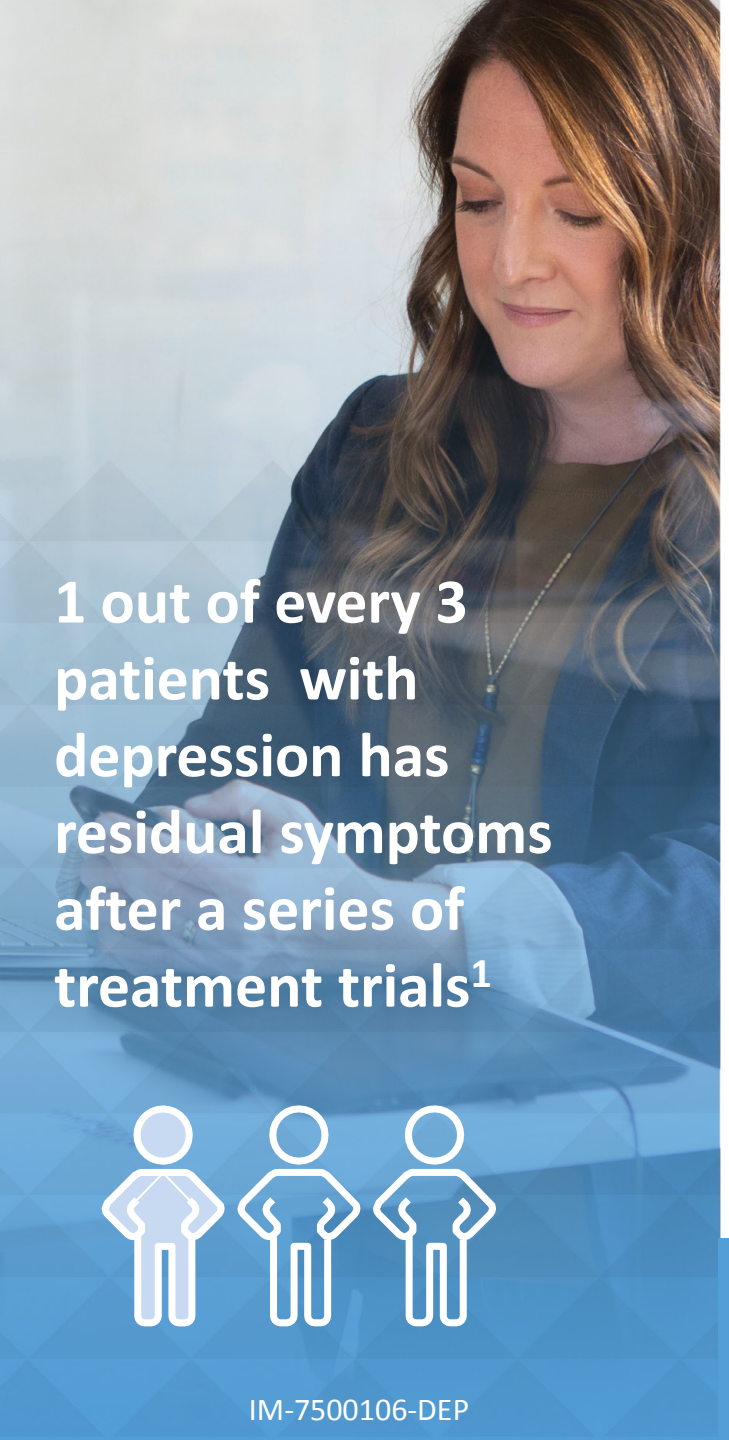
WHAT IF...

small things
became easier?

SYMMETRY

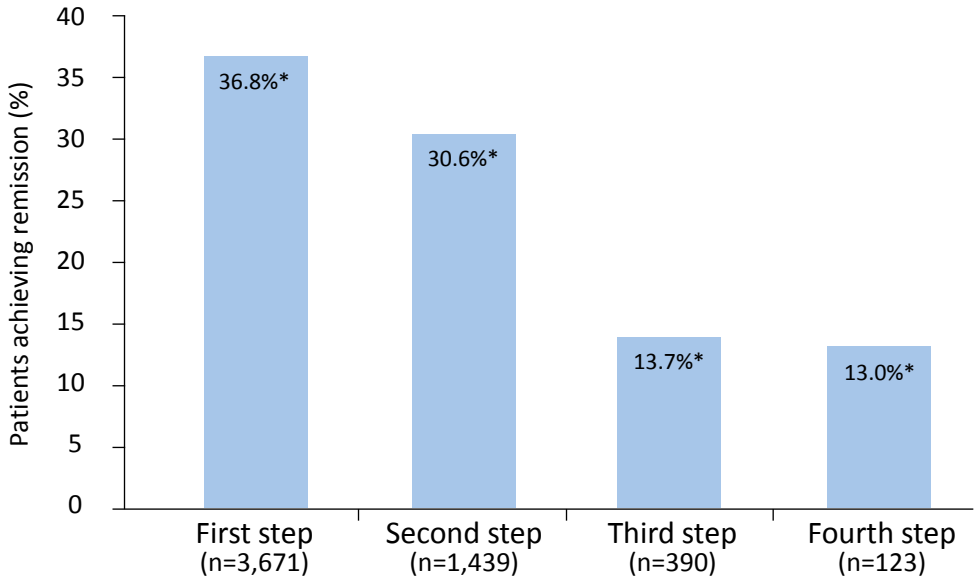
Treat Depression Differently

The VNS Therapy System is indicated for the treatment of chronic or recurrent depression in patients that are in a treatment-resistant or treatment-intolerant major depressive episode.



1 out of every 3 patients with depression has residual symptoms after a series of treatment trials[1]

Success becomes less attainable with each antidepressant treatment[1]



* Remission defined as QIDS-SR[16] score ≤ 5 at exit from the indicated treatment step

Approximately 50% of all patients with depression will experience a chronic or recurrent course of illness[2].

1. Rush AJ et al. Am J Psychiatry 2006;163:1905-17.
2. Keitner GA et al. Psychiatr Clin N Am 2012;35:249-65.

SYMMETRY™

Treat Depression Differently

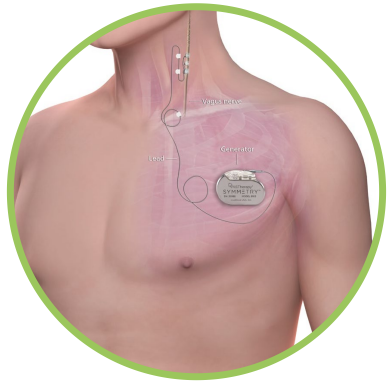
If you're struggling with depression that is difficult to treat

GET WELL AND STAY WELL—WITH SYMMETRY

IM-7500106-DEP

VNS Therapy®: The antidepressant therapy that provides long-term protection from depression symptoms with a one-time procedure[1,2]

VNS Therapy® is indicated for the treatment of chronic or recurrent depression in patients who are in a treatment-resistant or treatment-intolerant major depressive episode[3].



- The procedure consists of a small generator and lead implanted under the skin below the collarbone (similar to a pacemaker)[1].
- An attached electrode passes stimulation to the vagus nerve, which in turn sends electrical pulses to areas of the brain associated with mood regulation[4].
- VNS Therapy is a proven technology with 100,000 patients implanted across multiple diseases[5].

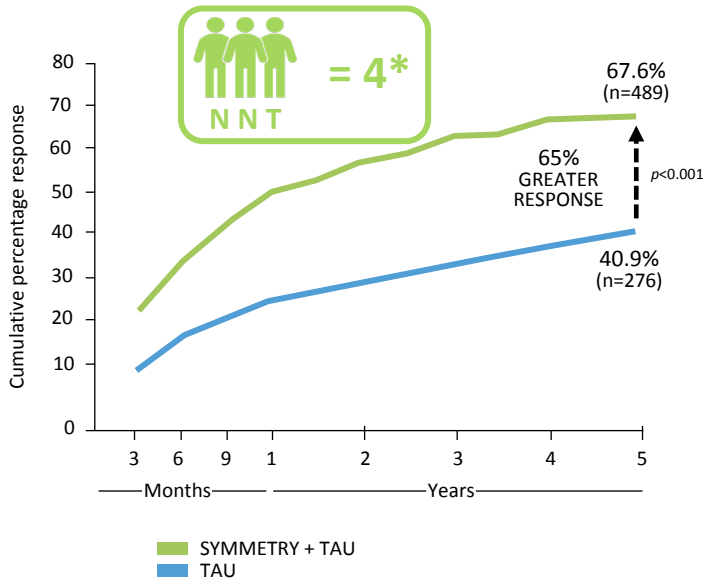
1. livaNova VNS Therapy® Patients Guide for Depression. September 2019.
2. Aaronson ST et al. Am J Psychiatry 2017;174:640-48.
3. EC Design-Examination Certificate;DEKRA,issued nov 29,2019.
4. Nemeroff CB et al. Neuropsychopharmacol 2006;31:1345-55.
5. LivaNova Data on File.

SYMMETRY™

Treat Depression Differently

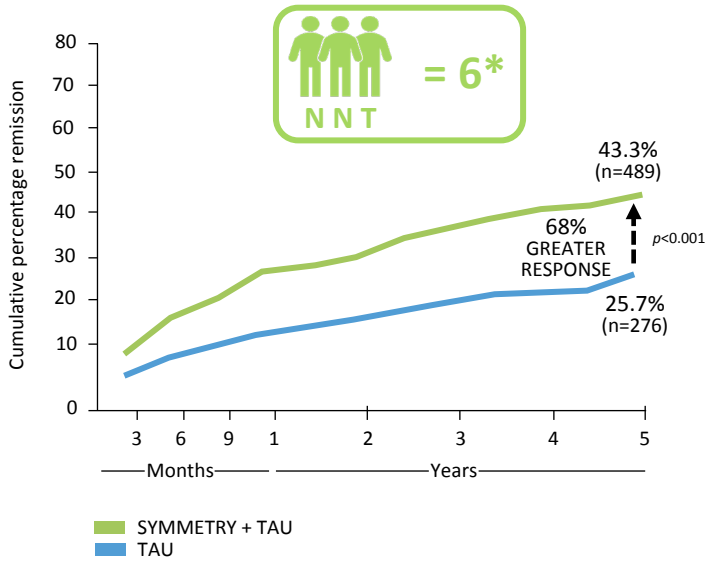
Symmetry (+TAU) delivered superior cumulative response and remission rates vs traditional treatment alone (p<0.001)

FIRST-TIME RESPONSE



Response is defined as a decrease of ≥50% in baseline MADRS score at any post baseline visit during the 5-year study.

FIRST-TIME REMISSION



Remission is defined as a MADRS score ≤ 9 at any post baseline visit during the 5-year study.

* The Number Needed to Treat (NNT) is the inverse of the Absolute Risk Reduction (ARR).

Aaronson ST et al. Am J Psychiatry 2017;174:640-48.

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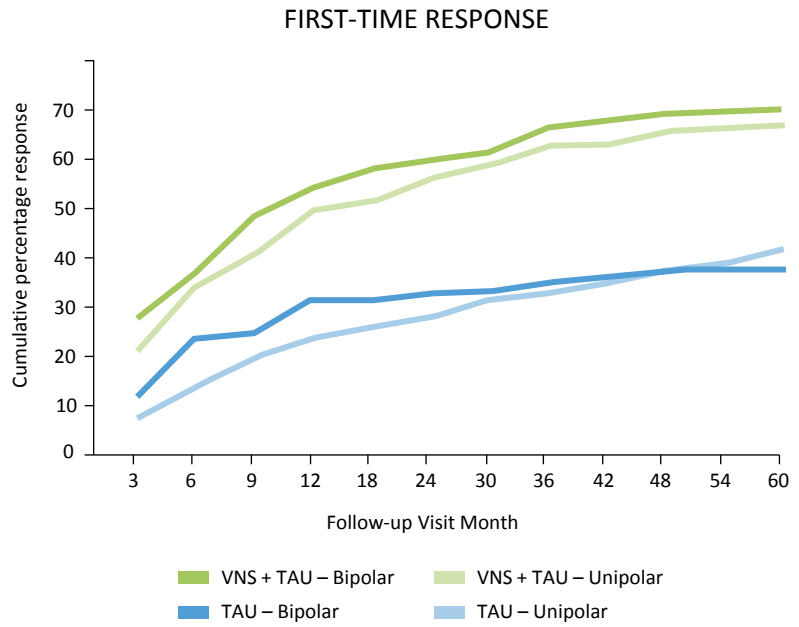
Treat Depression Differently

Symmetry (+TAU) is efficacious in both unipolar and bipolar depression and significantly better than TAU



Response is defined as a decrease of ≥50% in baseline MADRS score at any post baseline visit during the 5-year study.

Aaronson ST et al. Am J Psychiatry 2017;174:640-48.

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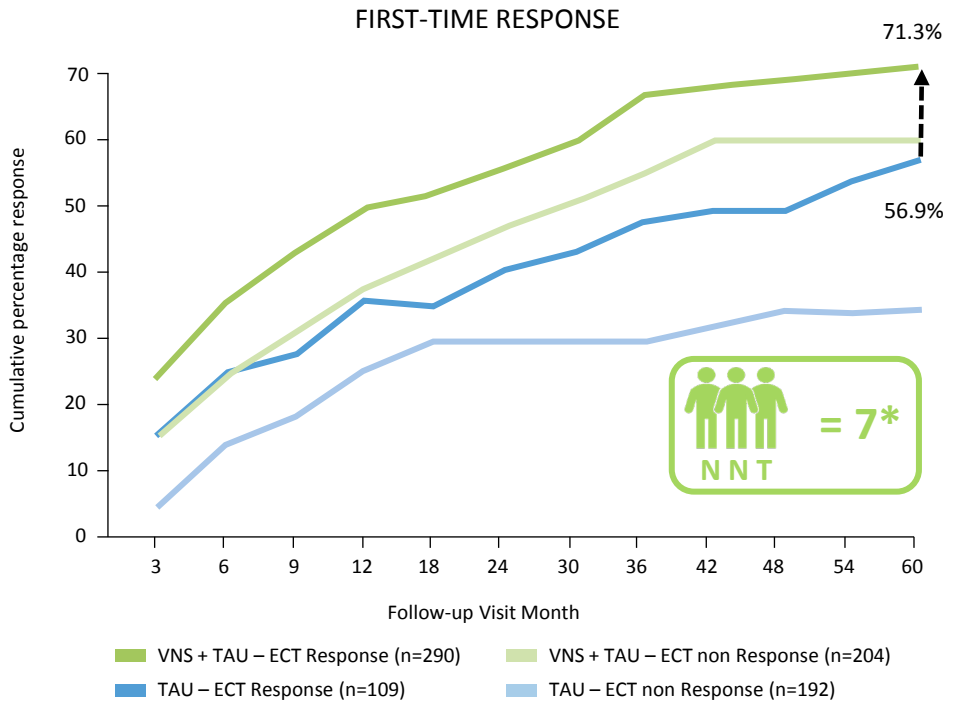
MADRS response by history of prior ECT response



Response is defined as a decrease of ≥50% in baseline MADRS score at any post baseline visit during the 5-year study.

The 5-year cumulative response rate for patients treated with VNS Therapy (+TAU) who had previously responded to ECT was significantly greater compared with patients treated with TAU alone (p=0.006)

- **VNS (+TAU): 71.3%**
- **TAU: 56.9%**

A significant difference was seen at 9 months, and it was maintained for the duration of the study.

* The Number Needed to Treat (NNT) is the inverse of the Absolute Risk Reduction (ARR).

SYMMETRY (+TAU) is more effective in terms of cumulative response vs treatment as usual alone

Aaronson ST et al. Am J Psychiatry 2017;174:640-48.

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SYMMETRY (+ TAU) patients could achieve a clinically meaningful increase in QOL when the MADRS drop from baseline is at least 34%

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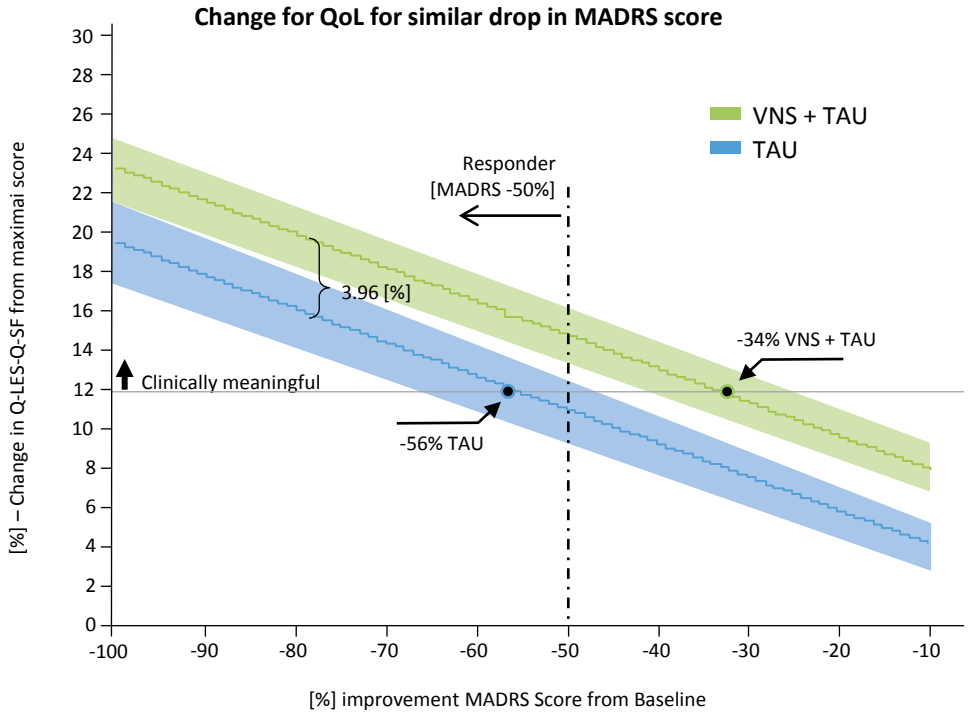
Symmetry (+ TAU) shows a significant improvement in the quality of life



Patients treated with Symmetry (+TAU) experienced quality of life improvements with MADRS reductions far below the classical 50% improvement definition of depression response.

The TAU patients achieved the same increase when the MADRS drop from baseline is much bigger (at least 56%)

Conway CR et al. J Clin Psychiatry 2018;79:18m12178.

SYMMETRY™

Treat Depression Differently

Efficacy that protects your patients most at risk

SYMMETRY + TAU (=n489)

RATE OF SUICIDE

(Reduction in suicide rate
per 1,000 person years at 5 years)

50%

(1.01 vs 2.20 for TAU)

Rate of suicide decreased by 50%

ALL-CAUSE MORTALITY

(Reduction in all-cause mortality
per 1,000 person years at 5 years)

60%

(3.53 vs 8.63 for TAU)

All-cause mortality decreased by 60%

Aaronson ST et al. Am J Psychiatry 2017;174:640-48.

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Treat Depression Differently

There is safety in our numbers

Initial Implant-related adverse events (>10%)[1]	Stimulation-related adverse events (≥10%)[1]
Incision pain (36%)	Voice alteration (55%)
Voice alteration (33%)	Increased cough (24%)
Incision site reaction (29%)	Dyspnea (19%)
Device-site pain (23%)	Neck pain (16%)
Device site reaction (14%)	Dysphagia (13%)
Pharyngitis (13%)	Laryngismus (11%)
Dysphagia (11%)	Paresthesia (10%)
Hypersthesia (11%)	

Symmetry is well tolerated, and side effects were less noticeable over time[3]

IM-7500106-DEP

1. VNS Therapy® System Depression Physician's Manual, Aug 2020. 2. LIvaNova Data on File. 3. Berry SM et al. Med Devices (Auckl) 2013;6:17-35.

* Across multiple diseases

VNS Therapy: The antidepressant therapy that provides long-term protection with a one-time procedure

- Symmetry is indicated for the treatment of chronic or recurrent depression in patients who are in a treatment-resistant or treatment-intolerant major depressive episode.
- Symmetry (+TAU) delivers superior cumulative response and remission rates vs Treatment as Usual (TAU) alone over 5 years
- Symmetry (+ TAU) shows a significant improvement in the quality of life
- Symmetry is well tolerated, and side effects were less noticeable over time

SYMMETRY™

Treat Depression Differently

IM-7500106-DEP

Brief Summary

Brief Summary[1] of Safety Information for the VNS Therapy® System [Depression Indication] (February 2021)

1. INTENDED USE / INDICATIONS

Depression (OUS)—The VNS Therapy System is indicated for the treatment of chronic or recurrent depression in patients who are in a treatment-resistant or treatment-intolerant major depressive episode.

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 contra indication.

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 ≥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.

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.

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Treat Depression Differently

Brief Summary

4. WARNINGS — DEPRESSION

This device is a permanent implant. It is only to be used in patients with severe depression who are unresponsive to standard psychiatric management. It should only be prescribed and monitored by physicians who have specific training and expertise in the management of treatment-resistant depression 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.

Physicians should warn patients that VNS Therapy has not been determined to be a cure for depression.

Patients being treated with adjunctive VNS Therapy should be observed closely for clinical worsening and suicidality, especially at the time of VNS Therapy stimulation parameter changes or drug or drug dose changes.

Use of the magnet to activate stimulation is not recommended for patients with depression.

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 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.

Brief Summary

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.

Brief Summary

7. ADVERSE EVENTS — DEPRESSION

Implant-related adverse events reported during the pivotal study in ≥ 5% of patients are listed in order of decreasing occurrence: incision pain, voice alteration, incision site reaction, device site pain, device site reaction, pharyngitis, dysphagia, hypesthesia, dyspnea, nausea, headache, neck pain, pain, paresthesia, and cough increased.

Stimulation-related adverse events reported during the acute sham-controlled study by ≥ 5% of VNS Therapy-treated patients are (in order of decreasing occurrence): voice alteration, cough increased, dyspnea, neck pain, dysphagia, laryngismus, paresthesia, pharyngitis, nausea, and incision pain.

[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.

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