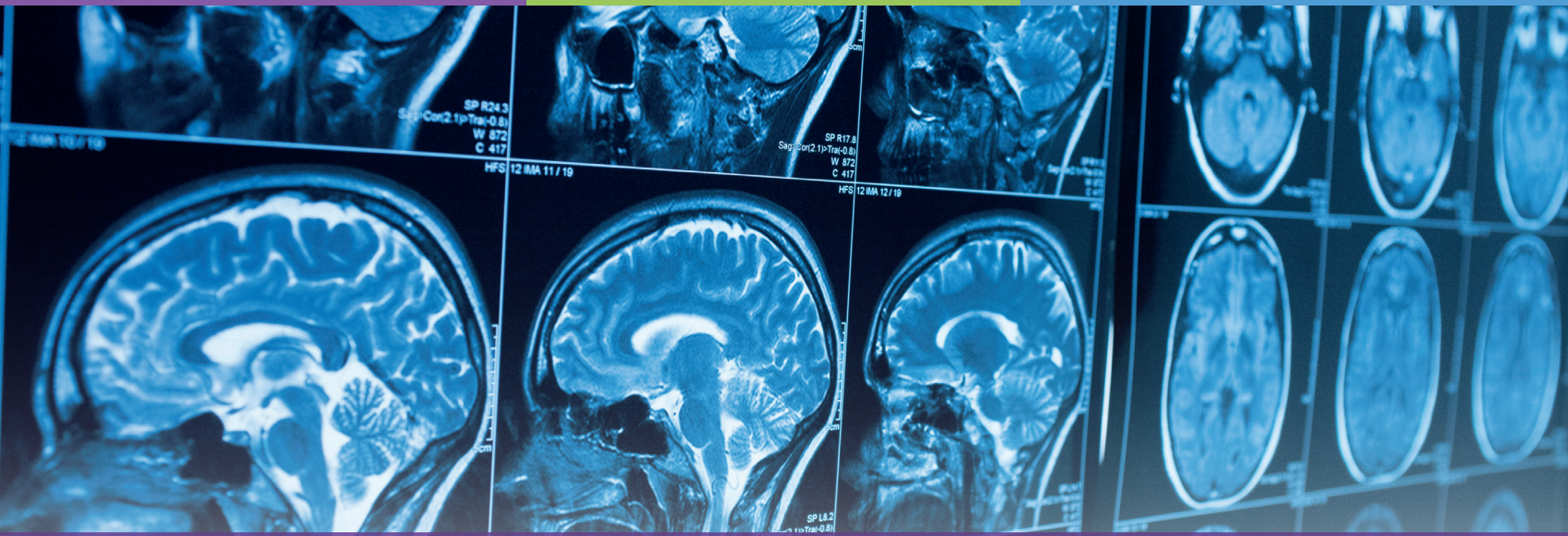
VNS Therapy®

MRI Guidelines for VNS Therapy®



The new MRI labeling allows patients with an implanted VNS Therapy System to receive fast and high quality scans – also with use of Body Coils*.

MRI can be safely performed on patients with VNS Therapy provided that specified guidelines are followed.

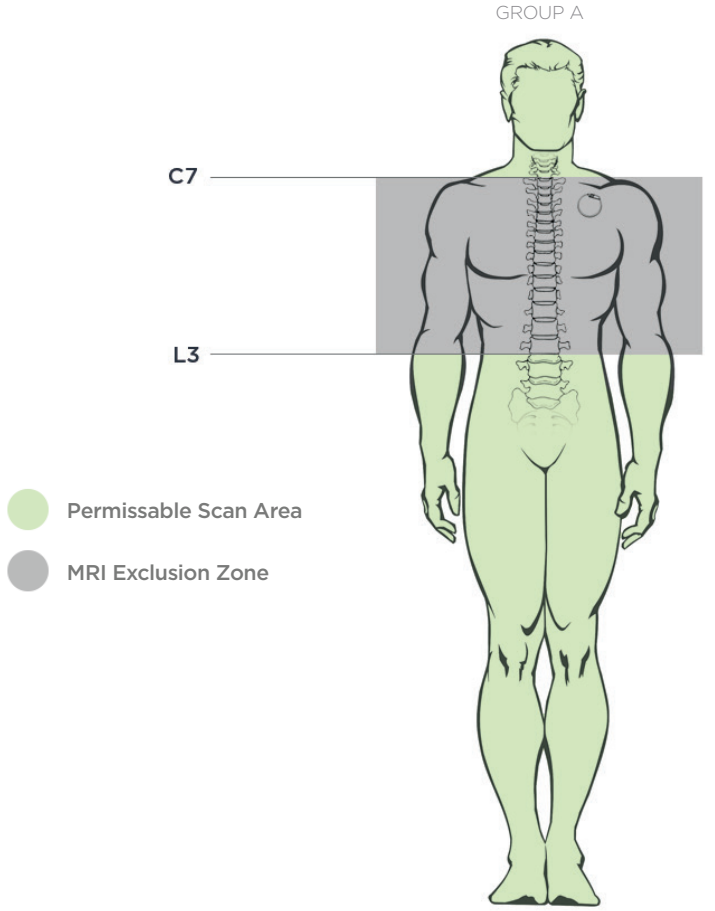
*only for DemiPulse® Model 103, Aspire HC® Model 105, AspireSR® Model 106, SenTiva® Model 1000 or Symmetry™ Model 8103 with scan conditions as listed on page 2

Safe MRI Conditions with the usage of **Transmit Body Coil**

Performing MRI with a body coil is safe when the below conditions are followed:

No local transmit-receive coil required

DemiPulse® Model 103, Aspire HC® Model 105, AspireSR® Model 106, SenTiva® Model 1000 or Symmetry™ Model 8103 and the generator location according LivaNova implanting guidelines in the upper left chest at or above armpit (above rib 4)†

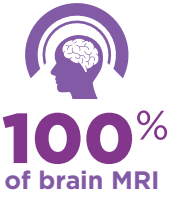


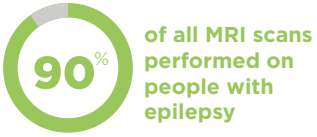
Imaging techniques such as computed tomography, x-ray, and ultrasound are safe to perform in the MRI exclusion zone.

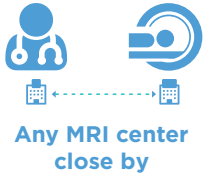
† Patients with implants in other locations must follow alternate scan conditions as listed on page 4

Safe MRI Conditions with the usage of **Transmit Body Coil**

DemiPulse® Model 103, Aspire HC® Model 105, AspireSR® Model 106, SenTiva® Model 1000 or Symmetry™ Model 8103 and the generator location according LivaNova implanting guidelines in the upper left chest at or above armpit (above rib 4)†







Review the most current labelling prior to performing an MRI scan. For full MRI safety information, refer to MRI Instructions for Use at **www.VNSTherapy.com**

† Patients with implants in other locations must follow alternate scan conditions as listed on page 4

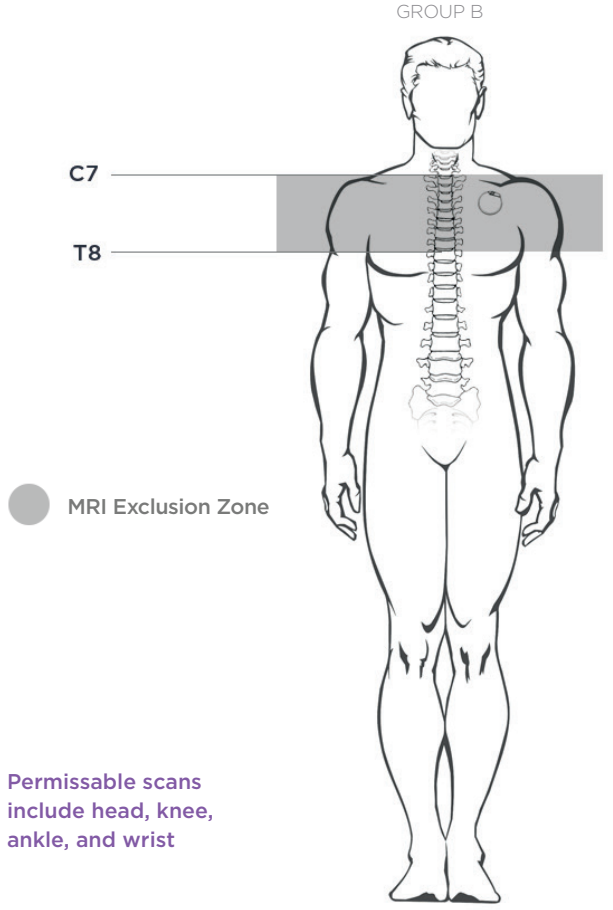
MR Conditional	Yes
Static Magnet Strength	1.5T or 3T
Scanner Type	Horizontal field, cylindrical closed-bore 1.5T or 3T scanner
Operating Mode	Normal Operating Mode
Exclusion Zone	**Body coil:** C7-L3 **Transmit-receive head or extremity coil:** C7-T8
Max Spatial Gradient	≤ 3000 Gauss/cm
Max Slew Rate	200 T/m/s
RF Coil	**Transmit:** Body coil or Transmit-receive head or extremity coils **Receive:** No Restrictions
Max SAR	**Transmit head coil:** 3.2 W/kg **Transmit body coil:** 2.0 W/kg
System Programming	Stimulation OFF Sensing OFF• •for select models with AutoStim mode Optional device features OFF (Model 1000 only)
Exposure Time	**Transmit head or extremity coil:** No restrictions **Transmit body coil:** ≤ 15 minutes of active scan time within a 30 minute window

Safe MRI Conditions with **Transmit-Receive Local Coil**

Performing MRI with a transmit-receive coil is safe when the below conditions are followed:

Local transmit-receive coil required

Pulse™ Model 102, Pulse Duo™ Model 102R, DemiPulse Duo® Model 104 and DemiPulse® Model 103, AspireHC® Model 105, AspireSR® Model 106, SenTiva® Model 1000 or Symmetry™ Model 8103. **NOT** located in the upper left chest, at or above armpit (above rib 4).



Permissable scans include head, knee, ankle, and wrist

Imaging techniques such as computed tomography, x-ray, and ultrasound are safe to perform in the MRI exclusion zone.

Safe MRI Conditions with the usage of **Transmit-Receive Local Coil**

Pulse™ Model 102, Pulse Duo™ Model 102R, DemiPulse Duo® Model 104 and AspireHC® Model 105, AspireSR® Model 106 or SenTiva® Model 1000. **NOT** located in the upper left chest, at or above armpit (above rib 4).

100% access to brain MRI

Requires special local transmit-receive coils

Access to extremity scans including knee, ankle, and wrist

MR Conditional	Yes
Static Magnet Strength	1.5T or 3T
Scanner Type	Horizontal field, cylindrical closed-bore 1.5T or 1.3T scanner
Operating Mode	Normal Operating Mode
Exclusion Zone	C7-T8
Max Spatial Gradient	≤3000 Gauss/cm
Max Slew Rate	200 T/m/s
RF Coil	Transmit-receive head or extremity coils
Max SAR	**Transmit-receive head coil:** 3.2 W/kg
System Programming	Stimulation OFF Sensing OFF* *for select models with AutoStim mode Optional device features OFF (Model 1000 only)
Exposure Time	**Transmit-receive head or extremity coil:** No restrictions
Additional Restrictions	None

Review the most current labelling prior to performing an MRI scan. For full MRI safety information, refer to MRI Instructions for Use at **www.VNSTherapy.com**

Special MRI scenarios

Performing MRI is safe when the guidelines are followed:

Suspected Lead Break	OR	Lead Only ≥ 2cm remaining
		
MR Conditional	Yes	
Static Magnet Strength	1.5T or 3T	
Scanner Type	Horizontal field, cylindrical closed-bore	
Operating Mode	Normal Operating Mode	
Exclusion Zone	C7-T8	
Max Spatial Gradient	≤ 3000 Gauss/cm	
Max Slew Rate	200 T/m/s	
RF Coil	Transmit-Receive head or extremity coils only	
Max SAR	**Transmit-Receive head coil**: 3.2 W/kg	

Lead Only ≤ 2cm remaining*	
	
Exclusion Zone	None
MR Conditional	Yes
Static Magnet Strength	1.5T or 3T
Operating Mode	Normal Operating Mode
Max Spatial Gradient	≤ 3000 Gauss/cm
Max Slew Rate	200 T/m/s
RF Coil	**Transmit**: Body or transmit-receive head or extremity coils **Receive**: No Restrictions
Max SAR	**Transmit head coil:** 3.2 W/kg **Transmit body coil:** 2.0 W/kg

* Equivalent to clipping the lead at the anchor tether

Pre- and Post-MRI Instructions

Pre-MRI instructions

An appropriate healthcare professional with access to a VNS Therapy programming system must prepare the VNS Therapy generator before the patient enters an MR system room.

1. Interrogate the VNS Therapy generator and record the generator settings
2. Perform System Diagnostics to ensure proper operation of the generator
3. Reprogram the Output Current parameter settings for Normal Mode, Magnet Mode, and AutoStim Mode† as follows:
   - Normal Output Current (mA): 0.0
   - Magnet Current (mA): 0.0
   - Model 106 and 1000 only
     - Detection “OFF”
     - AutoStim Output Current: 0 mA
4. Turn off any other optional device features (Model 1000 only).
5. Interrogate the generator to verify that programming was successful
6. Verify that placement of the VNS Therapy system is located between the C7 and T8 vertebrae
7. Instruct the patient to notify the MR system operator of pain, discomfort, heating, or other unusual sensations so the operator can terminate the procedure, if needed.

† for select models with AutoStim mode

Pre- and Post-MRI Instructions

Post-MRI instructions

After the MRI procedure, an appropriate healthcare professional with access to a VNS Therapy programming system should assess the condition of the VNS Therapy system.

To assess the VNS Therapy system:

1. Interrogate the VNS Therapy generator
2. If the generator was reset during the scan, reprogram the serial number, patient ID and implant date, as needed*
3. Program the patient's therapeutic parameters as they were **before the MRI procedure**
4. Perform System Diagnostics. Results should indicate **Impedance = OK**
5. Interrogate the generator again to confirm that reprogramming was successful.

For patients with Tuberous Sclerosis currently MRI is considered the modality of choice for the evaluation of the brain. Computer Tomography is the modality of choice for evaluating renal lesions.[1]

To ensure effective communication with the MRI centre, complete the Patient MRI Form.
Send with the patient to their MRI appointment. Form can be downloaded at **easy-mri.com**

* When an interrogation is performed by the programming software, the generator serial number, implant date, stimulation parameters, and generator operating time are automatically logged in the programmer database. This information may be retrieved from the database at any time after interrogation.

Brief Summary* of Safety Information for the VNS Therapy® System

[Epilepsy Indication] (October 2017)

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 that occurs when "ON" time is greater than "OFF" time) and high frequency stimulation (i.e., stimulation at ≥50Hz) 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 allpotential 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. 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 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

VNS Therapy®

References:
1. Bennett S Greenspan, MD et al.; Medscape Nov 30, 2015 Tuberous Sclerosis Imaging; Overview http://emedicine.medscape.com/article/385549-overview

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AspireSR®, AspireHC® and SenTiva® are CE mark approved and commercial distribution may vary by country.

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