Call your doctor right away if your voice is always hoarse a few days after surgery. (There could be other explanations for this symptom.)

6.2.2. Infrequent surgical side effects

Surgical side effects that were reported in the D-02 study less frequently than those listed above, but by at least 1% of patients, were as follows: allergic reactions, weakness, fever, bleeding, heart palpitations, difficulty sleeping, neck rigidity, loss of appetite, heartburn, vomiting, bruising, swelling, itching, ear pain, ringing in the ears, and tightness in the throat. Additional serious side effects (reported in less than 1% of patients) were: transient heart stoppage (occurred in the operating room), decrease in heart rate (occurred in the recovery room), abnormal thinking (occurred in the post-operative period, thought due to narcotics), aspiration pneumonia (occurred in the post-operative period), and acute kidney failure.

6.2.3. Surgical scars

There are surgical techniques that may minimize surgical scars. Talk to your surgeon if you have specific concerns.

6.3. Stimulation of the Vagus Nerve

Side effects can occur from stimulation of the vagus nerve by the VNS Therapy System. Generally, the side effects become less noticeable over time for most patients. Only 3% of patients discontinued VNS Therapy because of side effects during the first year of treatment in the D-02 study. Sometimes your doctor can lessen the side effects by changing the device settings.

The VNS Therapy System is not a drug. It does not cause drug-related side effects and does not interact with drugs, including antidepressant medications you may be taking.

6.3.1. Side effects that may occur from stimulation of the vagus nerve

Table 1 shows the side effects that were most commonly reported as being related to stimulation of the vagus nerve by the VNS Therapy System during the D-02 study. Side effects reported in at least 3% of the patients are included. Table 1 shows the percentage of patients who had these side effects after 3 months, 12 months, and 24 months of stimulation.

Table 1. Stimulation-Related Side Effects Reported by Greater Than or Equal To 3% of Patients—Study D-02

	Months of Stimulation		
	3	12	24
Voice alteration	59%	54%	52%
Increased cough	24%	7%	4%
Shortness of breath	14%	16%	14%
Neck pain	16%	13%	15%
Difficulty swallowing	13%	5%	5%
Paresthesia (tingling)	11%	4%	4%
Tightness in throat	10%	6%	5%
Pain	6%	6%	5%
Nausea	6%	1%	1%
Pharyngitis (inflammation of the throat)	6%	5%	4%
Headache	5%	3%	3%
Chest pain	4%	2%	2%
Heart palpitations	4%	3%	2%
Difficulty sleeping	4%	1%	1%
Heartburn	3%	2%	2%
Increased muscle tension	3%	4%	3%

While many of the incidences of these side effects resolved over time, some patients continued to report the side effects throughout the study. This was particularly true for voice

alteration, shortness of breath, and neck pain. Some of the side effects caused by stimulation typically occur only during stimulation (the ON time of the stimulation cycle).

6.3.2. Other side effects reported during VNS Therapy

The following is an alphabetical list of additional side effects reported as at least possibly due to vagus nerve stimulation during the 12-month D-02 study: abnormal dreams, abnormal thinking, agitation, amenorrhea (stoppage of menstrual periods), amblyopia (visual disturbance), amnesia, anxiety, arthralgia (joint pain), asthma, colitis, constipation, deafness, diarrhea, dry mouth, emotional lability, eructation (belching), eye pain, flatulence, flu syndrome/viral infection, gastritis, hiccup, hypertension (high blood pressure), hypotension (low blood pressure), increased appetite, laryngitis, migraine, myalgia (muscle ache), myasthenia (muscle weakness), nervousness, postural hypotension (low blood pressure upon standing), rhinitis, sedation, stridor, sweating, syncope (fainting), tachycardia (fast heart beat), tremor, twitching, vasodilatation (flushing), weight gain, weight loss.

6.4. Additional Safety Considerations

6.4.1. Worsening depression

People who have depression can experience waxing and waning of their depressive symptoms even while receiving treatment. During the first phase of the D-02 study when half the patients had their VNS Therapy System turned on and the other half did not, the study doctors reported 12 serious events of worsening depression requiring hospitalization. Four of these events occurred in patients who had their device turned on, and the other

eight occurred in patients who did not have their device turned on. During the long-term phase of the D-02 study (months 3 through 12), study doctors reported 62 additional serious events of worsening depression in 31 patients. If your depression worsens during VNS Therapy, inform your doctor promptly.

6.4.2. Mania

Some patients being treated for depression may experience a manic or hypomanic episode characterized by an abnormal and persistently elevated or irritable mood. Patients with known bipolar disorder (manic depressive illness) are the people most likely to experience this phenomenon. It is believed that effective antidepressant treatments themselves can cause a manic or hypomanic episode. In the D-02 study (through the 12-month long-term phase), six hypomanic or manic episodes were observed. Five of the six patients had a known history of prior hypomanic or manic episodes. One of these events was considered serious enough to require hospitalization; the other five events were either treated with medication or only required observation. If you experience symptoms of an elevated or irritable mood during VNS Therapy, inform your doctor promptly.

6.4.3. Suicides

People with depression may experience the emergence of suicidal thoughts and behavior (suicidality) whether or not they are receiving treatment. In the D-02 study (through the 12-month long-term phase), there were one suicide and seven additional suicide attempts in six patients. If you or someone else notices your depression worsening or indications of suicidality, inform your doctor promptly. Additionally, if you or someone else notices any of the following symptoms, inform your doctor immediately as they may indicate an increased risk of suicide: new or worse anxiety, feeling agitated or restless, panic attacks, difficulty sleeping, new or worse irritability, acting aggressive, being angry or violent, acting on dangerous impulses, an extreme increase in activity and talking, other unusual changes in behavior or mood.

6.4.4. Deaths that occurred during the depression studies

In the D-02 study (through the 12-month long-term phase), there were four deaths. One occurred in a patient who had enrolled in the study but had not yet received a VNS Therapy System implant. The causes of death for the other three patients were as follows: suicide (described above), sudden death of unknown cause, multi-organ system failure.

6.5. Analysis of Medical Device Reports Submitted to FDA from July 1, 1997 through October 8, 2004 for the VNS Therapy System Epilepsy Indication

Once a medical device is approved for commercial distribution, the United States Food and Drug Administration (FDA) regulations require certain parties, including manufacturers of medical devices, to report to the FDA deaths and serious injuries to which a device has or may have caused or contributed. The required report is referred to as a medical device report (MDR). The FDA Office of Biometrics and Surveillance analyzed all MDRs submitted for the VNS Therapy System from July 1, 1997 through October 8, 2004. During this period, the VNS Therapy System had a single approved indication, epilepsy. The analysis included 2,887 reports, 2,453 of which were reported from sites within the United States. By the end of the period analyzed, there were 32,065 VNS Therapy device implants and 80,144 device-years of implant experience (the presence of the implanted device in an individual for a full year equals one "device-year"). **It is important to emphasize that, although the events occurred during treatment with the VNS Therapy System, the submission of an MDR does not necessarily mean the product caused or contributed to the event being reported.**

6.5.1. Deaths

A total of 524 deaths were reported to the FDA during the period from July 1, 1997 through October 8, 2004. By the end of the period, there were 32,065 VNS Therapy device implants and 80,144 device-years of implant experience. Of the 524 deaths, 102 (20%) were of an "unknown cause," including 24 deaths of unknown cause that occurred during sleep (5% of total deaths). Of those deaths with a reported cause, the following were the most common etiologies:

- seizure disorder (152 reports; 29% of total deaths), including sudden unexplained death in epilepsy and status epilepticus (These are recognized risks in patients with epilepsy—the rate of sudden unexplained death in patients treated with VNS Therapy is within the range of the rates reported for similar patients who are treated with antiepileptic drugs without VNS Therapy.)
- respiratory events (99 reports; 19% of total deaths), including pneumonia, pulmonary edema, reduced oxygen supply to body tissues
- cardiac events (51 reports; 10% of total deaths), including heart stoppage, heart attack, and irregular heart beat
- neurovascular events (24 reports; 5% of total deaths), including stroke and brain hemorrhage (bleeding)
- cancer (19 reports; 3% of total deaths), including brain and colon
- suicide (9 reports; 2% of total deaths)

6.5.2. Serious injuries

A total of 1,644 serious injuries were reported to the FDA during the period from July 1, 1997 through October 8, 2004. By the end of the period, there were 32,065 VNS Therapy device implants and 80,144 device-years of implant experience. The most frequently reported serious injury was infection (525 reports). Approximately 40% of these were known to have required device removal. The second most common serious injury reported was increased seizure activity (324 reports). Others included:

- vagus nerve injury (181 reports) including vocal cord paralysis (109) and hoarseness (71)
- respiratory injuries (141 reports) including sleep apnea (cessation of breathing during sleep, 33 reports) shortness of breath (50), and aspiration (inhaling foreign matter or stomach contents into the lungs, 14 reports)
- cardiac events (123 reports) including fast or slow heart rates, palpitations, high or low blood pressure, fainting, and cessation of heart beat
- pain (81 reports) including chest and neck pain
- gastrointestinal events (60 reports) including difficulty swallowing (24) and weight loss (24)
- depression (21 reports)

Of the 1,644 reports of serious injury, 694 (42%) were associated with subsequent device removal in that subject.

6.5.3. Device malfunctions

A total of 708 device malfunctions were reported to the FDA during the period from July 1, 1997 through October 8, 2004. By the end of the period, there were 32,065 VNS Therapy device implants and 80,144 device-years of implant experience. Some of the most common malfunctions reported were an abnormal lead test (which can be indicative of a poor connection between the lead and vagus nerve or lead and generator or can indicate a broken lead, 351 reports), lead breakage (116), device failure (44), and a shift in device location (20).

7. BENEFITS OF VNS THERAPY

The effectiveness of VNS Therapy in decreasing depressive symptoms was primarily demonstrated by improved scores on standardized tests after 12 months and 24 months of VNS Therapy in the D-02 study. See "Overview of Clinical Studies" in the preceding section for a description of the D-02 study.

7.1. Effectiveness Results From the D-02 Clinical Study

7.1.1. Three-month results

At the end of the first 3 months, the proportion of patients who had at least a 50% reduction in depression symptoms was 15% in the group of patients receiving active stimulation, slightly better than for patients who were not receiving stimulation (10% of these patients had at least a 50% reduction in symptoms). (See Table 2.) This finding suggested that the full effects of VNS Therapy might require more than 3 months of treatment.

7.1.2. One-year results

After 1 year of VNS Therapy, the results showed that 30% of the study patients were responders (at least a 50% improvement in depressive symptoms) and 17% were remitters (minimal to no depressive symptoms). The results from a second rating scale of depression symptoms showed that 22% of the group were responders and 15% were remitters, and the results from a third rating scale showed that 32% were responders and 23% were remitters (see Table 2). It should be noted that about one in four or five people who were implanted with the device during the study were not included in these calculations of success at 12

months. Therefore it is possible that the percentage of patients having successful outcomes may be lower than is represented by the results described above.

7.1.3. Two-year results

After 2 years of VNS Therapy, the results showed that 32% of the patients were responders and 17% were remitters. The results from a second rating scale of depression symptoms showed that 27% of the group were responders and 13% were remitters (see Table 2). It should be noted that about one in three people who were implanted with the device during the study were not included in these calculations of success at 24 months. Therefore it is possible that the percentage of patients having successful outcomes may be lower than is represented by the results described above.

Table 2. Percent of Responders and Remitters After VNS Therapy

Standardized Test	$HRSD_{24}$		IDS-SR		MADRS	
	Responders	Remitters	Responders	Remitters	Responders	Remitters
3 months	15%	7%	14%	6%	17%	10%
12 months	30%	17%	22%	15%	32%	23%
24 months	32%	17%	27%	13%	N/A	N/A

Responders - ≥50% improvement in depressive symptoms.
Remitters – minimal to no depressive symptoms.

7.1.4. Additional categorization of clinical benefit

After 12 months of VNS Therapy, the patients were also assessed to categorize the degree of improvement in their depression symptoms. The amount of improvement was categorized as follows:

Worsened – depressive symptoms worse than when VNS Therapy was started

Minimal to no change – 0% to 24% improvement in depressive symptoms

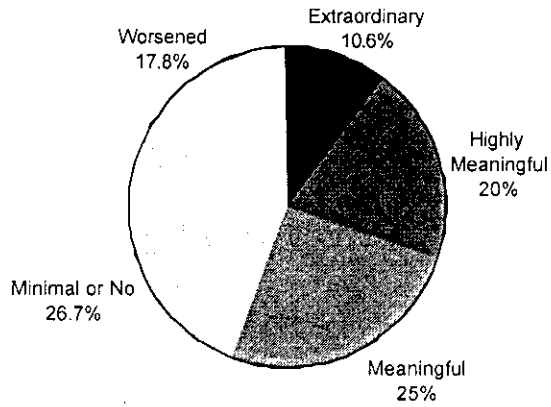
Meaningful clinical benefit – 25% to 49% improvement in depressive symptoms

Highly meaningful clinical benefit – 50% to 74% improvement in depressive symptoms

Extraordinary clinical benefit – over 75% improvement in depressive symptoms

Figure 3 shows the percentage of patients who were in the different categories after 12 months of VNS Therapy. It should be noted that about one in four people who were implanted with the device during the study were not included in these calculations of success at 12 months. Therefore it is possible that the percentage of patients having successful outcomes may be lower than is represented by the results shown in the figure.

Figure 3. Categories of Clinical Benefit After 12 Months of VNS Therapy ($HRSD_{24}$)



7.1.5. Maintenance of benefit over time

Although less than one in three or one in four patients (depending on the rating scale used) appeared to respond to VNS Therapy, most—but not all—of those patients continued to be responders over time. For example, among the 30 patients who were responders on the $HRSD_{24}$ rating after their first 3 months of VNS Therapy, 60% continued to be responders after one year of VNS Therapy, and 70% were responders after two years of VNS Therapy. Among the 54 patients who were responders after 12 months of VNS Therapy, 69% continued to be responders after two years of VNS Therapy.

7.2. Quality of Life Measurements in the D-02 Clinical Study

In addition to improvements in depressive symptoms, patients who received VNS Therapy for one year in the D-02 study reported improvements in quality of life.

7.3. Expected Rate of Response to VNS Therapy

For patients in whom VNS Therapy is effective, the benefits are not always seen right away. In fact, the 12-week acute studies did not show a significant difference between patients receiving VNS Therapy and those who were not receiving it. Depressive symptoms may improve slowly over the first year of treatment.

7.4. Treatment Continuation Rates

Not all patients continue on VNS Therapy. During the D-02 study, 92% of the patients continued to receive therapy at 12 months and 82% continued to receive therapy at 24 months.

7.5. Limitations of VNS Therapy

VNS Therapy has not been shown to cure depression. It does not work for everyone. For most patients in whom it is effective, improvement in depressive symptoms will be slow (see "Expected Rate of Response to VNS Therapy" above). Some patients may have no change in symptoms with VNS Therapy, and some may actually get worse while receiving VNS Therapy. At present, doctors have no way to predict which patients will respond to VNS Therapy.

8. HAVING THE DEVICE IMPLANTED

VNS Therapy requires surgical placement of the Pulse Generator and Lead by a surgeon. At office visits, your doctor checks the settings and changes them as needed.

8.1. Surgery (Operation)

Surgery lasts from about 1 to 2 hours and typically involves general anesthesia, though local anesthesia is sometimes used. You may stay in the hospital overnight.

The surgeon makes a small incision on the left side of the neck and a second incision below the collarbone in the chest or armpit. The surgeon passes the Lead under the skin between the two incisions. Next the surgeon attaches the Lead to the left vagus nerve in the neck. Then the surgeon attaches the other end of the lead to the Pulse Generator, which is subsequently placed in a "pocket" created at the site of the incision that was made below the collarbone. Finally, the surgeon closes the incisions. See Figure 1.

⚠ The operation can be reversed if you and your doctor ever decide to have the VNS Therapy System removed. Removal of the generator and/or lead requires another surgical procedure. Sometimes when a surgeon removes a VNS Therapy System, the surgeon will decide to leave a portion of the Lead behind in order not to risk damaging the vagus nerve. This may pose certain risks (**see the "Medical Hazards" section of this manual**).

8.2. Follow-up After Surgery

The Pulse Generator is usually turned on 2 weeks after it is implanted. (Your doctor will program the Pulse Generator to the proper settings for you.) At that office visit and at subsequent visits, your doctor will check the VNS Therapy System. Your doctor will make sure that it is working well and that the treatment is not uncomfortable for you.

⚠ **Cyberonics recommends that you see your doctor at least once every 6 months. Your doctor will check the VNS Therapy System for safe and effective operation.**

You will be given an Implant and Warranty Registration Card. It has information about your Pulse Generator and Lead.

You will also receive a Patient Emergency Information Card. It has phone numbers to call in case of a device-related emergency.

⚠ **Carry the Patient Emergency Information Card at all times.**

⚠ **Your doctor is your first source for health-related questions and information. Cyberonics *cannot* provide health care advice or services.**

8.3. Antidepressant Medications

Most patients treated with VNS Therapy in the clinical studies also continued to take antidepressant medications. A significant number of patients had new medications added or doses of their old medications increased during the studies.

Your doctor may advise you to continue taking your antidepressant medications after you begin receiving VNS Therapy. Your doctor may also decide to add new medications to your treatment. Always follow your doctor's instructions regarding your medications.

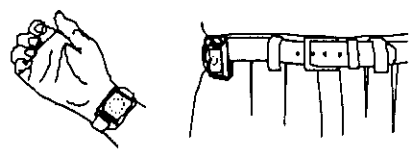
9. THE CYBERONICS MAGNETS

9.1. Handling the Cyberonics Magnets

After your operation, your doctor will give you two magnets. You should carry one of the Magnets with you at all times in your pocket, in your purse away from credit cards, or in another convenient place. If you prefer, you can wear them like a watch or a pager (see Figure 4).

If the Magnets are handled carefully, they should last many years.

Figure 4. The Cyberonics Magnets



Cyberonics Magnet (watch-style)

Cyberonics Magnet (pager-style)

⚠ **Never put or store the Magnets near credit cards, televisions, computers, computer disks, microwave ovens, watches, or other magnets. Keep them at least 10 inches (25 centimeters) away.**

⚠ **Do not drop the Magnets.** They can break if dropped on a hard surface.

⚠ **Carry a Magnet with you at all times.** Show your family members or caregivers how to use the Magnet.

9.2. Using Your Cyberonics Magnets

Keep a Magnet with you at all times in case you need to turn OFF the Pulse Generator.

The Magnet can be used to stop stimulation temporarily or turn OFF the Pulse Generator:

- when you plan to sing or speak in public (if stimulation bothers you when you do this)
- when you are eating (if you have swallowing problems)
- if stimulation becomes uncomfortable or painful

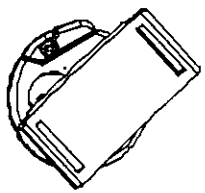
⚠ The correct position for the Magnet may vary from patient to patient. The position depends on how the Pulse Generator is implanted. Find the position that works best for you.

9.2.1. To stop stimulation

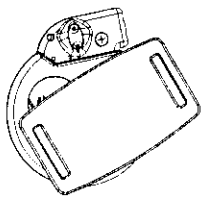
1. Put the Magnet over the Pulse Generator (see Figure 5). If the stimulation stays on, move the Magnet around until it stops.

Figure 5. Stopping Stimulation

Model 101



Model 102



Model 102R

Note: To show the correct position of the Magnet with the Pulse Generator, the Magnet has been drawn without the belt clip or wristband. The belt clip and wristband use the same Magnet.

2. Leave the Magnet over the Pulse Generator. If needed, tape it to your chest or use an elastic, wrap-around bandage.
3. If you stopped the stimulation because it was painful or felt unusual, call your doctor right away.

The Pulse Generator will not stimulate while the Magnet is in place, but it will start when the Magnet is removed.

9.3. How the Magnets Work

The VNS Therapy System senses a magnetic field. Holding a Magnet over the Pulse Generator causes **a Reed Switch** inside the Pulse Generator to close. This switch works like a gate. When the Magnet closes it, the signal (stimulation) cannot pass. The Pulse Generator is temporarily turned OFF.

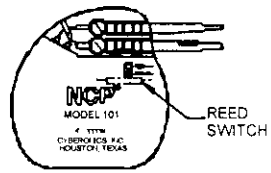
When the Magnet is removed, the switch (gate) opens right away. The VNS Therapy System is turned back ON and can stimulate again.

9.3.1. Finding the Reed Switch

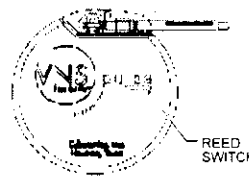
You may need to move the Magnet around to find the Reed Switch and stop stimulation (Figure 6).

The label side of the Magnet should face the Reed Switch. Figure 6 shows the position of the switch.

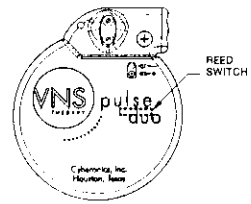
Figure 6. Reed Switch Position



Model 101



Model 102



Model 102R

9.3.2. Know your Magnets

These tips are also given elsewhere in these instructions. Be sure that you understand them.

- Use the Magnet only when necessary to turn off stimulation.
- **With your doctor's permission, it is okay to leave the Magnet in place** for a short while, for example, to sing a song. The Pulse Generator will not stimulate while the Magnet is in place. The stimulation cycle begins again when the Magnet is removed.

- **If stimulation hurts,** hold the Magnet over the Pulse Generator and keep it there. The stimulation will stop as long as the Magnet is there. If necessary, tape the Magnet in place. Contact your doctor right away.
- **Always carry the Magnet with you.** If you have pain because of stimulation, you can stop it by placing the Magnet over the Pulse Generator.
- Keep the Magnets away from credit cards, computer disks, watches, and other items affected by strong magnetic fields.
- **If you lose one of your Magnets,** you may buy a new one from Cyberonics. A Magnet Order Form is included in your Patient Essentials Kit. You may also buy new Magnets by contacting Cyberonics' Customer Service department (see number on back cover of this manual).
- And remember—if you are not sure about using the Magnets, ask your doctor to show you how.

⚠ All Magnets can **lose their effectiveness** over time. If you suspect that either of your Magnets is not working, call your doctor.

9.4. Replacing the Cyberonics Magnets

To order a new Magnet, contact Cyberonics' Customer Service department at the number on the back cover of this manual. A Magnet Order Form, with prices, is included in your Patient Essentials Kit.

10. OTHER IMPORTANT INFORMATION ABOUT YOUR VNS THERAPY SYSTEM

10.1. Device Complications

Complications linked to the VNS Therapy System can result from:

- Surgery
- Pulse Generator malfunction (not working)
- Battery depletion (running out)
- Touching or moving the device through the skin

10.1.1. Surgery

Like a heart pacemaker, the VNS Therapy device is implanted during surgery. One incision is made in the neck to attach the Lead to the vagus nerve, and a second incision is made in the chest for the Pulse Generator. All types of surgery carry some risks. In addition to the risks described in the earlier section of this Manual that summarized the experience from clinical studies, there are potential mechanical complications related to the surgical implantation of the device. The Pulse Generator and/or Lead can—but rarely do—move or come through the skin. Also, the Lead can break or become disconnected from the Pulse Generator.

10.1.2. Pulse Generator malfunction (device not working right)

The Pulse Generator can malfunction, though this is rare. The stimulation from a Pulse Generator that is not working right can cause intense neck pain, hoarseness, choking, or trouble breathing.

⚠ Stimulation from a Pulse Generator that is not working right could damage the vagus nerve and lead to permanent hoarseness or other complications. Malfunction of the Pulse Generator could cause the battery to run out sooner than expected. If you have any of these symptoms, or if stimulation becomes painful, irregular, or nonstop, place the Magnet over the Pulse Generator. Hold it there to stop stimulation (see the "Using Your Cyberonics Magnets" section of this manual). Then call your doctor right away.

10.1.3. Battery depletion (running out)

The battery in your Pulse Generator will normally last between 1 to 16 years, depending on the settings. The Pulse Generator battery will slowly lose its power when it starts to run out. It will begin to stimulate differently. You may sense this change as irregular stimulation. At the end, the stimulation will stop completely.

⚠ *After stimulation stops* **(when the Pulse Generator battery runs out), you may notice a change in your depressive symptoms. If you think that the Pulse Generator might not be working right, call your doctor.**

When the battery in your Pulse Generator runs out, the Pulse Generator must be replaced in order for you to continue to receive VNS Therapy. This requires an additional surgical procedure. The operation involves anesthesia and generally takes less than an hour to complete.

Replacement or removal of the Lead is a different procedure. It is not required for routine replacement of the Pulse Generator.

10.1.4. Manipulation of the Pulse Generator and Lead

The Pulse Generator is secured into place during surgery, but the device can move slightly. It may be possible to feel the Lead under the skin after surgery. This feeling is normal. It should become less apparent over time (several weeks). Manipulation of the Lead should be prevented at all times.

⚠ Never move or twist the Pulse Generator or manipulate the Lead. Doing so could damage the Lead or your vagus nerve. It could require that the Pulse Generator and Lead be replaced.

11. CYBERONICS' PATIENT WARRANTY AND SAFETY LISTING

Government agencies require makers of implantable devices to contact people in case of emergencies related to the device. Cyberonics has a listing of people who have had the Pulse Generator and Lead implanted. The information is kept in confidential files. It is a permanent record of the implantation surgery. Cyberonics will release a file only if required by law.

⚠ Please send Cyberonics **a change of address notice** if you move.

12. FREQUENTLY ASKED QUESTIONS

Patients and their family members often ask these questions.

How do most people respond to VNS Therapy? When the device was tested in the clinical trials, depressive symptoms decreased for most patients. Some patients had no change in depressive symptoms and some got worse while receiving VNS Therapy. Among those patients who did improve while receiving VNS Therapy, some did not improve until they had been receiving VNS Therapy for 6 months or longer.

Can I know if I will be helped before I am implanted with the Pulse Generator and Lead? At this time, there is no way to predict what your response will be.

What are the results of the VNS Therapy clinical studies? This Manual provides a summary of important safety and effectiveness results from the clinical studies. Your doctor can give you more information about the clinical (research) studies.

What is the implantation surgery like? You will be given a general or local anesthetic. The operation usually takes 1 to 2 hours. The operation will be done with you as an outpatient (you go home the same day) or you may stay in the hospital overnight. Ask your surgeon to tell you more about the anesthetic, the operation, and the hospital stay so that you will know what to expect.

Are there risks linked with the surgery? Any surgery has some type of risk. It is important that you discuss this question with your surgeon.

Will the scars be noticeable? Each person has different healing and scarring results. You should expect some scarring from surgery. Most people do not think the scarring after surgery is a major concern. If this is a special concern for you, discuss it with your surgeon.

Will people be able to see the implanted device through my skin? The Pulse Generator is shaped like a disk. The Model 101 is 5.4 centimeters (2.1 inches) across and 1 centimeter (0.4 inch) thick; it weighs about 38 grams (1.34 ounces). The Model 102 is 5.2 centimeters (2.0 inches) across and 0.7 centimeter (0.27 inch) thick; it weighs about 25 grams (0.88 ounce). The Model 102R is 5.2 centimeters (2.0 inches) by 5.8 centimeters (2.3 inches) and 0.7 centimeter (0.27 inch) thick, weighing about 27 grams (0.95 ounce). If you have a small frame or are very thin, the device may be visible below your left collarbone.

What happens after the surgery? After surgery (usually 2 weeks later), your doctor will set the treatment settings of your device. If the stimulation feels uncomfortable, your doctor can change it to make you more comfortable. The doctor will use the Programming Wand to check and fine-tune your stimulation settings at subsequent visits.

Will I be able to tell when the stimulator is on? Many people note a change in their voice (often described as hoarseness) or discomfort in the neck (typically mild pain or a tingling sensation) during stimulation. In general, most side effects become less noticeable over time.

What are the side effects of VNS Therapy? The most common side effects reported during VNS Therapy are voice alteration (often described as hoarseness), discomfort in the neck (typically mild pain or a tingling sensation), cough, shortness of breath, difficulty swallowing, and a feeling of tightness in the throat. Often these events only occur when the stimulator is ON. Other less common side effects are discussed in the earlier section of this manual that summarized the experience from clinical studies. In general, most side effects become less noticeable over time.

When should I use the Magnet? Use the Magnet to stop stimulation temporarily or to turn OFF the Pulse Generator when you plan to sing or speak in public (if stimulation bothers you when you do this), when you are eating (if you have swallowing problems), or if stimulation becomes uncomfortable or painful. If you need to use the Magnet for any of these reasons or any other reason, inform your physician.

How does the Magnet work? The Pulse Generator has a sensor (the Reed Switch) that recognizes the Magnet and stops stimulation.

Can any magnet be used? Only the Cyberonics Magnet should be used with your VNS Therapy System. If you lose your Magnet or require extra Magnets, contact your doctor. In an emergency, you may try other strong magnets. The use of other, non-Cyberonics magnets will not harm the VNS Therapy System. But there is no way to know in advance whether a magnet other than the Cyberonics Magnet will work.

What if the Magnet is accidentally kept in place over the Pulse Generator for an extended period? No stimulation will be

delivered while the Magnet is kept over the device. Stimulation will resume only after the Magnet is removed.

Is it possible to stop all stimulation using the Magnet? Yes. To stop stimulation, hold the Magnet over the Pulse Generator and keep it there. Use this method if you have unusual or painful stimulation. Then call your doctor right away. The Magnet will stop all stimulation while it is held in place. You may need to secure the Magnet by taping it over the implanted device.

Who should carry the Magnet? You should carry the Magnet so that it is always with you. You may also want your family members or caregivers to have access to a Cyberonics Magnet.

Is the Magnet an environmental hazard? The Cyberonics Magnet can damage computer disks, credit cards, watches, and other items affected by strong magnetic fields. Keep your Magnet at least 25 centimeters (10 inches) away from any of these items. Do not store Magnets near such items.

Other Questions? If you have other questions about the VNS Therapy System, any of its parts, or VNS Therapy in general, talk to your doctor.