

Additional Information

Please see important safety information or visit
www.livanova.com/epilepsy-vnstherapy/en-au/hcp/physician-manuals

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 generalisation) or generalised seizures that are refractory to seizure medications.

Incidence of adverse events following stimulation (>5%) were voice alteration, increased coughing, pharyngitis, paresthesia, dyspnea, dyspepsia and nausea. The most common side effect of the procedure is infection.

This information is not intended to serve as a substitute for a complete and thorough understanding of the material presented in the Physician's Manuals for the VNS Therapy system and its component parts and does not represent full disclosure of all pertinent information concerning the use of this product, potential safety complications, or efficacy outcomes.

References:

1. Helmers SL, et al. Acta Neurol Scand 2012; 126(5):336-43
2. Heck C, Helmers SL, DeGiorgio CM. Neurology 2002; 59 (6 Suppl 4):S31-7
3. Patient's Guide for Epilepsy (OUS), LivaNova USA, Inc.
4. Bialer M et al. Epilepsy Research 2017; 130: 27-36
5. VNS Therapy™ System Epilepsy Physician's Manual (OUS), LivaNova USA, Inc.

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Not approved in all geographies. Please consult your labelling.

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EPI-2300529



Advanced Dosing

AspireSR™
SenTiva™



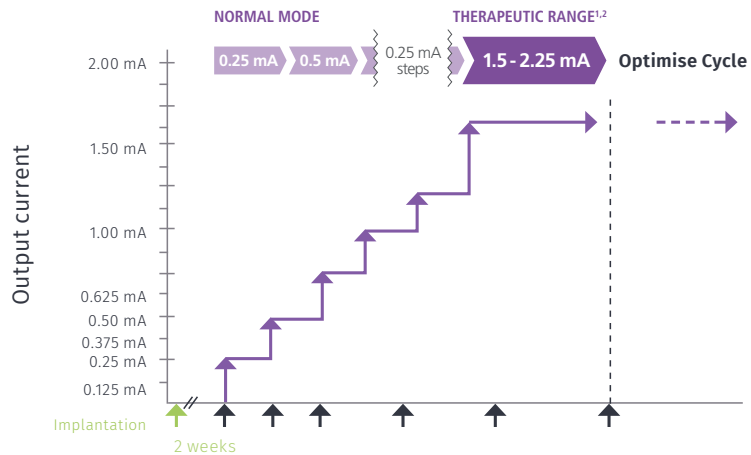
Optimising Programming

Objective 1 - Increase Output Current

Initial Programming Settings

Normal	Output Current	0.25 mA
	Frequency	20/30 Hz
	Pulse Width	250 μ sec
	DUTY CYCLE: 10%	
	ON Time	30 sec
	OFF Time	5 min
Magnet	Output Current	0.5 mA
	ON Time	60 sec
	Pulse Width	250/500 μ sec

Optimise Output Current



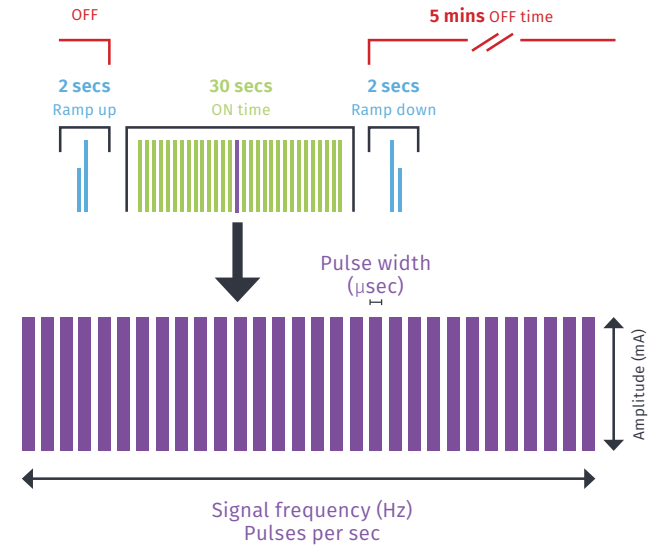
Multiple 0.25 mA increases may be made in a single visit to reach therapeutic range sooner; ensure patient tolerability before making additional adjustments.

Dosing Notes

- ▶ Continue to optimise dose to therapeutic effect or tolerability
- ▶ Give patient time to adapt to parameter changes before making additional adjustments

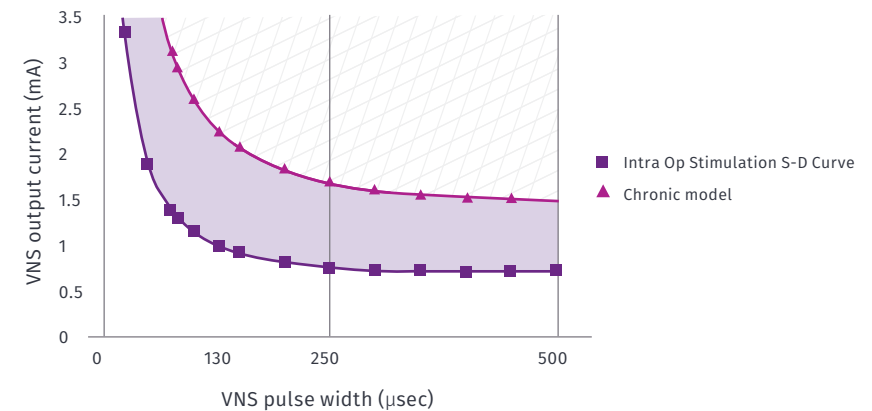
Stimulation Parameters

Stimulation Parameter Example



Strength-Duration Curve for VNS Therapy^{TM1}

Example only - individual titration required*



* Output current above the upper line may decrease battery life and have unnecessary side effects. Output Current below the lower line may be subtherapeutic.

Standard Protocol Default Settings

	Step	1	2	3	4	5	6	7	
NORMAL	Output Current	mA	0.25	0.5	0.75	1.0	1.25	1.5	1.75
	Signal Frequency	Hz	20	20	20	20	20	20	20
	Pulse Width	µsec	250	250	250	250	250	250	250
	Signal ON Time	seconds	30	30	30	30	30	30	30
	Signal OFF Time	minutes	5	5	5	5	5	5	5
AUTOSTIM™	Output Current	mA	0.375	0.625	0.875	1.125	1.375	1.625	1.875
	Pulse Width	µsec	250	250	250	250	250	250	250
	ON Time	seconds	60	60	60	60	60	60	60
MAGNET	Output Current	mA	0.5	0.75	1.0	1.25	1.5	1.75	2.0
	Pulse Width	µsec	500	500	500	500	500	500	500
	ON Time	seconds	60	60	60	60	60	60	60

- ▶ Suggest programming settings ≥ 2 weeks post-op
- ▶ Multiple 0.25 mA increases may be made in a single visit to reach therapeutic range sooner; ensure patient tolerability before making additional adjustments
- ▶ Increases in output current may be done at 0.125 mA intervals if required to improve tolerability

See VNS Therapy™ Physician's Manual for complete information on programming and diagnostics.

NOTE: At the end of each office visit, the generator must be interrogated by selecting **INTERROGATE** followed by **END SESSION** to ensure creation and accuracy of the Session Reports

Strategies to Manage Side Effects

- ▶ Evaluate tolerability after each adjustment
- ▶ Side effects become less noticeable over time for most patients³

Side Effects Management

1. Pulse Width	500 → 250 µsec
2. Signal Frequency	30 → 25 or 20 Hz
3. Change Duty Cycle	30 sec ON/5 min OFF versus 7 sec ON/1.8 min OFF
4. Output Current	↓ 0.125 mA or ↓ 0.25 mA

For AutoStim-related Side Effects

1. Verify Heartbeat Sensitivity Calibration	Adjust Heartbeat Sensitivity, if necessary
2. Output Current	AutoStim mode: ↓ 0.125 mA
3. Threshold for AutoStim	If patient reports "overstimulation": Autostim Threshold ↑ 10% If patient reports "understimulation": Autostim Threshold ↓ 10%

LivaNova recommends that stimulation with Normal Mode ON time > OFF time be avoided. Duty Cycle = (ON Time + 4 seconds) / (ON time + OFF Time), for which ON and OFF Time are measured in seconds.

Optimising Programming

Objective 2 - Optimise Seizure Response

Initial Settings for Responsive VNS Therapy™

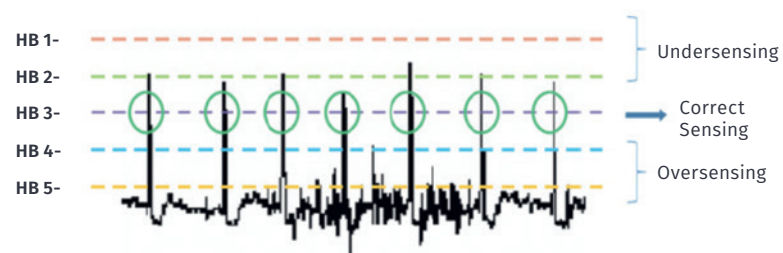
(with AspireSR™, SenTiva™)

AutoStim	Output Current	0.125mA higher than Normal mode settings
	Pulse Width	Equal to Normal mode settings
	ON Time	30/60 sec
Seizure Detection		ON
Heartbeat Detection	Sensitivity Range 1-5	Verify by comparing the heart rate shown on the VNS Therapy™ programming system with that measured by a heart-rate sensing device. If the heartbeat detection is inaccurate, adjustments of heartbeat detection sensitivity may be needed. Refer to the sensitivity levels below.
Threshold for AutoStim	% heart rate change Range 20-70%	Refer to Detection Threshold

The initial sensitivity level may be set at HB 1 but adjusted if necessary

(See VNS Therapy Physician's Manual).

Example:



Undersensing (reduced or inconsistent detection)

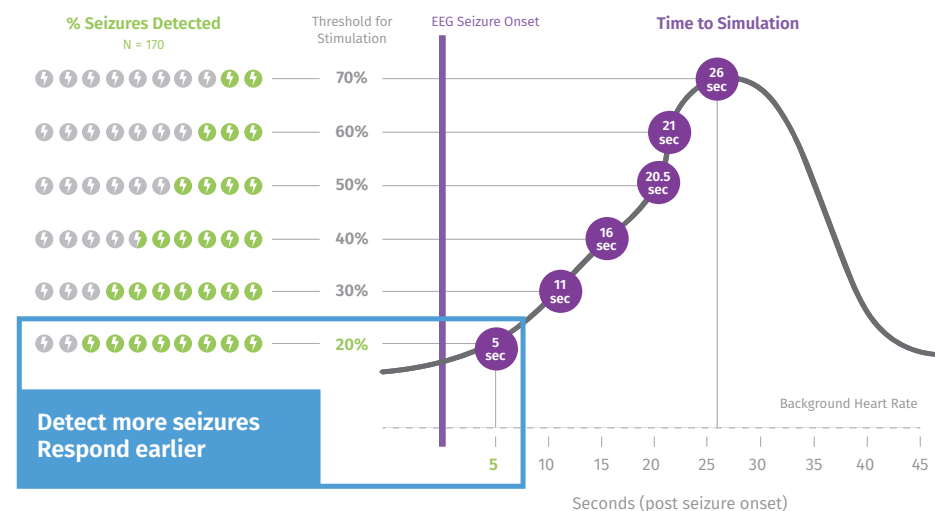
Oversensing (additional detection of “noise” between heartbeats)

Detection Threshold

The initial seizure response threshold may be set at 20%

- ▶ The threshold (20-70%) determines the relative heart rate increase that will trigger AutoStim, thereby also influencing detection latency⁴.
- ▶ Ensure early, tolerable and reliable seizure detection in patients with seizures associated with ictal tachycardia.

Example seizure with heart rate increase⁴



Detect more seizures
Respond earlier

Optimising Programming

Objective 3 - Optimise Duty Cycle

Standard Duty Cycle (DC) is 10%

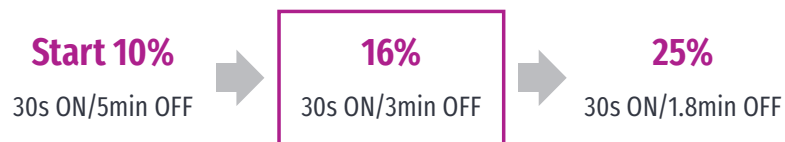
(30 sec ON and 5 min OFF)

- If clinical response is suboptimal 3 month after completing the Objective 2, consider changes in duty cycle (typically, decreasing the OFF time). Adjustments to duty cycle should be less frequent (3 - 6 months).⁵

ON TIME (seconds)	OFF TIME (minutes)									
	0.2	0.3	0.5	0.8	1.1	1.8	3	5	10	
7	58%	44%	30%	20%	15%	10%	6%	4%	2%	
14	69	56	41	29	23	15	9	6	3	
21	76	64	49	36	29	19	12	8	4	
30	81	71	57	44	35	25	16	10	5	
60	89	82	71	59	51	38	27	18	10	

- Recommended
- Not available with AutoStim feature enabled
- Not recommended*

Recommended progression for duty cycle:

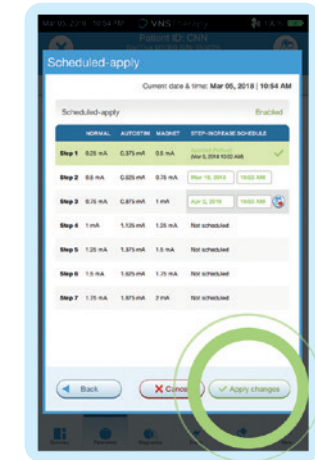
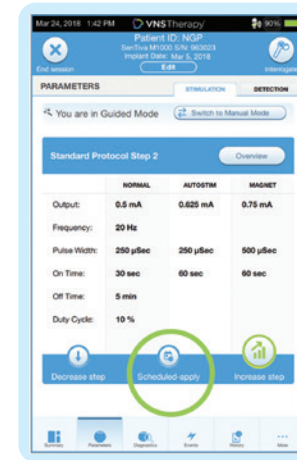


*LivaNova recommends that stimulation with Normal Mode ON time > OFF time be avoided. Duty Cycle = (ON Time + 4 seconds) / (ON time + OFF Time), for which ON and OFF Time are measured in seconds.

Customisable Programming Features

(SenTiva™ only)

Scheduled Programming*



- Optional feature allowing the programming of a titration schedule in one office visit. The titration changes will be applied at the defined intervals while the patient lives their life. Follow an approved Standard Protocol or create a custom protocol.

***Caution:** This feature 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.

Day-Night Programming



- Two independent sets of parameters within a 24 hour period can be customised and delivered based on each patient's needs. Parameters will alternate based on time of day. Select which parameters will change, what time the change will occur, and the duration of the change.

Brief Summary¹ of Safety Information for the VNS Therapy™ System

[Epilepsy Indication] (December 2022)

1. INTENDED USE / INDICATIONS

Epilepsy (ANZ)—The VNS Therapy System (exclusive of SenTiva™) 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™ features an Automatic Stimulation Mode which is intended for patients who experience seizures that are associated with cardiac rhythm increases known as ictal tachycardia.

The SenTiva™ pulse generator 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 (with or without secondary generalisation) or generalised seizures that are refractory to antiepileptic medications. SenTiva features an Automatic Stimulation Mode which is intended for patients who experience seizures that are associated with cardiac rhythm increases known as ictal tachycardia.

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" 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 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.

The Wand, Programmer, and patient magnet are MR unsafe devices. These devices are projectile hazards and must not be brought into the MR scanner room.

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)].

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 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 explanted. The patient should be given antibiotics preoperatively.

The surgeon should ensure that all instruments are sterile prior to the procedure. Children (<12 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 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 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.

SenTiva 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. 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.

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); hypoesthesia (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.

¹The 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.

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