The most proven device therapy in use for drug-resistant epilepsy patients

Proven Experience

More than 25 years of worldwide patient experience

>100,000 patients treated[1]

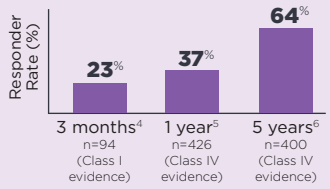
>30,000 children treated[1] (<18y)

AAN Guidelines indicate VNS Therapy for epilepsy is both safe and effective[2,3]

Restoring Wellness

VNS (closed & open loop technology)

Responder rate



Seizure Freedom[12] **8.2%** > 24 months on therapy (Engel Class 1)

QOLIE-89[7] **+5.5** *1 year mean improvement over baseline*

SUDEP rate[8]

>30% Reduction in age-adjusted SUDEP rate *from years 1 and 2 compared to years 3-10*

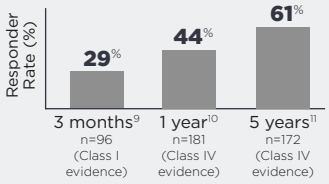
2.47 ➡ 1.68/1000 person-years

Side Effect Profile[5,6]

SURGICAL		
Infection	2.1%	
STIMULATION	**Year 1**	**Year 3**
Hoarseness	29%	2%
Paresthesia	12%	0%
Cough	8%	2%
Shortness of Breath	8%	3%

RNS (closed loop technology)

Responder rate



Seizure Freedom[11] **12.9%** any 12 month period

QOLIE-89[13] **+3.6** *1 year mean improvement over baseline*

SUDEP rate[14]

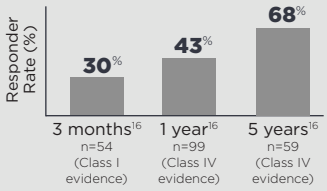
2.0/1000 person-years

Side Effect Profile[9,15]

DEVICE-RELATED SERIOUS ADVERSE EVENTS	
Infection	6.3%
Intracranial Hemorrhage	2.7%
DEVICE-RELATED ADVERSE EVENTS	**Implant to 1 year***
Implant site pain	15.7%
Headache	10.5%
Procedural headache	9.4%
Dysesthesia	6.3%
Simple partial seizures (sensory)	6.3%
Complex partial seizures	5.8%
Complex partial seizures increased	5.8%

DBS (open loop technology)

Responder rate



Seizure Freedom[17] **7.3%** any 12 month period

QOLIE-31[17] **+5.0** *13 month mean improvement over baseline*

SUDEP rate[16]

2.5/1000 person-years

Side Effect Profile[16]

DEVICE-RELATED ADVERSE EVENTS	
Infection	13.6%
Intracranial Hemorrhage	5.5%
DEVICE-RELATED ADVERSE EVENTS	**Implant to 1 year***
Implant site pain	19.1%
Paresthesia	19.1%
Lead(s) not within target	8.2%
Sensory disturbance	7.3%
Post-procedural pain	6.4%
Memory impairment	5.5%

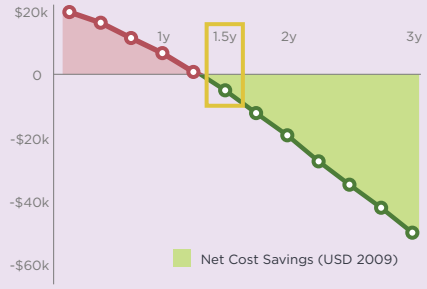
Note: The three therapies have not been compared in a head-to-head trial designed to provide comparative data. * *Occurring in ≥5% of subjects*

Ease of Use

	VNS[18,19]	RNS[21,22,23]	DBS[16,24,25,26,27,28]
Seizure Indication	Not limited by number of seizure foci **4+ years old**	Limited to 1 - 2 well-defined foci 18+ years old	Not limited by number of seizure foci 18+ years old
MRI	MR 1.5T and 3T MRI can be safely performed on patients with VNS Therapy provided specific guidelines are followed	MR 1.5T MRI can be safely performed on patients with some RNS devices provided specific guidelines are followed	MR 1.5T MRI can be safely performed on patients with some DBS devices provided specific guidelines are followed
Surgical Procedure	Minimally invasive, typically outpatient procedure	Invasive brain surgery, inpatient hospital stay	Invasive brain surgery, inpatient hospital stay
Implant Requirements	Implantable in both the community and all Comprehensive Epilepsy Centers	Must be level 4 Comprehensive Epilepsy Center to implant	Must be implanted by surgeon with experience in functional stereotactic neurosurgery
Battery Life	4.9 - 10+ years	5.1 - 9.4 years	Dependent upon programmed settings
Rescue Therapy	Additional therapy can be delivered using magnet	Not Available	Patient programmer can reset stimulation
Event Logs	Captures event detections and displays at point-of-care	Maximum of 53 minutes of ECOG activity segments	Seizures can be logged by pressing seizure key

Providing Value

Net total healthcare cost savings after 1.5 years[20]



*Negative net costs indicate lower costs in the Post-VNS period relative to the mean quarterly cost in the Pre-VNS period.

N=1,655

Net total healthcare cost savings

None Published

Net total healthcare cost savings

None Published

Indication

The VNS Therapy System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients **4 years of age and older** with partial onset seizures that are refractory to antiepileptic medications.

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.

*See important safety information at **VNSTherapy.com***

Indication

The RNS® System is an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures who have undergone diagnostic testing that localized no more than 2 epileptogenic foci, are refractory to two or more antiepileptic medications, and currently have frequent and disabling seizures (motor partial seizures, complex partial seizures and / or secondarily generalized seizures). The RNS® System has demonstrated safety and effectiveness in patients who average 3 or more disabling seizures per month over the three most recent months (with no month with fewer than two seizures), and has not been evaluated in patients with less frequent seizures.

Indication

Bilateral stimulation of the anterior nucleus of the thalamus (ANT) using the Medtronic DBS System for Epilepsy is indicated as an adjunctive therapy for reducing the frequency of seizures in individuals 18 years of age or older diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization, that are refractory to three or more antiepileptic medications. The Medtronic DBS System for Epilepsy has demonstrated safety and effectiveness for patients who average six or more seizures per month over the three most recent months prior to implant of the DBS system (with no more than 30 days between seizures). The Medtronic DBS System for Epilepsy has not been evaluated in patients with less frequent seizures.

LivaNova USA, Inc.
100 Cyberonics Boulevard
Houston, Texas 77058
Tel: +1.800.332.1375
Fax: +1.281.218.9332
www.VNSTherapy.com

LivaNova Belgium NV
Ikaroslaan 83
1930 Zaventem
Belgium
Tel: +32.2.720.95.93
Fax: +32.2.720.60.53

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Brief Summary[1] of Safety Information for the VNS Therapy® System [Epilepsy Indication] (September 2017)

1. Intended Use / Indications

Epilepsy (US)—The VNS Therapy System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients 4 years of age and older with partial onset seizures that are refractory to antiepileptic medications.

2. 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.

3. 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" section 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 manuals. 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 and those with a history of drooling or hypersalivation are at greater risk for aspiration. Use of the magnet to temporarily stop stimulation while eating may mitigate the risk of 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 (that is, one that occurs when "ON" time is greater than "OFF" time) and high frequency stimulation (i.e., stimulation at ≥ 50 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 currently being managed by devices or 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)].

Generators with AutoStim only—For anticipated use of the AutoStim feature, it is important to follow the recommended pre-surgical surface assessment described in the Implantation Procedure to determine a location for the generator to reside in which it can accurately detect heart beats

4. 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.

5. 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 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 explanted. The patient should be given antibiotics preoperatively. The surgeon should ensure that all instruments are sterile prior to the procedure. Children 4-11 years of age may have a greater risk for infection when compared to adolescent and adult patients (≥ 12 years). Careful monitoring for site infection as well as the avoidance of manipulation of the surgical site post implant in children should be stressed.

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, defibrillatory 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 generator disables or turns the device OFF (output current = 0 mA). For Model 100, 101, 102 and 102R, resetting the generator will result in device history loss.

Patients who smoke may have an increased risk of laryngeal irritation.

Generators with AutoStim only—Because the device senses changes in heart rate, false positive detection may cause unintended stimulation. Examples of instances where the heart rate may increase include exercise, physical activity, and normal autonomic changes in heart rate, both awake and asleep, etc. Adjustments to the AutoStim feature's detection threshold should be considered; which may include turning the feature OFF.

Generators with AutoStim only—The physical location of the device critically affects the feature's ability to properly sense heart beats. Care must be taken to follow the implant location selection process outlined in the Implantation Procedure.

Generators with AutoStim only—Talk to your patient about use of the AutoStim feature since use of the feature will result in faster battery drain and the potential for more frequent device replacements. The physician's manual describes the impacts to the battery life. The patient should return to their physician at appropriate intervals to further evaluate whether they are receiving benefit from the current AutoStim settings.

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.

6. 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, 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 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 *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.

7. 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.

LivaNova USA, Inc.
100 Cyberonics Boulevard
Houston, Texas 77058
USA
Tel: +1 (281) 228-7200 / 1 (800) 332-1375
Fax: +1 (281) 218-9332

www.livanova.com

[1] 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.