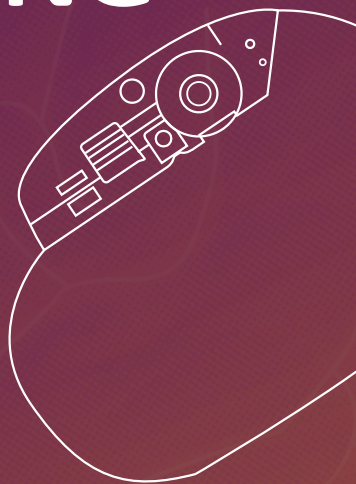


PROTECTING YOUR FUTURE.



Introducing Vagus Nerve Stimulation (VNS) Therapy™ –
helping you take control of your seizures



Are you suffering from seizures that your medication alone can't control?

Most people with epilepsy take medication to manage their seizures.

But some people still experience seizures, even after trying two or more different anti-epileptic medications and following their doctor's advice.



This is called drug-resistant epilepsy, or DRE.¹

Data suggests about one in three people with epilepsy have seizures that are difficult to treat with medication alone.²⁻⁵

Furthermore, research has shown that if two different anti-epileptic medications have failed to give you seizure freedom, the chance of becoming seizure free

VNS Therapy™ – take control and protect your future

When medication alone is not adequately managing your seizures, and surgery is not suitable, there is another solution.

with another is just up to 4%.^{5,6} Experiencing uncontrolled seizures can be stressful and unsettling, and have serious consequences including:

- Disruption of critical periods of brain development in infancy and childhood⁷
- Interference with important processes for learning and memory, which is most serious in infancy⁷
- Accidents and injury during seizures^{8*}
- An increased risk of epilepsy-related premature death^{9,10}

That means it's very important to get seizures under control as soon as possible.

* Accident & injury associated with epilepsy is reported more frequently in adults. Investigators believe fewer reports in children may be due to greater family or caregiver supervision.

Effective seizure control with VNS Therapy™



If you are still having seizures despite trying a few different anti-epileptic medications, your doctor might talk to you about other options.

One of these options is VNS Therapy™ – it may help you get your DRE under control.

It is not another medication – it is a small device that can control seizures, improve the quality of your everyday life and reduce the risks of uncontrolled epilepsy.

VNS Therapy™ has an established safety profile and is well tolerated, demonstrated by over 20 years of research and experience.

It is not a drug, therefore it doesn't have the same side effects, nor does it interact with medications.

How the VNS Therapy™ device works

The VNS Therapy™ device is a small generator, similar to a pacemaker, **Your device will automatically deliver a tailored dose** that is placed under the skin during a short day case procedure. It sits directly on the heart or brain.



Device generators (actual size).

VNS Therapy™ can benefit you by:

- Reducing the intensity of your seizures
- Reducing the number of seizures you have over time
- Improving how quickly you recover from seizures
- Reducing the number of hospital visits
- Reducing the risks associated with uncontrolled epilepsy

Some people find VNS Therapy even improves their mood, alertness and memory.

All of these benefits may help to improve the quality of your everyday life and protect your future.

The earlier patients with DRE start VNS Therapy, the better outcomes they have.



throughout the day, so you don't have to remember anything or worry about missing a dose. on the left chest area but does not act



The device has a thin flexible wire that sends mild pulses to the left vagus nerve in the neck. The vagus nerve passes these pulses to the brain

You may also be given a magnet which can be used to give yourself an additional dose of VNS Therapy™ if you experience reducing seizures, and/or their severity. a breakthrough seizure.

If you and your neurologist agree that VNS Therapy™ would be a good option for you, you will be referred to a neurosurgeon who will carry out the procedure to fit your device. Side effects tend to occur only during stimulation and usually decrease over time.¹⁸⁻²¹

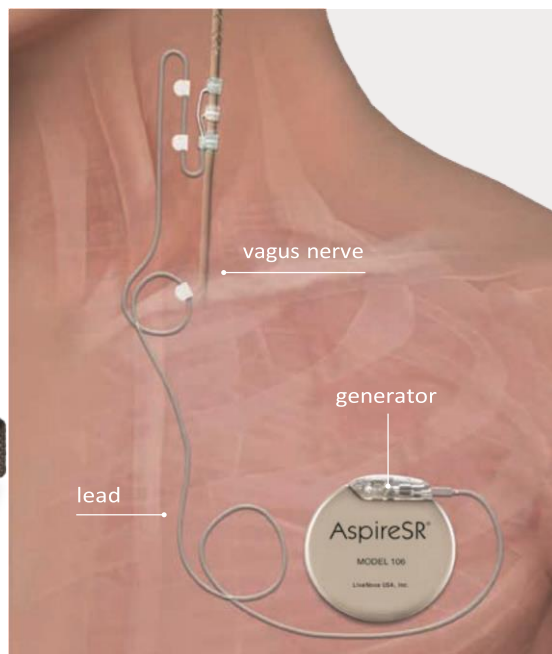
the simple procedure to fit your device.

The most common side effects include:¹⁹

Once your device is in place, your doctor or nurse will gradually adjust its programming. A prickling feeling in the skin or throat
weeks. This ensures your amount of stimulation If you – a dose that provides device speaking or when exercising.

Hoarseness or changes in voice tone
Shortness of breath about once every two
Sore

Coughing device delivers the right
experience side effects, you can use the magnet to stop your temporarily. This can be helpful during activities like singing, the greatest seizure public control. Thereafter, you'll only need to visit your doctor every few months to check the device settings.



VNS Therapy™ works to control seizures by intermittently stimulating the vagus nerve automatically, 24 hours a day, regardless of whether a patient chooses to use the magnet.



Frequently asked questions

VNS Therapy™?

If you have tried several medications and are still having seizures, VNS Therapy™ might be right for you. You should ask your doctor about VNS Therapy™ if several medications have not given you acceptable seizure relief or have side effects that are difficult to tolerate.

Am I a good candidate for

immediately?

Response to treatment varies for each person. Typically, there is a two-week period before stimulation is turned on. Then your neurologist will adjust your dose settings during routine visits. Regular post-implantation visits to set the dosing are critical to ensure the best effects. Studies show that the benefits of VNS Therapy™ continue

Does the device work

need to take medications?

VNS Therapy™ does not replace your medications, nor does it

If I have VNS Therapy™, will I still

anywhere from a few months to one or two years to see the full benefits.

to improve over time, so it may take

stop you from trying new ones.

How many people have

While some people are able to VNS

Therapy™?

cut back on their medications while on VNS Therapy™, you and

To date, more than 100,000 people your doctor will determine the worldwide have used VNS Therapy™, right treatment plan for you. It is a proven long-term solution for important to always follow your people with uncontrolled seizures. doctor's recommendations about your medications.

5 Will electrical and electronic equipment affect the VNS Therapy™ device?

Generally household appliances, such as microwave ovens, toasters, hair dryers, and cell phones will not affect the device. A full list of warnings and precautions is included in the Patient's Manual in the Patient Essentials Kit you will receive after the procedure.

Magnets contained in some tablet computers and covers, such as Apple® iPad® products, may be strong enough to cause accidental activation of VNS Therapy™ stimulation under certain conditions. Patients with VNS Therapy™ should use reasonable caution around devices

that generate a strong electric or magnetic field and keep these types of devices at least 15 cm away from the body area where the generator is implanted. If you have additional questions please contact your physician.

6 What will happen when the battery in my VNS Therapy™ device goes out?

Another procedure is required to replace the generator once the battery is depleted. This minor procedure requires only one incision and usually takes less than an hour.

7 Will metal detectors (such as airport security) affect the VNS Therapy™ device?

Anti-theft devices and metal detectors should not affect the VNS Therapy™ device or be affected by it. As a precaution, however, move through a metal detector at a steady pace; do not linger in the area.

Brief Summary of Safety Information for the VNS Therapy™ System

INTENDED USE / INDICATIONS:

Epilepsy (Non-US)—The VNS Therapy™ System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients whose epileptic disorder is dominated by partial seizures (with or without secondary generalization) or generalized seizures that are refractory to seizure medications. AspireSR® and SenTiva™ feature an Automatic Stimulation Mode which is intended for patients who experience seizures that are associated with cardiac rhythm increases known as ictal tachycardia.

CONTRAINDICATIONS:

Vagotomy—The VNS Therapy™ System cannot be used in patients after a bilateral or left cervical vagotomy. Diathermy—Do not use short-wave diathermy, microwave diathermy, or therapeutic ultrasound diathermy on patients implanted with a VNS Therapy™ System. Diagnostic ultrasound is not included in this contraindication.

WARNINGS — GENERAL:

Physicians should inform patients about all potential risks and adverse events discussed in the physician's manuals. This document is not intended to serve as a substitute for the complete physician's manuals. The safety and efficacy of the VNS Therapy™ System have not been established for uses outside the "Intended Use/Indications" chapter of the physician's manuals. The safety and effectiveness of the VNS Therapy™ System in patients with predisposed dysfunction of cardiac conduction systems (re-entry pathway) have not been established. Post-implant electrocardiograms and Holter monitoring are recommended if clinically indicated. Postoperative bradycardia can occur among patients with certain underlying cardiac arrhythmias. It is important to follow recommended implantation procedures and intraoperative product testing described in the Implantation Procedure chapter of the physician's manual. During the intraoperative System Diagnostics (Lead Test), infrequent incidents of bradycardia and/or asystole have occurred. If asystole, severe bradycardia (heart rate < 40 bpm), or a clinically significant change in heart rate is encountered during a System Diagnostics (Lead Test) or during initiation of stimulation, physicians should be prepared to follow guidelines consistent with Advanced Cardiac Life Support (ACLS). 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. Dyspnea (shortness of breath) may occur with active 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. 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. Device malfunction could cause painful stimulation or direct current stimulation. Either event could cause nerve damage. 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. Patients with the VNS Therapy™ System or any part of the VNS Therapy™ System implanted should have MRI procedures performed only as described in the MRI with the VNS Therapy™ System instructions for use. In some cases, surgery will be required to remove the VNS Therapy™ System if a scan using a transmit RF body coil is needed. Excessive stimulation at an excess duty cycle (i.e., one

stimulation (i.e., stimulation at $\geq 50\text{Hz}$) has resulted in degenerative nerve damage in laboratory animals. Patients who manipulate the generator and lead through the skin (Twiddler's Syndrome) may damage or disconnect the lead from the generator and/or possibly cause damage to the vagus nerve. Generators with AutoStim only — The AutoStim Mode feature should not be used in patients with clinically meaningful arrhythmias or who are using treatments that interfere with normal intrinsic heart rate responses (e.g., pacemaker dependency, implantable defibrillator, beta adrenergic blocker medications). Patients also should not have a history of chronotropic incompetence [commonly seen in patients with sustained bradycardia (heart rate < 50 bpm)].

WARNINGS — EPILEPSY:

The VNS Therapy™ System should only be prescribed and monitored by physicians who have specific training and expertise in the management of seizures and the use of this device. It 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. The VNS Therapy™ System is not curative. Physicians should warn patients that the VNS Therapy™ System is not a cure for epilepsy and that since seizures may occur unexpectedly, patients should consult with a physician before engaging in unsupervised activities, such as driving, swimming, and bathing, and in strenuous sports that could harm them or others. Sudden unexpected death in epilepsy (SUDEP): Through August 1996, 10 sudden and unexpected deaths (definite, probable, and possible) were recorded among the 1,000 patients implanted and treated with the VNS Therapy™ device. During this period, these patients had accumulated 2,017 patient-years of exposure. Some of these deaths could represent seizure-related deaths in which the seizure was not observed, at night, for example. This number represents an incidence of 5.0 definite, probable, and possible SUDEP deaths per 1,000 patient-years. Although this rate exceeds that expected in a healthy (nonepileptic) population matched for age and sex, it is within the range of estimates for epilepsy patients not receiving vagus nerve stimulation, ranging from 1.3 SUDEP deaths for the general population of patients with epilepsy, to 3.5 (for definite and probable) for a recently studied antiepileptic drug (AED) clinical trial population similar to the VNS Therapy™ System clinical cohort, to 9.3 for patients with medically intractable epilepsy who were epilepsy surgery candidates.

PRECAUTIONS — GENERAL:

Physicians should inform patients about all potential risks and adverse events discussed in the VNS Therapy™ physician's manuals. Prescribing physicians should be experienced in the diagnosis and treatment of depression or epilepsy and should be familiar with the programming and use of the VNS Therapy™ System.

Physicians who implant the VNS Therapy™ System should be experienced performing surgery in the carotid sheath and should be trained in the surgical technique relating to implantation of the VNS Therapy™ System. The safety and effectiveness of the VNS Therapy™ System have not been established for use during pregnancy. VNS should be used during pregnancy only if clearly needed. The VNS Therapy™ System is indicated for use only in stimulating the left vagus nerve in the neck area inside the carotid sheath. The VNS Therapy™ 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. 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

that occurs when "ON" time is greater than "OFF" time) and high frequency

explanted. The patient should be given antibiotics preoperatively. The surgeon should ensure that all instruments are sterile prior to the procedure. The VNS Therapy™ System may affect the operation of other implanted devices, such as cardiac pacemakers and implanted defibrillators. Possible effects include sensing problems and inappropriate device responses. If the patient requires concurrent implantable pacemaker, defibrillator therapy or other types of stimulators, careful programming of each system may be necessary to optimize the patient's benefit from each device. Reversal of lead polarity has been associated with an increased chance of bradycardia in animal studies. It is important that the electrodes are attached to the left vagus nerve in the correct orientation. It is also important to make sure that leads with dual connector pins are correctly inserted (white marker band to + connection) into the generator's lead receptacles. The patient can use a neck brace for the first week to help ensure proper lead stabilization. Do not program the VNS Therapy™ System to an "ON" or periodic stimulation treatment for at least 14 days after the initial or

replacement implantation. For Models 100, 101, 102 and 102R do not use frequencies of 5 Hz or below for long-term stimulation. Resetting the pulse generator turns the device OFF (output current = 0 mA). For Model 100, 101, 102 and 102R resetting the pulse generator will result in device history loss. Patients who smoke may have an increased risk of laryngeal irritation. Generators with AutoStim only — For devices that sense changes in heart rate, false positive detection may cause unintended stimulation. Examples of instances where heart rate may increase include exercise, physical activity, and normal autonomic changes in heart rate, both awake and asleep, etc. Generators with AutoStim only — For the AutoStim feature, the physical location of the device critically affects this its ability to properly sense heart beats. Therefore, care must be taken to follow the implant location selection process outlined in the Implantation Procedure. Note that this implant location selection procedure may be performed preoperatively as part of the patient's surgical work-up. M1000 only — Since the Scheduled Programming feature allows the generator to apply therapy increases at scheduled intervals, it may not be appropriate for use in patients who are nonverbal or are unable to use the patient magnet to stop undesired stimulation. Similarly, exercise caution for use of this feature in patients with a history of obstructive sleep apnea, shortness of breath, coughing, swallowing difficulties, or aspiration.

ENVIRONMENTAL AND MEDICAL THERAPY HAZARDS: Patients should exercise reasonable caution in avoiding devices that generate a strong electric or magnetic field. If a generator 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. VNS Therapy™ System operation should always be checked by performing device diagnostics after any of the procedures mentioned in the physician's manuals. For clear imaging, patients may need to be specially positioned for mammography procedures, because of the location of the generator in the chest. Therapeutic radiation may damage the generator's circuitry. 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 generator. Use of electrosurgery [electrocautery or radio frequency (RF) ablation devices] may damage the generator. Magnetic resonance imaging (MRI) should not be performed using a transmit RF body coil for certain VNS Therapy™ device configurations or under certain specific conditions. In some cases, heating of the lead caused by the transmit RF body coil during MRI may result in serious injury. Static, gradient, and radio frequency (RF) electromagnetic fields associated with MRI may change the generator settings (i.e., reset parameters) or activate the VNS device if the Magnet Mode output remains "ON". Note that certain magnetic resonance (MR) system head coils operate in receive-only mode and require use of the transmit RF body coil. Other MR systems use a transmit/ receive RF head coil. Local or surface coils may also be receive-only RF coils that require the transmit RF body coil for MRI. The use of a receive RF coil does not alter hazards of the transmit RF body coil. Exposure of the VNS Therapy™ System to any transmit RF coil must be avoided. Do not perform MRI scans using any transmit RF coil in the defined exclusion zones. See the MRI with the VNS Therapy™ System instructions for use for details or further

instructions for special cases such as lead breaks or partially explanted VNS Therapy™ systems. Extracorporeal shockwave lithotripsy may damage the generator. If therapeutic ultrasound therapy is required, avoid positioning the area of the body where the generator 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 generator output to 0 mA for the treatment, and then after therapy, reprogram the generator 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 generator should be set to 0 mA or function of the generator should be monitored during initial stages of treatment. Routine therapeutic ultrasound could damage the generator and may be inadvertently concentrated by the device, causing harm to the patient. For complete information related to home occupational environments, cellular phones, other environmental hazards, other devices, and ECG monitors, refer to the physician's manuals.

ADVERSE EVENTS — EPILEPSY

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); nausea; pain; paresthesia (prickling of the skin); pharyngitis (inflammation of the pharynx, throat); voice alteration (hoarseness); vomiting. Adverse events reported in clinical investigation of the AutoStim feature were comparable.

*The information contained in this Brief Summary for Physicians represents partial excerpts of important prescribing information taken from the physician's manuals. (Copies of VNS Therapy™ physician's and patient's manuals are posted at www.livanova.com) The information is not intended to serve as a substitute for a complete and thorough understanding of the material presented in all of the physician's manuals for the VNS Therapy™ System and its component parts nor does this information represent full disclosure of all pertinent information concerning the use of this product, potential safety complications, or efficacy outcomes.

26-0009-0100/4 (OUS) — 1 For full safety

information, please visit:

www.VNSTherapy.com

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Not all models are available in all countries

There is another solution for managing your uncontrolled seizures...



When medication alone isn't fully managing your seizures, VNS Therapy™ can be added to your epilepsy management to:

- Reduce the intensity of seizures^{13,14}
- Improve how quickly you recover from seizures^{13,14}
- Reduce how often you have seizures¹²
- Improve the quality of your everyday life¹⁵⁻¹⁷
- Reduce the risks of uncontrolled epilepsy⁷⁻¹¹

If you would like to find out more about VNS Therapy™, talk to your doctor.

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