Protocol

Vagus Nerve Stimulation

(70120)

Medical Benefit		**Effective Date**: 01/01/15	**Next Review Date**: 11/20
Preauthorization	No	**Review Dates**: 01/07, 05/08, 11/08, 03/09, 01/10, 01/11, 01/12, 01/13, 01/14, 11/14, 11/15, 11/16, 11/17, 11/18, 11/19	

Preauthorization is not required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With seizures refractory to medical treatment	Interventions of interest are: • Vagus nerve stimulation	Comparators of interest are: • Standard of care: antiepileptic drugs or resective surgery	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes
Individuals: • With treatment-resistant depression	Interventions of interest are: • Vagus nerve stimulation	Comparators of interest are: • Standard of care : antidepressant drugs	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes
Individuals: • With chronic heart failure • With upper-limb impairment due to stroke	Interventions of interest are: • Vagus nerve stimulation	Comparators of interest are: • Standard of care: medication management and physical rehabilitation	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes
Individuals: • With other neurologic conditions (e.g., essential tremor, headache, fibromyalgia, tinnitus or autism)	Interventions of interest are: • Vagus nerve stimulation	Comparators of interest are: • Standard of care: medication and behavioral therapy	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes
Individuals: • With chronic headache • With cluster headache	Interventions of interest are: • Transcutaneous vagus nerve stimulation • With standard of care to prevent cluster headaches	Comparators of interest are: • Standard of care: medication to prevent cluster headaches	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes • Quality of life
Individuals: • With cluster headache • With migraine • With headache	Interventions of interest are: • Transcutaneous vagus nerve stimulation to treat acute migraine headache	Comparators of interest are: • Standard of care: to treat acute migraine headache	Relevant outcomes include: • Symptoms • Change in disease status • Quality of life • Functional outcomes

Populations	Interventions	Comparators	Outcomes
Individuals: • With other neurologic, psychiatric, or metabolic disorders	Interventions of interest are: • Transcutaneous vagus nerve stimulation	Comparators of interest are: • Standard of care: medication and behavioral therapy	Relevant outcomes include: • Symptoms • Change in disease status • Functional outcomes

DESCRIPTION

Stimulation of the vagus nerve can be performed using a pulsed electrical stimulator implanted within the carotid artery sheath. This technique has been proposed as a treatment for refractory seizures, depression, and other disorders. There are also devices available that are implanted at different areas of the vagus nerve. This evidence review also addresses devices that stimulate the vagus nerve transcutaneously.

SUMMARY OF EVIDENCE

VAGUS NERVE STIMULATION

For individuals who have seizures refractory to medical treatment who receive vagus nerve stimulation (VNS), the evidence includes randomized controlled trials (RCTs) and multiple observational studies. Relevant outcomes are symptoms, change in disease status, and functional outcomes. The RCTs have reported significant reductions in seizure frequency for patients with partial-onset seizures. The uncontrolled studies have consistently reported large reductions in a broader range of seizure types in both adults and children. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have treatment-resistant depression who receive VNS, the evidence includes an RCT, nonrandomized comparative studies, and case series. Relevant outcomes are symptoms, change in disease status, and functional outcomes. The RCT only reported short-term results and found no significant improvement in the primary outcome. Other available studies are limited by small sample sizes, potential selection bias, and lack of a control group in the case series. The evidence is insufficient to determine the effects of the technology on health outcomes.

OTHER CONDITIONS

For individuals who have chronic heart failure who receive VNS, the evidence includes RCTs and case series. Relevant outcomes are symptoms, change in disease status, and functional outcomes. The RCTs evaluating chronic heart failure did not show significant improvements in the primary outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have upper-limb impairment due to stroke who receive VNS, the evidence includes a single pilot study. Relevant outcomes are symptoms, change in disease status, and functional outcomes. This pilot study has provided preliminary support for improvement in functional outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have other neurologic conditions (e.g., essential tremor, headache, fibromyalgia, tinnitus, autism) who receive VNS, the evidence includes case series. Relevant outcomes are symptoms, change in disease status, and functional outcomes. Case series are insufficient to draw conclusions regarding efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

TRANSCUTANEOUS VAGUS NERVE STIMULATION

For individuals with episodic cluster headaches who receive transcutaneous VNS, the evidence includes three RCTs. One RCT for a cluster headache showed a reduction in headache frequency but did not include a sham treatment group. Two randomized, double-blind, sham-controlled studies showed efficacy of achieving pain-free

status within 15 minutes of treatment with noninvasive VNS in patients with episodic cluster headaches but not in patients with chronic cluster headaches. The RCTs for episodic cluster headaches are promising; however, additional studies with larger relevant populations are required to establish the treatment efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with cluster headache who receive noninvasive transcutaneous VNS (nVNS) to treat acute cluster headache, the evidence includes RCTs. Relevant outcomes are symptoms, change in disease status, quality of life and functional outcomes. The ACT1 andACT2 RCTs compared nVNS to sham for treatment of acute cluster headache in patients including both chronic and episodic cluster headache. In ACT1, there was no statistically significant difference in the overall population in the proportion of patients with pain score of 0 or 1 at 15 minutes into the first attack and no difference in the proportion of patients who were pain-free at 15 minutes in 50% or more of the attacks. In the episodic cluster headache subgroup (n=85) both outcomes were statistically significant favoring nVNS although the interaction p-value was not reported. In ACT2, the proportion of attacks with pain intensity score of 0 or 1 at 30 minutes was higher for nVNS in the overall population (43% versus 28%, p=0.05) while the proportion of attacks that were pain-free at 15 minutes was similar in the two treatment groups in the overall population (14% vs. 12%). However, a statistically significantly higher proportion of attacks in the episodic subgroup (n=27) were pain-free at 15 minutes in the nNVS group compared to sham (48% vs. 6%, p<0.01). These studies suggest that people with episodic and chronic cluster headaches may respond differently to acute treatment with nVNS. Studies designed to focus on episodic cluster headache are needed. Quality of life and functional outcomes have not been reported. Treatment periods ranged from only two weeks to one month with extended open-label follow-up of up to three months. There are few adverse events of nVNS and they are mild and transient. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with migraine headache who receive noninvasive transcutaneous VNS (nVNS) to treat acute migraine headache, the evidence includes one RCT. Relevant outcomes are symptoms, change in disease status, quality of life and functional outcomes. One RCT has evaluated nNVS for acute treatment of migraine with nVNS in 248 patients with episodic migraine with/without aura. There was not a statistically significant difference in the primary outcome of the proportion of participants who were pain-free without using rescue medication at 120 minutes (30% vs. 20%; p = 0.07). However, the nVNS group had a higher proportion of patients with decrease in pain from moderate or severe to mild or no pain at 120 minutes (41% vs. 28%; p=0.03) and a higher proportion of patients who were pain-free at 120 for 50% or more of their attacks (32% vs. 18%; p=0.02). There are few adverse events of nVNS and they are mild and transient. Quality of life and functional outcomes were not reported and the double-blind treatment period was four weeks with an additional four weeks of open-label treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have other neurologic, psychiatric, or metabolic disorders (e.g., epilepsy, depression, schizophrenia, noncluster headache, impaired glucose tolerance) who receive transcutaneous VNS, the evidence includes RCTs and case series for some of the conditions. Relevant outcomes are symptoms, change in disease status, and functional outcomes. The RCTs are all small and have various methodologic problems. None showed definitive efficacy of transcutaneous VNS in improving patient outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY

Vagus nerve stimulation may be considered **medically necessary** as a treatment of medically refractory seizures.

Vagus nerve stimulation is considered **investigational** as a treatment of other conditions, including but not limited to depression, heart failure, upper-limb impairment due to stroke, essential tremor, headaches, fibromyalgia, tinnitus, and traumatic brain injury.

Transcutaneous (nonimplantable) vagus nerve stimulation devices are considered **investigational** for all indications.

POLICY GUIDELINES

Medically refractory seizures are defined as seizures that occur despite therapeutic levels of antiepileptic drugs or seizures that cannot be treated with therapeutic levels of antiepileptic drugs because of intolerable adverse events of these drugs.

Vagal nerve stimulation requires not only the surgical implantation of the device, but also subsequent neurostimulator programming, which occurs intraoperatively and typically during additional outpatient visits.

MEDICARE ADVANTAGE

For Medicare Advantage, the seizures must be medically refractory *partial-onset* seizures for which surgery is not recommended or for which surgery has failed for vagus nerve stimulator to be considered **medically necessary**.

BACKGROUND

Vagus nerve stimulation (VNS) was initially investigated as a treatment alternative in patients with medically refractory partial-onset seizures for whom surgery is not recommended or for whom surgery has failed. Over time, the use of VNS has expanded to include generalized seizures, and it has been investigated for a range of other conditions.

While the mechanisms for the therapeutic effects of VNS are not fully understood, the basic premise of VNS in the treatment of various conditions is that vagal visceral afferents have a diffuse central nervous system projection, and activation of these pathways has a widespread effect on neuronal excitability. An electrical stimulus is applied to axons of the vagus nerve, which have their cell bodies in the nodose and junctional ganglia and synapse on the nucleus of the solitary tract in the brainstem. From the solitary tract nucleus, vagal afferent pathways project to multiple areas of the brain. VNS may also stimulate vagal efferent pathways that innervate the heart, vocal cords, and other laryngeal and pharyngeal muscles, and provide parasympathetic innervation to the gastrointestinal tract.

Other types of implantable vagus nerve stimulators that are placed in contact with the trunks of the vagus nerve at the gastroesophageal junction are not addressed in this evidence review.

REGULATORY STATUS

Table 1 includes updates on FDA approval and clearance for VNS stimulators devices pertinent to this evidence review.

Table 1. FDA-Approved or -Cleared Vagus Nerve Stimulators

Device Name	Manufacturer	Approved/ Cleared	PMA/510(k)	Product Code(s)	Indications
NeuroCybernetic Prosthesis (NCP®)	LIvaNov (Cyberonics)	1997	P970003		Indicated or adjunctive treatment of adults and adolescents >12 y of age with medically refractory partial-onset seizures

Device Name	Manufacturer	Approved/ Cleared	PMA/510(k)	Product Code(s)	Indications
		2005	P970003/S50		Expanded indication for adjunctive long-term treatment of chronic or recurrent depression for patients ≥18 y of age experiencing a major depressive episode and have not had an adequate response to ≥4 adequate antidepressant treatments
		2017	P970003/S207		Expanded indicated use as adjunctive therapy for seizures in patients ≥4 y of age with partial-onset seizures that are refractory to antiepileptic medications
gammaCore®	ElectroCore	2017/2018	DEN150048/ K171306/ K173442	PKR, QAK	Indicated for acute treatment of pain associated with episodic cluster and migraine headache in adults using noninvasive VNS on the side of the neck
gammaCore-2®, gammaCore-Sapphire®	ElectroCore	2017/2018	K172270/ K180538/ K182369	PKR	Indicated for: • Adjunctive use for the preventive treatment of cluster headache in adult patients. • The acute treatment of pain associated with episodic cluster headache in adult patients. • The acute treatment of pain associated with migraine headache in adult patients.

FDA: Food and Drug Administration; PMA: premarket approval; VNS: vagus nerve stimulation.

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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