LivaNova Epilepsy | VNS Therapy™

THE RIGHT DOSE AT THE RIGHT TIME.

Aligning clinical practice to increase chances to achieve a therapeutic response in your patients

Approximately 50%

of VNS Therapy™ patients take longer than **1 year to reach target dosing**[1]

Although VNS Therapy has effectively helped manage Drug-Resistant Epilepsy (DRE) for more than 25 years, post-marketing surveillance of dosing practice revealed that approximately 50% of VNS Therapy patients take longer than 1 year to reach target dosing. Yet achieving a therapeutic response is key to improving patient outcomes.[1,2]

LivaNova Epilepsy | VNS Therapy™

References

1. Tzadok, M., Verner, R., Kann, L., Tungala, D., Gordon, C., El Tahry, R., & Fahoum, F. (2022). Rapid Titration of VNS Therapy Reduces Time-To-Response in Epilepsy. Epilepsy and Behavior.
2. Fahoum F, Boffini M, Kann L, et al. VNS parameters for clinical response in epilepsy. Brain Stimul. 2022;(15):814-821.

The goal of dosing[1]

Generate an action potential on the vagus nerve by creating a charge

Adjust stimulation parameters to reach a therapeutic dose and maximize therapeutic effect

Minimize side effects

References

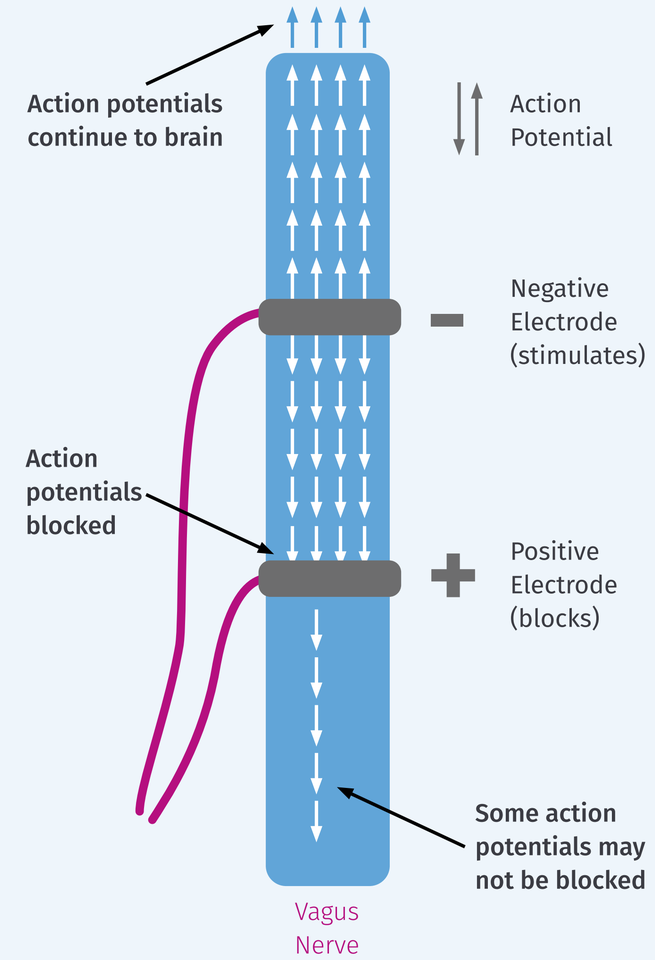
1. VNS Therapy™ System Epilepsy Physician's Manual (OUS), LivaNova USA, Inc.

How VNS Therapy™ works

Action potential propagation[1]

Negative electrode **generates action potentials** that **travel primarily afferently** via sensory fibers.[1]

Efferently traveling action potentials **are mostly blocked** by positive electrode. Those not blocked could cause side effects.[1]



References

1. Ahmed, U., Chang, YC., Cracchiolo, M. et al. Anodal block permits directional vagus nerve stimulation. Sci Rep 10, 9221 (2020). https://doi.org/10.1038/s41598-020-66332-y

How VNS Therapy™ works

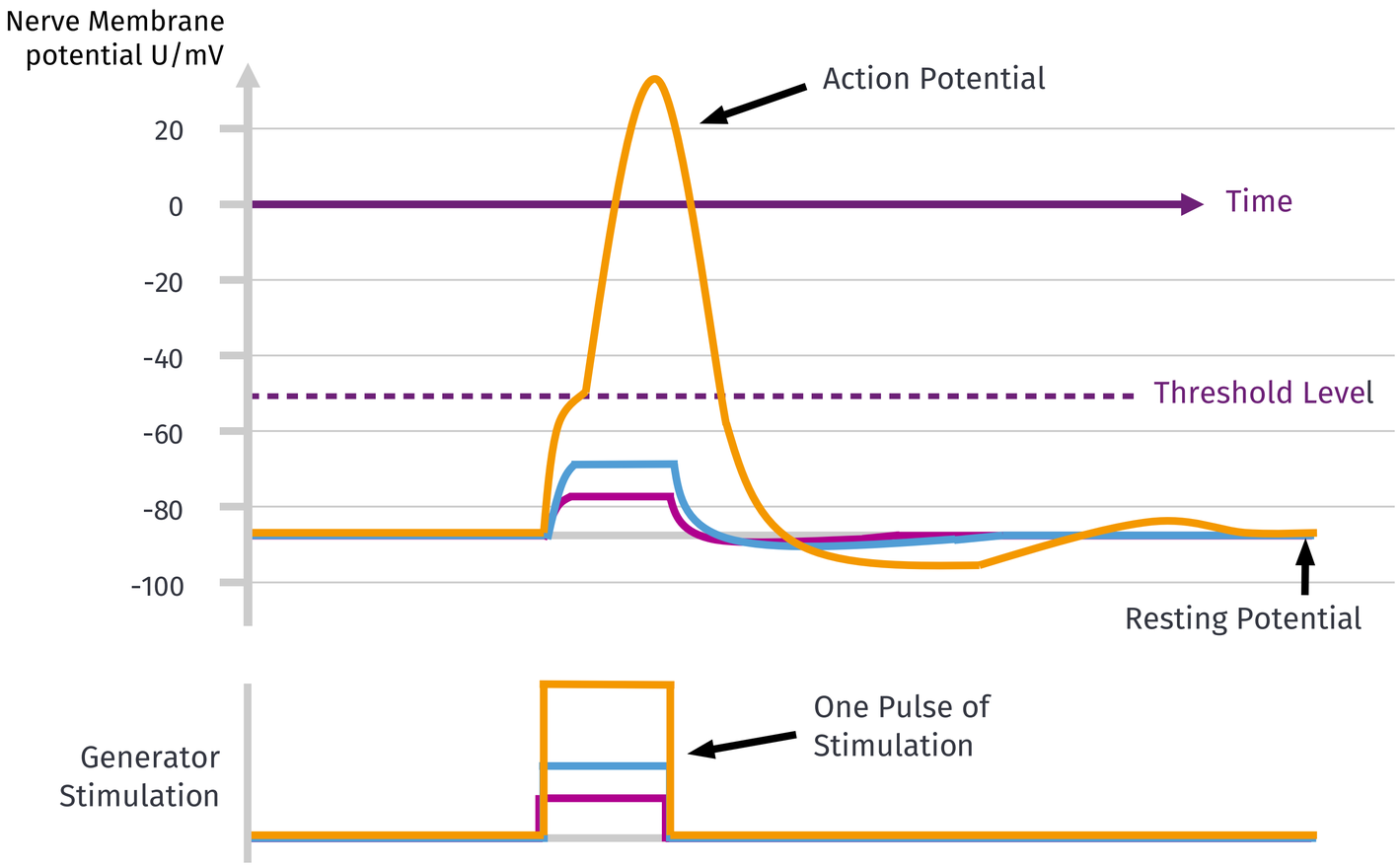
Action Potential Initiation[1]

Stimulation must be high enough for membrane potential to reach Threshold Level

Stimulation not enough to reach Threshold Level

Stimulation not enough to reach Threshold Level

When Threshold Level is met, Action Potential is initiated



References

1. Barker R, Cicchetti F, Neal MJ. Resting membrane and action potential. In: Neuroscience at a glance. 4th ed. Wiley-Blackwell. 2012

How VNS Therapy™ works

Response to stimulation[1]

The position, composition of the fascicles (A,B,C fibers) and key fascicles needed for effective stimulation **vary among patients**.

The VNS Therapy™ **electrode** will not fully encircle the nerve (max. 270 degrees).

If the **fibers of interest** are in the uncovered region, they may require **more charge** for activation.

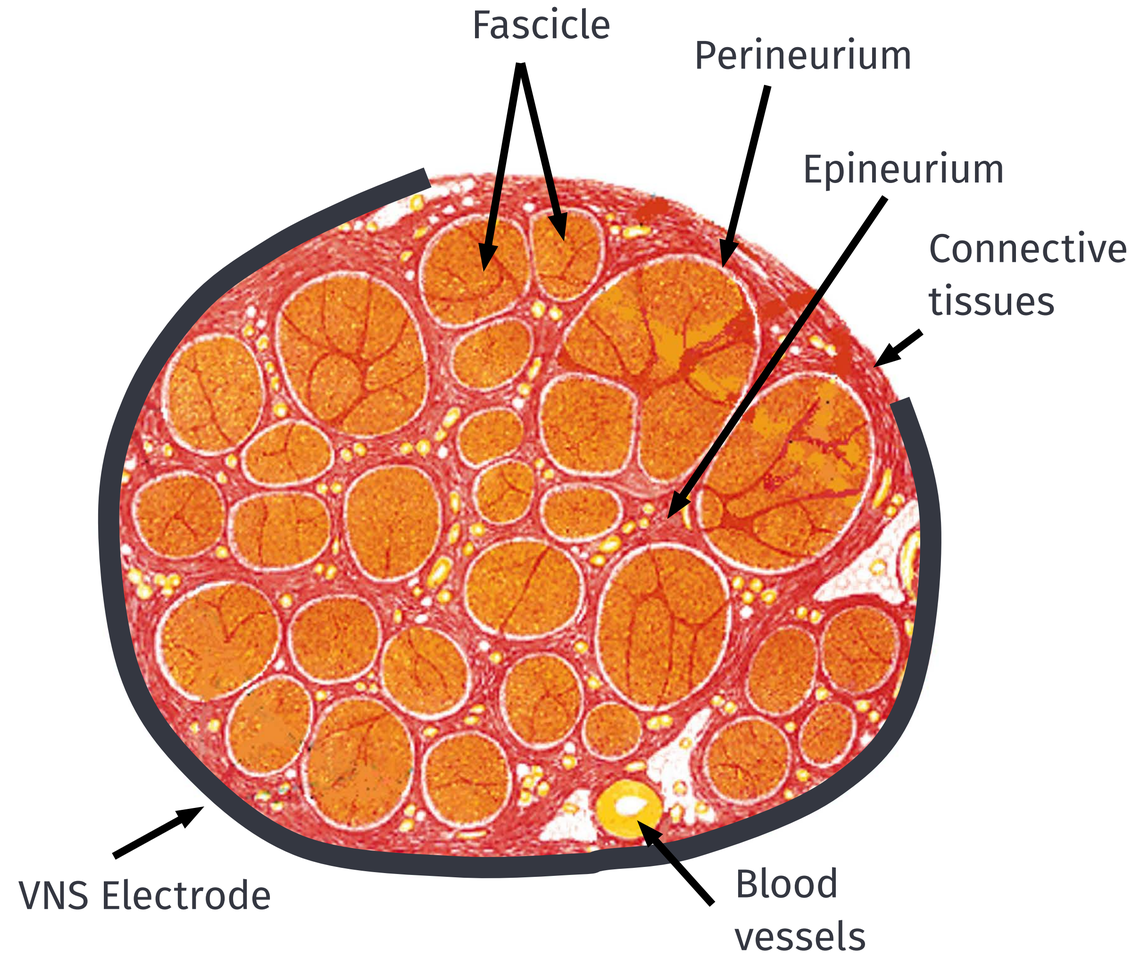


Illustration of a peripheral nerve with fibre bundles and connective tissues

References

1. Helmers SL, et al. Acta Neurologica Scand. 2012;126(5):336-43.

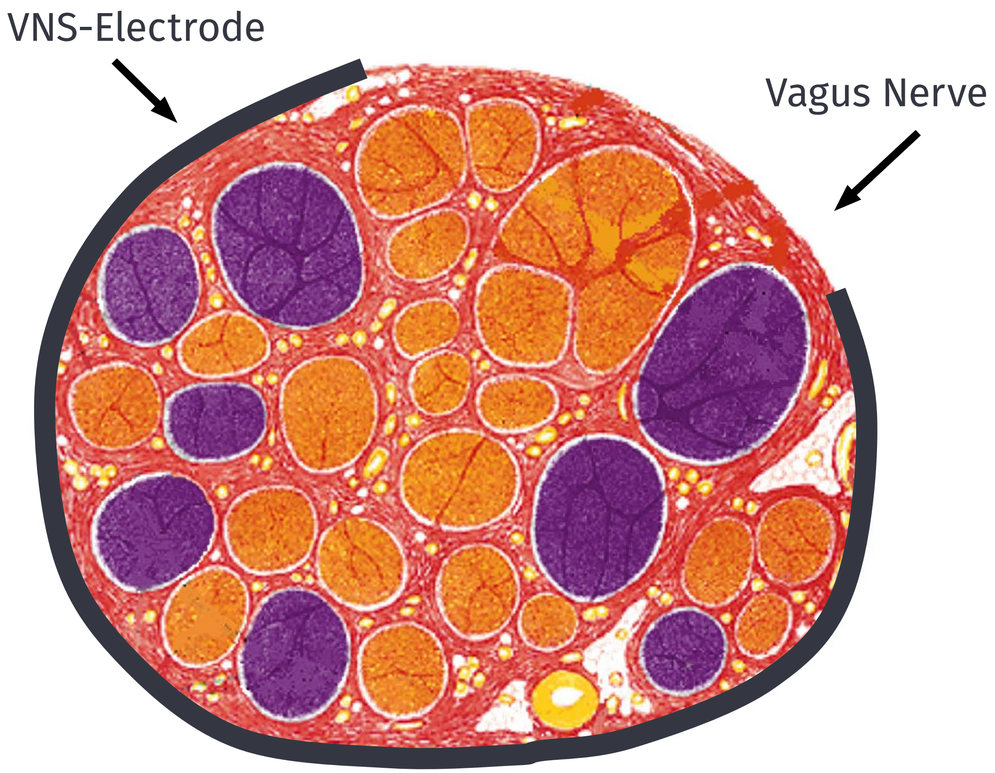
How VNS Therapy™ works

Response to stimulation[1]

Schematic illustration for VNS Therapy™

Stimulus

While ramping up the stimulation current, more and more nerve fibers in a mixed nerve get activated and create action potentials.



Illustration

References

1. Helmers SL, et al. Acta Neurologica Scand. 2012;126(5):336-43.

How VNS Therapy™ works

Response to stimulation[1]

Schematic illustration for VNS Therapy™

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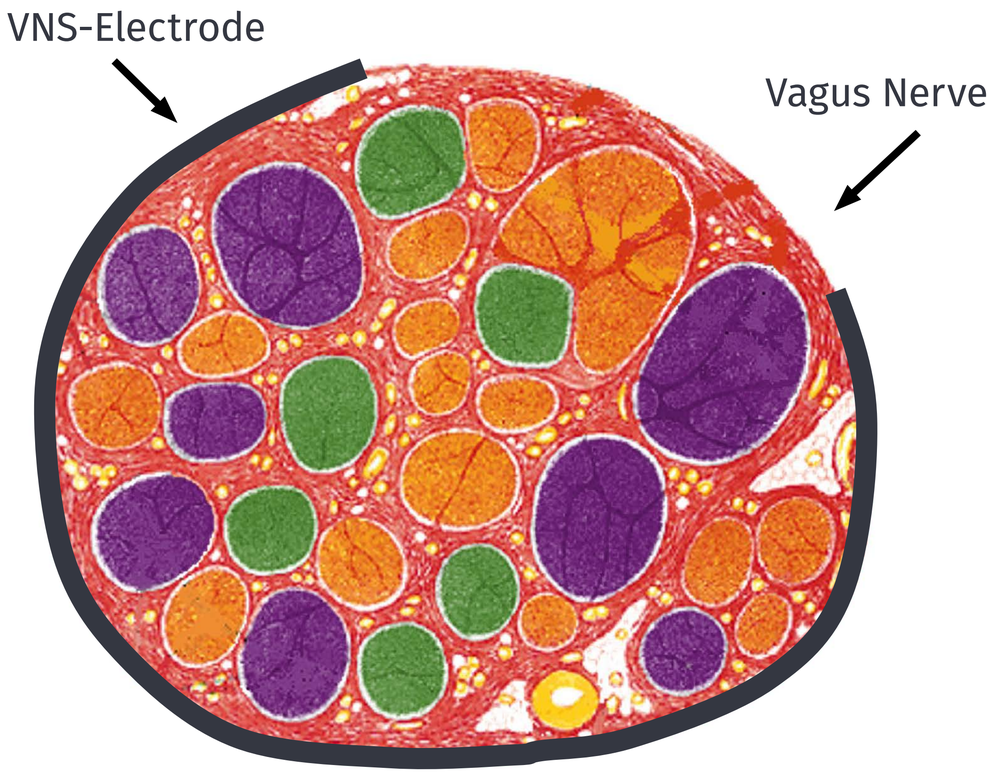


Illustration

References

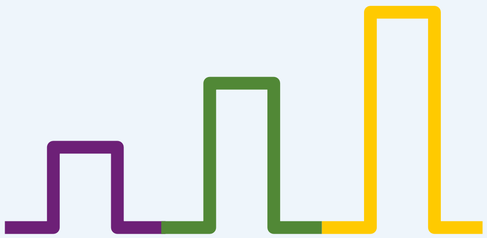
1. Helmers SL, et al. Acta Neurologica Scand. 2012;126(5):336-43.

How VNS Therapy™ works

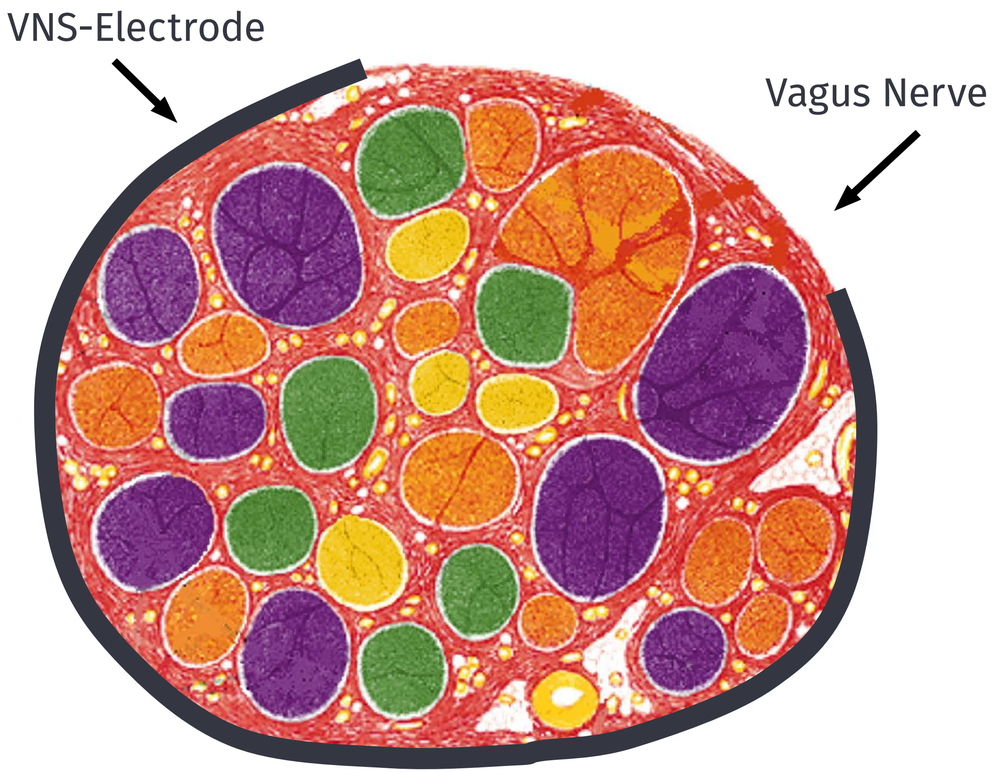
Response to stimulation[1]

Schematic illustration for VNS Therapy™

Stimulus



While ramping up the stimulation current, more and more nerve fibers in a mixed nerve get activated and create action potentials.



Illustration

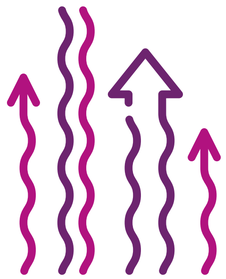
References

1. Helmers SL, et al. Acta Neurologica Scand. 2012;126(5):336-43.

Key parameters to consider in dosing

Dose of VNS Therapy™

Dosing frequency



Output Current

Pulse Width

Signal Frequency

Duty Cycle

Target volume

Therapeutic message

Together, output current, pulse width, and signal frequency can be considered **the dose of VNS Therapy™.** Duty cycle can be regarded as **dosing frequency.** Output current and pulse width comprises the target volume whereas signal frequency and duty cycle can be considered as the therapeutic neural modulation ‘message’ for VNS Therapy.[1]

Patients implanted and dosed shortly after their initial DRE diagnosis were shown to benefit from VNS Therapy. However, chronically underdosed patients currently on VNS Therapy may still benefit from target-range titration.[1]

LivaNova Epilepsy | VNS Therapy™

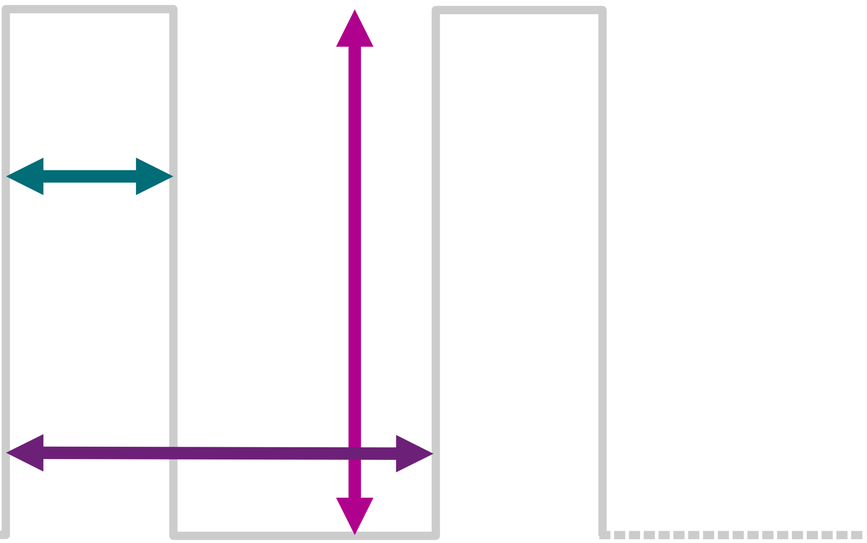
References

1. Fahoum F, Boffini M, Kann L, et al. VNS parameters for clinical response in epilepsy. Brain Stimul. 2022;(15):814-821.

The key parameters in dosing explained[1]

Output Current (mA)
Amount of electrical current delivered in a single pulse of stimulation.

Pulse Width (µsec)
Duration of a single pulse within a stimulation period.



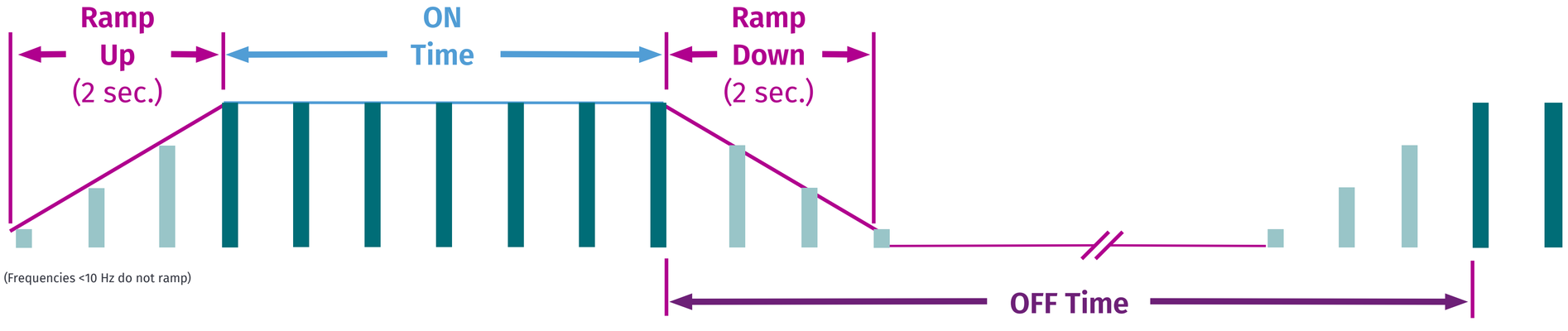
Signal Frequency (Hz)
Number of pulses per second.

References

1. VNS Therapy™ System Epilepsy Physician's Manual (OUS), LivaNova USA, Inc.

The key parameters in dosing explained[1]

Duty cycle: the amount of time stimulation is being delivered in a 24-hour period



(Frequencies <10 Hz do not ramp)

Ramp Up/Down Period
Gradual Increase/Decrease in output current intensity at the beginning/end of stimulation pulses

ON Time (sec)
Duration of time that the Generator delivers pulses at the programmed output current

Off Time (min)
Interval between programmed ON Times (includes Ramp Up/Down periods)

References

1. VNS Therapy™ System Epilepsy Physician's Manual (OUS), LivaNova USA, Inc.

Focus on getting within target range for stimulation volume

The combination of output current and pulse width comprises the ‘volume’ of critically important neural stimulation. Combined with the physical size and shape of the VNS Therapy™ electrode, they jointly determine the intensity of electrical stimulation— working in concert to activate vagus nerve fibers by way of the electrode-tissue interface.[1]

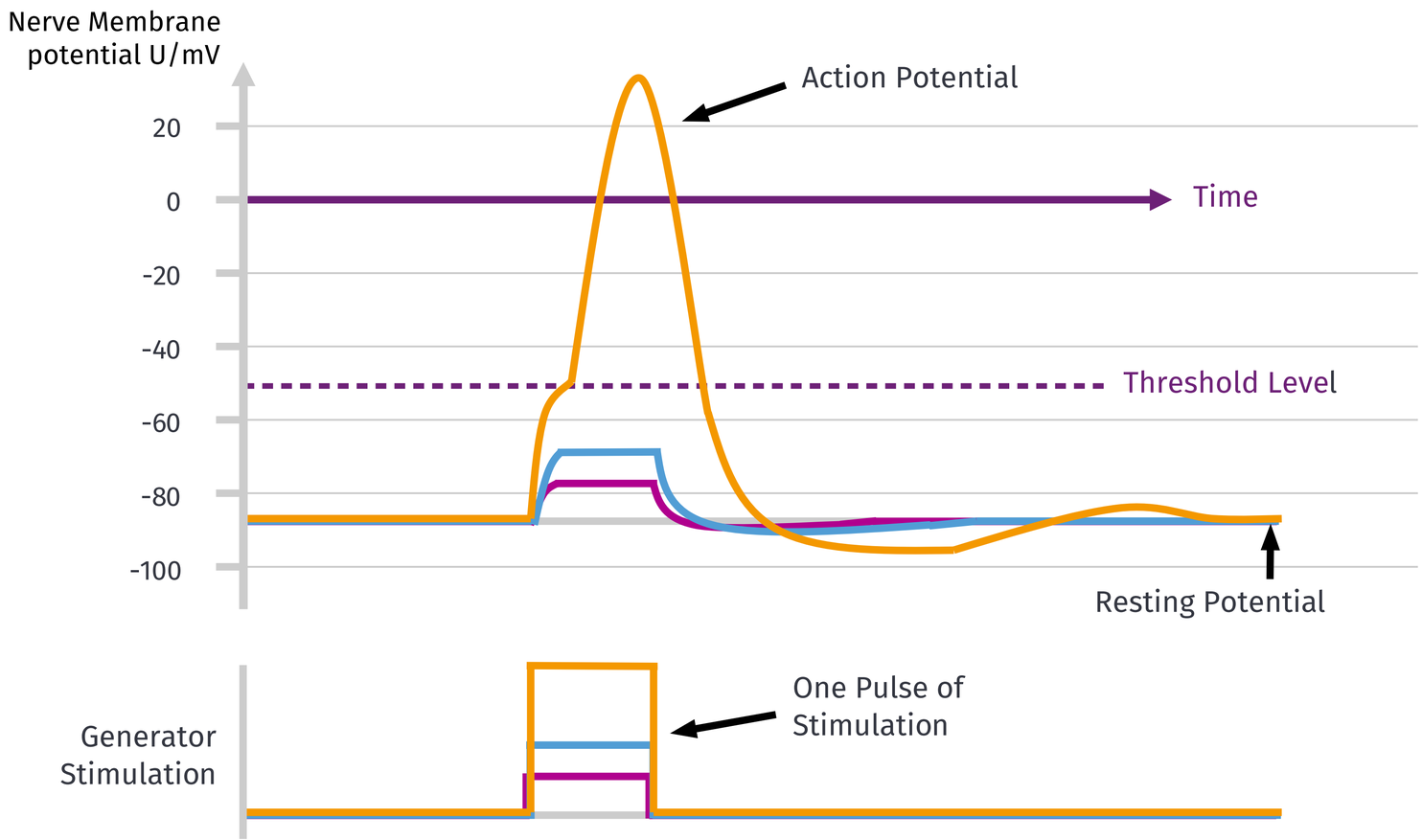
References

1. Fahoum F, Boffini M, Kann L, et al. VNS parameters for clinical response in epilepsy. Brain Stimul. 2022;(15):814-821.

Focus on getting within target range for stimulation volume

Achieving action potential is a critical component

An action potential is only initiated when a charge density is strong enough to depolarize the nerve.[1]



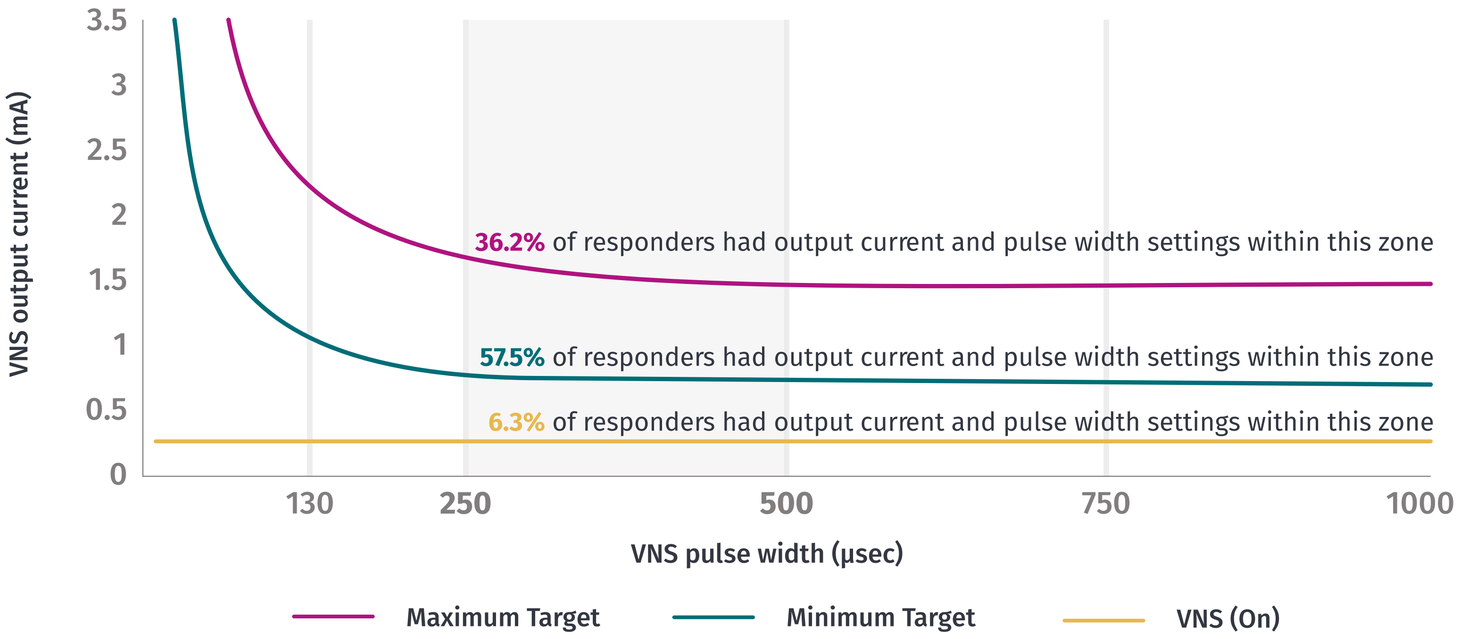
References

1. Barker R, Cicchetti F, Neal MJ. Resting membrane and action potential. In: Neuroscience at a glance. 4th ed. Wiley-Blackwell. 2012

Focus on getting within target range for stimulation volume

Vagus Nerve Stimulation Threshold Strength-Duration Curve for Responders

Output Current-Pulse Width Range[1]



57.5%
of responders*

had output current and pulse width above the minimum and below the maximum target[1]

Only 6.3%
of patients responded*

to output current and pulse width below the minimum target[1]

The top line represents data from responders in the LivaNova E05 extension study and the VNS Therapy Registry. The curved line in the middle is based on data collected by Evans et al. Because the study was conducted intraoperatively, it should be noted that the results may not fully represent the stimulation needed to recruit fibers as fibrosis develops.[1]

***Response is defined as a reduction in seizure frequency that is 50% or greater from baseline.[1]**

LivaNova Epilepsy | VNS Therapy™

References

1. Helmers SL, Begnaud J, Cowley A, et al. Application of a computational model of vagus nerve stimulation. Acta Neurol Scand. 2012;126(5):336-43. DOI: 10.1111/j.1600-0404.2012.01656.x.

Focus on getting within target range for stimulation volume

Getting the volume right increases response[1]

A retrospective analysis of VNS Therapy parameters revealed a dose of VNS for epilepsy associated with seizure frequency reduction that lies within the target range in the product labeling. Patients titrated near this dose experienced greater seizure frequency reduction than those titrated above or below it.

	N	12-month Responder Rate	Median Seizure Reduction
Output Current <1 mA	44	36%	34.46%
Output Current 1.5-1.75 mA	392	47%	43.27%
Output Current >= 2.5 mA	32	41%	32.76%

Clinical outcomes of people with VNS titrated to settings near the model-selected dose of 1.625mA. Patients in each group were selected to have the listed output current at any pulse width at 12-months of follow up. The response rate was calculated at 12 months after implant.

TARGET RANGE SETTINGS DELIVER THE RIGHT MESSAGE AT THE RIGHT VOLUME

References

1. Fahoum F, Boffini M, Kann L, et al. VNS parameters for clinical response in epilepsy. Brain Stimul. 2022;(15):814-821.

Focus on getting within target range for stimulation volume

Getting the volume right increases response[1]

VNS responders titrated to the appropriate VNS parameters at or before 12 months after implant had a durable response to the therapy at future follow-up. Those who stayed at settings within the 1.5 mA-1.75 mA range had the highest likelihood of prolonged response to VNS.

	N (Unique Visits After 12 Months)	Responder Rate	Median Seizure Frequency Reduction
Output Current <1.5 mA	7	71%	100%
Output Current 1.5-1.75 mA	209	87%	86.13%
Output Current > 1.75 mA	98	80%	75.72%

Long-term clinical outcomes of VNS responders titrated to the target intensity of VNS (1.5mA – 1.75mA) by 12 months after implant (n = 184 subjects). Patients initially titrated to this dose may have increased or decreased their VNS dose at follow up visits after 12 months.

TARGET RANGE SETTINGS DELIVER THE RIGHT MESSAGE AT THE RIGHT VOLUME

LivaNova Epilepsy | VNS Therapy™

References

1. Fahoum F, Boffini M, Kann L, et al. VNS parameters for clinical response in epilepsy. Brain Stimul. 2022;(15):814-821.

Sending the right therapeutic message

Use signal frequency to send the right therapeutic message

Signal frequency and duty cycle can be considered as the therapeutic neural modulation ‘message’ for VNS Therapy.[1]

SIGNAL FREQUENCIES OF 20 HZ - 30 HZ ARE THE ONLY RECOMMENDED OPTIONS

as there is no evidence that lower or higher frequencies improve efficacy and could lead to lower tolerability.[1]

References

1. Fahoum F, Boffini M, Kann L, et al. VNS parameters for clinical response in epilepsy. Brain Stimul. 2022;(15):814-821.

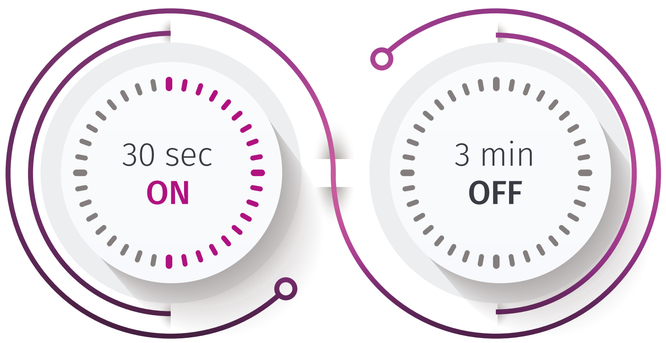
Sending the right therapeutic message

Adjust duty cycle to repeat the therapeutic message as often as necessary

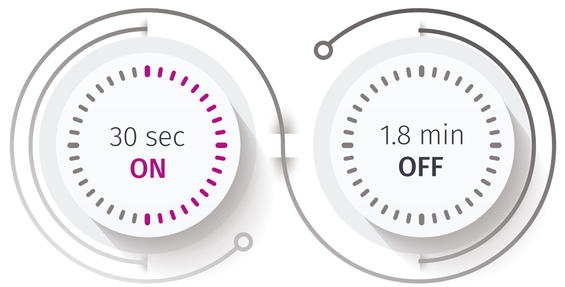
The duty cycle defines the cadence or dose repetition of VNS Therapy™.[1]

INITIAL DUTY CYCLE = 10%—DEFINED AS[1]:

A 16% DUTY CYCLE—DEFINED AS:



A 25% DUTY CYCLE—DEFINED AS:



INCREASING DUTY CYCLE MAY IMPROVE EFFICACY*[1]

It provides greater repetition of the therapeutic message and may increase the likelihood of response. There is limited data on higher duty cycles, and higher duty cycles will affect battery life.[2]

Duty Cycle = (ON Time + 4 seconds) / (ON Time + OFF Time), for which ON and OFF Time are measured in seconds.

***As a safety precaution, duty cycles above 50%, even at lower frequencies are highly discouraged.[1]**

LivaNova Epilepsy | VNS Therapy™

References

1. VNS Therapy™ System Epilepsy Physician's Manual (OUS), LivaNova USA, Inc.
2. Fahoum F, Boffini M, Kann L, et al. VNS parameters for clinical response in epilepsy. Brain Stimul. 2022;(15):814-821.

Sending the right therapeutic message

Titrate to target range quickly

FASTER TITRATION TO TARGET RANGE =

EARLIER THERAPEUTIC RESPONSE

Patients who were titrated to target range within 3 months per the recommended protocol achieve onset of response faster.[1,2]

Consider the speed of titration, especially in light of evidence from a post-hoc analysis supporting earlier therapeutic response to VNS Therapy™ when patients were titrated according to labeling recommendations compared to those who were not, often without an increase in rates of adverse events.[3]

References

1. Tzadok, M., Verner, R., Kann, L., Tungala, D., Gordon, C., El Tahry, R., & Fahoum, F. (2022). Rapid Titration of VNS Therapy Reduces Time-To-Response in Epilepsy. Epilepsy and Behavior.
2. VNS Therapy™ System Epilepsy Physician's Manual (OUS), LivaNova USA, Inc.
3. Fahoum F, Boffini M, Kann L, et al. VNS parameters for clinical response in epilepsy. Brain Stimul.2022;(15):814-821.

Sending the right therapeutic message

Scheduled programming makes it easier to reach the target dose

Safely titrate multiple steps without office visits[1]

VNS THERAPY™ SCHEDULED PROGRAMMING*:

Reduce the number of patient visits necessary to achieve target output current range

Plan the exact timing of up to 7 increments of 0.125 mA or 7 increments of 0.25 mA

Spend less time and resources on VNS Therapy™ titration per patient

***Scheduled programming is only available in models 1000 and 1000D.**

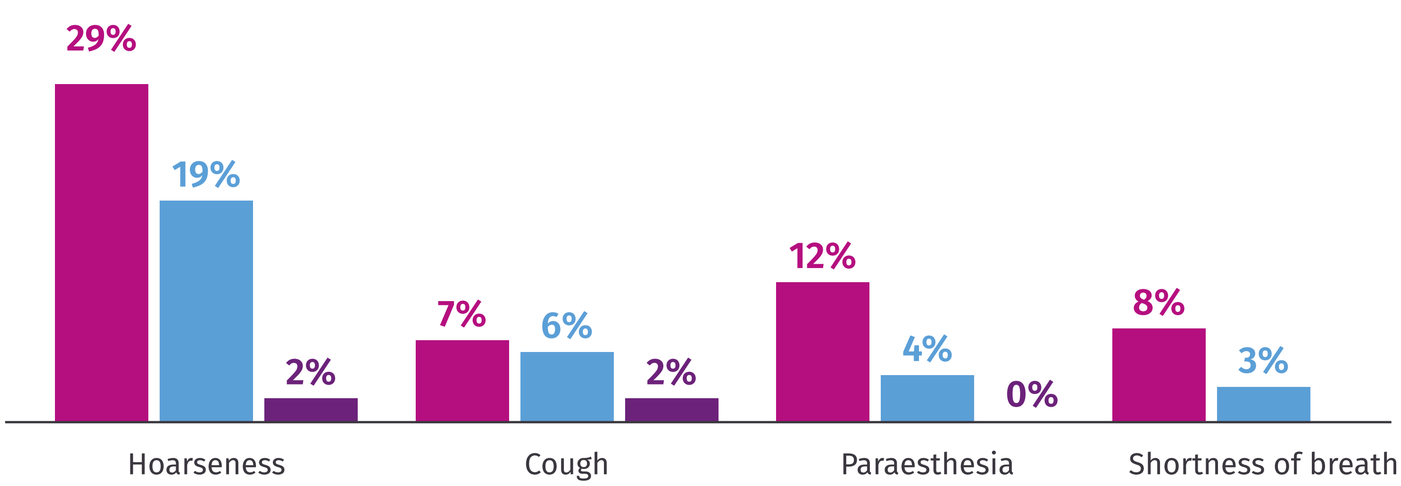
References

1. VNS Therapy™ System Epilepsy Physician's Manual (OUS), LivaNova USA, Inc.

VNS Therapy Safety Profile

Non-pharmacological side effect profile:

- Most side effects occur only during stimulation and generally diminish over time[1,2]
- Most side effects may be diminished or eliminated by the adjustment of parameter settings[1,3]



Most common VNS Therapy side effects
(adults and children, (N=440))[2]

Most common adverse events related to implantation of VNS Therapy were device site pain, device site reaction, incision pain, dysphagia, hypoesthesia, pharyngitis, voice alteration and incision site reaction / infection.

Lower rates of adverse events

A smaller output current step size of 0.125 mA is available (up to 2 mA) to allow for patient tolerability to device stimulation. If the output currents are reduced to address side effects, but the target level (i.e., adequate seizure control with minimal side effects) has not been reached, future attempts at increasing output current are recommended.[4]

LivaNova Epilepsy | VNS Therapy™

References

1. Ben-Menachem, EJ., (2001) Clin Neurophysiol 18(5):415-8.
2. Morris, GL., 3rd et al. (1999) Neurology 53(8):1731-5.
3. Heck, C., et al. (2002) Neurology 59(6 Suppl 4):S31-7.
4. VNS Therapy™ System Epilepsy Physician's Manual (OUS), LivaNova USA, Inc.

Strategies to alleviate side effects[1]

Reduce the pulse width from 500 µsec to 250 µsec

Reduce Duty Cycle: 30 sec ON/5 min OFF vS 7 sec ON/1.8 min

Reduce signal frequency from 30 Hz to 25 Hz or 20 Hz.

If the patient cannot tolerate a pulse width of 250 µsec, **reduce output current by 0.25 mA (or 0.125 mA** where available)

LivaNova Epilepsy | VNS Therapy™

References

1. VNS Therapy™ System Epilepsy Physician's Manual (OUS), LivaNova USA, Inc.

The keys to improving patient outcomes*

Reach target range for dosing

Consider the target dose combination for DRE patients as[1]:

If 500 µsec / 30 Hz → 1.5 mA

If using a pulse width of 500 microseconds at a signal frequency of 30 hertz, the output current should be 1.5 milliamps.

If 250 µsec / 20 Hz → 1.75 mA

If using a pulse width of 250 microseconds at a signal frequency of 20 hertz, the output current should be 1.75 milliamps.

Use rapid titration

Patients who were titrated to target within 3 months according to the recommended protocol achieve onset of response faster.[1,3]

Side effects for VNS Therapy™ in DRE patients may be similar regardless of the speed of titration schedule.[3] Adjust settings as needed to ensure tolerability as patients habituate to stimulation.

***Based on a retrospective analysis of VNS Therapy™ titration and dosing practice that compiled patient data from 12 clinical studies. Analysis includes randomized controlled trials and open-label observational studies. Clinical response was defined as a reduction in seizure frequency from baseline of 50% or greater.[2]**

LivaNova Epilepsy | VNS Therapy™

References

1. VNS Therapy™ System Epilepsy Physician's Manual (OUS), LivaNova USA, Inc.
2. Fahoum F, Boffini M, Kann L, et al. VNS parameters for clinical response in epilepsy. Brain Stimul. 2022;(15):814-821.
3. Tzadok, M., Verner, R., Kann, L., Tungala, D., Gordon, C., El Tahry, R., & Fahoum, F. (2022). Rapid Titration of VNS Therapy Reduces Time-To-Response in Epilepsy. Epilepsy and Behavior.

Brief Summary* 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 generalization) or generalized 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 ≥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.

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)].

LIVANOVA AUSTRALIA
1/63 Wells Road
Chelsea Heights
VIC, 3196
Tel.: +1800 452 650

www.VNSTherapy.com.au

IM-7601512-EPI - ANZ

CE 0344

LivaNova Epilepsy | VNS Therapy™

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

Epilepsy indication, December 2022

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 this its ability to properly sense heart beats. Therefore, care must be taken to follow

LIVANOVA AUSTRALIA
1/63 Wells Road
Chelsea Heights
VIC, 3196
Tel.: +1800 452 650

www.VNSTherapy.com.au

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LivaNova Epilepsy | VNS Therapy™

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

Epilepsy indication, December 2022

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. 26-0009-0100/6 (OUS) - 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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