Medical Coverage Policy

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Vagus Nerve Stimulation (VNS)

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Overview

This Coverage Policy addresses the indications for use of an implantable vagus nerve stimulator (VNS) and a non-implantable transcutaneous VNS (tVNS) stimulator for the treatment of medically intractable seizures and as a treatment of other indications.

Coverage Policy

Vagus nerve stimulation (VNS) with an implantable vagus nerve stimulator is considered medically necessary for the treatment of medically intractable seizures when there is failure, contraindication or intolerance to all suitable medical and pharmacological management.

The replacement/revision of an implantable vagus nerve stimulator and/or leads is considered medically necessary for the treatment of medically intractable seizures when a previously implanted VNS is no longer functioning appropriately.

VNS with an implantable vagus nerve stimulator is considered experimental, investigational or unproven for any other indication including, but not limited to, refractory depression.

Transcutaneous vagus nerve stimulation (tVNS) is considered experimental, investigational or unproven for any indication.

General Background

Vagus nerve stimulation (VNS) involves the subcutaneous implantation of a programmable generator in the left upper chest that delivers pulses of current via electrodes attached to the vagus nerve in the left side of the neck. VNS is used to reduce the frequency and severity of refractory seizures and has been proposed for numerous other indications including refractory depression and as an adjunct to stroke rehabilitation. It is recommended that the implantation procedure be performed by a licensed, trained, and experienced neurosurgeon who is familiar with performing surgery in the carotid sheath and familiar with vagal anatomy, particularly the of the cardiac branches. Transcutaneous vagus nerve stimulation (tVNS), or non-implantable VNS, has been proposed as a less invasive alternative to surgery. (Hayes, 2020).

Vagus Nerve Stimulation (VNS)

Seizures
A seizure is defined as a short change in normal brain activity and can be classified into two groups. Generalized seizures affect both sides of the brain and can manifest as rapid blinking or staring into space (i.e., absence seizure) or crying out, loss of consciousness, falling, muscle jerks or spasms (i.e., Tonic-clonic seizure). Focal seizures, or partial seizures, are localized to one area of the brain and can cause twitching or a change in taste or smell (i.e., simple focal seizure); confusion or inability to respond (i.e., complex focal seizure); or can start as a focal seizure originating in one part of the brain but then spreading to a generalized seizure (i.e., secondary generalized seizure). When two or more seizures have occurred, epilepsy is diagnosed. Epilepsy can be caused by stroke, brain tumor, traumatic brain injury, or a central nervous system infection. However, many times the cause is unknown. Pharmacotherapy is a first line treatment for epilepsy and is effective in two out of three people. Surgery is utilized for focal seizures in an effort to remove the part of the brain that is causing the seizure focus. This is most commonly utilized when the focus is located in the temporal lobe of the brain (Centers for Disease Control and Prevention, 2020).

According to a report by Nathan and Gutierrez (2018), the prevalence of epilepsy in nonwhite males is 1.3–2.2 times that of white males and in nonwhite females, it is 1.4–1.7 times that of white females. Between 1986 and 1990, the age adjusted prevalence rate of epilepsy for African Americans was 6.7 per 1,000 compared to 4.5 per 1,000 for whites. The prevalence rate for elderly Hispanic men was 15–18 per 1,000 compared to 12–16 per 1,000 for non-Hispanic men of a similar age group. African American and Hispanic individuals were less likely to receive surgical treatment, antiepileptic drugs (AEDs), and specialized care and more likely to receive care in an emergency room when compared to white individuals. The authors found that fear of treatment, access to care, communication barriers, education, trust between patient and physician, and social support are all contributing factors to these disparities.

U.S. Food and Drug Administration (FDA): The VNS Therapy System, formerly known as NeuroCybernetic Prosthesis (NCP) System®, (LivaNova, USA, Inc., Houston, TX) received premarket application (PMA) approval by the U.S. Food and Drug Administration (FDA) in 1997 for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over age 12 with medically refractory, partial-onset seizures. Since the original approval, there have been a number of modifications to the device, the instruments used to implant the electrodes, the stimulator, and the software used to control and program the stimulator. In a June 2017 approval order, the NeuroCybernetic Prosthesis (NCP) System® 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 that are refractory to antiepileptic medications (P970003/S207).

Literature Review: Evidence in the peer-reviewed scientific literature have shown that VNS may be a viable option to reduce the severity and shorten the duration of seizures in those patients who remain refractory despite optimal drug therapy or surgical intervention, as well as in those with debilitating side effects of antiepileptic medications. Seizure frequency is usually reduced by 50%, which is similar to the result of many drugs but

without the side effects. Most patients are not seizure-free after treatment with VNS. More recent studies have investigated the efficacy of VNS as an adjunct therapy for those epileptics with generalized seizures and for children. There is evidence that the use of VNS may provide significant health benefits for refractory pediatric patients and generalized seizures (Dibué, et al., 2021; Dibué-Adjei, et al., 2019; Ryvlin, et al., 2014; Klinkenberg, et al., 2012; Ardesch, et al., 2007; De Herdt, et al., 2007; You, et al., 2007).

Professional Societies/Organizations: The American Academy of Neurology (AAN) guideline on vagus nerve stimulation (VNS) for epilepsy states VNS may be considered for seizures in children, for Lennox-Gastaut syndrome (LGS)-associated seizures, and for improving mood in adults with epilepsy. VNS may be considered to have improved efficacy over time. Children should be carefully monitored for site infection after VNS implantation (Level C). Level C is defined as possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. The authors recommendations for further research state that more information is needed on the treatment of primary generalized epilepsy in adults and that parameter settings (e.g., cycle time length) would potentially help with better VNS management and use. Techniques to reduce infection risk at the VNS site in children should be developed and further information is needed on the effects of VNS on sleep apnea (Morris, et al., 2013; reaffirmed 2019).

Depression
Depression is categorized as a mood disorder that can be caused by a combination of genetic, biological, environmental, and psychological factors. The signs and symptoms of depression include but are not limited to: persistent sad, anxious, or empty mood; feelings of hopelessness; irritability; loss of interest in hobbies; decreased energy; difficulty concentrating; and thoughts of death or suicide. In order to be diagnosed with depression, symptoms must be present for at least two weeks. (National Institute of Mental Health, 2018; Centers for Disease Control and Prevention, 2014).

There are treatment modalities for which there is substantial evidence of effectiveness in the treatment of a major depressive episode (MDE): pharmacotherapy with antidepressant drugs (ADDs), specific forms of psychotherapy (e.g., cognitive behavior and interpersonal therapy), transcranial magnetic stimulation (TMS) and electroconvulsive therapy (ECT). ADDs are the usual first-line treatment for depression. Clinical trials have demonstrated efficacy for a number of pharmacologic classes of ADDs. Additional pharmacologic strategies can be used such as: switching to an alternative ADD, adding treatment with psychotherapy, or using an augmentation agent. For patients who have failed pharmacological treatment and psychotherapy, transcranial magnetic stimulation may be a treatment option. For treatment-resistant cases that exhibit a marked seasonal pattern, adding phototherapy to pharmacotherapy may also be an option (FDA, 2005). Vagus nerve stimulation (VNS) has been proposed as an adjunct therapy in patients with major depressive disorder or bipolar disorder.

U.S. Food and Drug Administration (FDA): In July 2005, the VNS Therapy system received FDA premarket approval (PMA) with limitations. The VNS Therapy System was approved to be used to treat depression for the following indications: “the VNS Therapy System is indicated for the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments.” The FDA limitations stated that post-approval studies must be conducted to further characterize the optimal stimulation dosing and patient selection criteria (FDA, 2005).

Literature Review: Studies supporting the use of the vagus nerve stimulation (VNS) system in subjects with treatment-resistant depression (TRD) include: a feasibility trial (Rush, et al., 2000) (referred to in the FDA summary of safety and effectiveness data documentation as D-01); a randomized, sham-controlled three-month clinical trial (Carpenter, et al., 2004; Rush et al., 2005a) (referred to in the FDA summary of safety and effectiveness data documentation as D-02, acute); a long-term (12- and 24-month) open-label extension (Rush, et al., 2005b) (referred to in the FDA summary of safety and effectiveness data documentation as D-02, long-term); and a long-term (12-month) observational study of subjects receiving standard-of-care treatments (D-04) for comparison to D-02 long-term (George, et al., 2005) (referred to in the FDA summary of safety and effectiveness data documentation as the D-02/D-04 comparison study) (FDA, 2005). These studies are outlined below. Although some studies suggest that VNS may be effective for resistant depression, a randomized-controlled trial did not find a statistically significant difference between sham and active VNS (Rush, et al.,

2005a, Rush, et al., 2005b). Long-term, controlled trials and additional studies designed to identify patient selection criteria are needed. The current available evidence is insufficient to permit conclusions regarding the efficacy and safety of VNS as an adjunct therapy in TRD and bipolar disorder.

In 2019, Bottomley, et al. conducted a systematic review of randomized controlled trials, non-randomized comparative studies, single-arm studies, and case series to compare treatment as usual (TAU) for treatment resistant depression (TRD) to vagus nerve stimulation (VNS) used as an adjunct to TAU. There were a total of 1,580 participants with individual sample sizes ranging from 5–795 participants. Studies (n=22) were included if they evaluated VNS as an adjunct to TAU or TAU alone and included an adult population diagnosed with TRD. The intervention was VNS used as an adjunct to TAU. Comparators included: sham, various stimulation levels, and TAU only. The primary outcomes included efficacy defined as patients achieving a ≥ 50% reduction from baseline in a depression rating scale and remission defined as maintenance of the reduction from baseline on a depression rating scale (e.g., Montgomery Asberg Depression Rating Scale (MADRS), Hamilton Rating Scale for Depression (HAMD)). Secondary outcome measures included: adverse events, hospitalizations, serious adverse events, suicide, all-cause mortality, mania, drop outs, and discontinuation of VNS. Follow-up ranged from three to over six years. The percent of individuals who underwent VNS plus TAU and achieved a ≥ 50% reduction from baseline on the MADRS scale was 23.9%, 38.9%, and 52.6% at six, 12, and 24 months, respectively. The percent of individuals who underwent TAU only and achieved a ≥ 50% reduction from baseline on the MADRS scale was 13.8%, 17.5%, and 18.5% at six, 12, and 24 months, respectively. For those studies using the HAMD scale, the percent of individuals achieving a ≥ 50% reduction from baseline was 29.9%, 43.4%, and 36.7% at six, 12, and 24 months. The pooled TAU only HAMD responder rate was only available at 12 months and was 9.6%. The pooled rate of serious adverse events in patients who underwent VNS plus TAU was 5.5% at 12 months. No serious adverse event data was available for those who underwent VNS plus TAU at six months or for those who underwent TAU only at any time point. The all-cause mortality rate for those who underwent VNS plus TAU at three, 12, and 24 months was 0.0%, 0.4%, and 1.4%, respectively. For those who underwent TAU only, the pooled mortality rate at three, six, 12, and 24 months was 0.3%, 0.3%, 0.3%, and 0.7% respectively. Author noted limitations of the review included: the lack of randomized controlled trials and heterogeneity of treatment protocols, study designs, follow-up, and severity of illness definitions. Additional, high quality and long-term reviews are needed to assess the safety and efficacy of VNS for the treatment of treatment resistant depression.

Aaronson et al. (2017) reported long-term outcomes from the five-year post-marketing surveillance study of individuals with treatment resistance depression treated with VNS or “treatment as usual.” The prospective, open-label, nonrandomized, observational registry study, was conducted at 61 U.S. sites. The study included a total of 795 patients who were experiencing a major depressive episode (unipolar or bipolar depression) of at least two years’ duration or had three or more depressive episodes (including the current episode), and who had failed four or more depression treatments (including ECT). Patients with a history of psychosis or rapid-cycling bipolar disorder were excluded. The primary efficacy measure was response rate, defined as a decrease of ≥50% in baseline Montgomery Åsberg Depression Rating Scale (MADRS) score at any post baseline visit during the five-year study. Secondary efficacy measures included remission. Patients had chronic moderate to severe depression at baseline (the mean MADRS score was 29.3 [SD=6.9] for the treatment-as-usual group and 33.1 [SD=7.0] for the adjunctive VNS group). The registry results indicate that the adjunctive VNS group had better clinical outcomes than the treatment- as-usual group, including a significantly higher five-year cumulative response rate (67.6% compared with 40.9%) and a significantly higher remission rate (cumulative first-time remitters, 43.3% compared with 25.7%). A sub-analysis demonstrated that among patients with a history of response to ECT, those in the adjunctive VNS group had a significantly higher five-year cumulative response rate than those in the treatment-as-usual group (71.3% compared with 56.9%). A similar significant response differential was observed among ECT nonresponders (59.6% compared with 34.1%). The naturalistic, observational study design did not allow for random assignment of participants to treatment groups; thus, participants were not blinded to treatment. A significant number of participants in both groups withdrew early from the study. Of the 358 patients (45%) who withdrew early, 195 were from the VNS arm (40%) and 163 were from the treatment-as-usual arm (54%). The reasons for early withdrawal were similar between the treatment arms. The significantly higher treatment response rate observed in the VNS arm may represent a placebo effect, as participants with an implanted device may have had a higher expectation of therapeutic improvement.

In a case series study, Cristancho et al. (2011) reported the outcomes of depressed patients treated with VNS. A total of 15 patients with treatment-resistant major depressive episodes, including 10 with major depressive

disorder and five with bipolar disorder (DSM-IV criteria), were implanted with a VNS device. Existing antidepressant treatment remained fixed as far as clinically possible. The primary outcome was change from baseline in the Beck Depression Inventory (BDI) score. Outcomes were assessed at six and 12 months postimplant. The six-month response rates were 21.4%, six-month remission rates 14.3% and one-year response rates were 28.6-43%. This study was limited by small sample size and lack of a comparator group.

In an uncontrolled open-label multicenter European study, Bajbouj et al. (2010) assessed the efficacy and the safety of VNS in 74 patients with TRD. Psychometric measures were obtained after three, 12, and 24 months of VNS. Mixed-model repeated-measures analysis of variance revealed a significant reduction at all the three time points in the 28-item Hamilton Rating Scale for Depression (HRSD28) score, the primary outcome measure. After two years, 53.1% (26/49) of the patients fulfilled the response criteria (≥50% reduction in the HRSD28 scores from baseline) and 38.9% (19/49) fulfilled the remission criteria (HRSD28 scores ≤10). The proportion of patients who fulfilled the remission criteria remained constant as the duration of VNS treatment increased. Voice alteration, cough, and pain were the most frequently reported adverse effects. Two patients committed suicide during the study; no other deaths were reported. No statistically significant differences were seen in the number of concomitant antidepressant medications. According to the investigators, the results of this two-year open-label trial suggest a clinical response and a comparatively benign adverse effect profile among patients with TRD. The lack of a control group limits the validity of the results of this study. This study extends the findings in the Schlaepfer et al. (2008) study.

Schlaepfer et al. (2008) reported the results of an uncontrolled open-label European study of VNS for TRD (D03) which was conducted to determine if the USA results (D01) could be replicated using a similar study design in a different patient population with different severity and in a different health-care environment. Seventy-four patients with TRD were enrolled from six European countries. The primary outcome was response rate which was defined as a ≥50% reduction in the 28-item Hamilton Depression Rating Scale (HAMD-28) was measured at baseline, three months and 12 months. The Montgomery-Asberg Depression Rating Scale (MADRS), the Inventory of Depressive Symptomatology Self-Rated (IDS-SR), and adverse events were also assessed at baseline, three months, and 12 months. After three months of VNS, the response rate was 37% and the remission rate (HAMD-28 score <10) was 17%. At one year, the response rate increased to 53% and the remission rate was 33%. Median time to response was nine months. The most frequent side effects were voice alteration and cough. Most of the efficacy ratings were in the same range as those reported in the USA study. At 12 months, however, the reduction of symptoms was significantly higher in the European study. This may be due to the significant difference in baseline measures of depression (HAMD-28) (D03 34.0±5.8 vs. D01 36.8±5.8; p=0.006). The authors reported that VNS may be effective in patients with very treatment resistant depression, but could not assess the contribution of the placebo effect on the results. The limitations of this study, including lack of control, blinding and randomization, did not allow definitive determinations to be made regarding the safety and efficacy of VNS for TRD at this time.

In 2005, Nahas and colleagues reported the response and remission rates of a two-year follow-up study of 59 participants with treatment-resistant, nonpsychotic depressive disorders (D-01 study participants). Response was defined as a ≥ 50% reduction from baseline of the HRSD score, and remission was defined as a Hamilton Rating Scale for Depression (HRSD) score ≤ 10. Changes in treatment, including VNS parameters, medication dose and type, and the use of electroconvulsive therapy were allowed after the 12-week acute phase. Response rates did not significantly increase from 30.5% at three months to 44.1% at 12 months (p=.096), nor did they decrease significantly to 42.4% at 24 months (p=.648). Remission rates showed a nonsignificant increase from 15.3% at three months to 27.1% at 12 months (p=.07) and a nonsignificant decrease to 22.0% from 12 to 24 months (p=.549). At 24 months, 48/59 participants (81%) were still receiving VNS. In the 24 months following initiation of stimulation, 40 serious adverse events occurred in 25 participants and included three for suicide attempts, 10 for worsened depression, one for dysphoria, two for a manic episode, one for agitation, and one for central nervous system toxicity. The follow-up data suggests that VNS therapy for treatment–resistant participants may be sustained over a 24-month period. This study is limited by the small sample size, the lack of control and comparator, and the use and changes in concomitant treatments.

Rush et al. (2005a) conducted a randomized, double-blind study (D-02, acute) of patients with treatment-resistant depression at 21 sites. A total of 222 participants were included; 112 were randomized to the active VNS group, and 110 were randomized to the sham VNS group. Inclusion criteria consisted of a current

Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) primary diagnosis of major depressive disorder (MDD) or bipolar I or II disorder (BPI or BPII). The participants were required to be in the current major depressive episode (MDE) for ≥ two years or to have had at least four lifetime major depressive episodes, including their current MDE. Results were based on response rates (≥ 50% reduction from baseline on the 24-item Hamilton Rating Scale for Depression [HRSD-24]). At ten weeks, the primary outcome, the HRSD-24 response rate, was 15.2% in the active VNS group and 10.0% in the sham group and was statistically insignificant. There was a statistically significant response in the Inventory of Depressive Symptomatology - Self Report (IDS-SR30), with a 17% response rate in the active VNS group and 7.3% in the sham group. The authors summarized that, although the VNS therapy was well-tolerated, there was no evidence of short-term efficacy for adjunctive VNS in treatment-resistant depression.

Rush et al. (2005b) conducted a 12-month study (D-02, long-term) of the symptomatic outcomes in patients receiving adjunctive VNS. Participants included in this study had been randomized to receive either active or sham VNS during a 12-week acute phase trial (D-02, active) (Rush et al., 2005a). The initial active VNS group received another nine months of VNS, while the initial sham group received 12 months of VNS. In total, there were 205 evaluable participants. The participants received antidepressant treatments and VNS. Changes in type or dose of any psychotropic or other medication as well as the introduction or discontinuation of somatic treatments (e.g., ECT and rTMS) or psychotherapy were allowed. The primary outcome (repeated measures linear regression) showed a reduction in the HRSD-24 scores (average improvement of 0.45 points per month). At conclusion of the study, the HRSD-24 response rate was 27.2%, and remission was 15.8%. The most common were voice alteration, dyspnea, and neck pain. Of the 205 participants, there were three reports of manic syndrome over the 12 months of this study, as well as 30 participants requiring hospitalization for depression. The authors reported that VNS was well-tolerated at one year with a potential benefit, although changes in depression treatments occurred. To determine if these benefits are due to VNS, long-term, comparative studies are needed.

George et al. (2005) reported a one-year comparison study of VNS of patients who had treatment as usual (TAU) for TRD to better understand the effects on long-term outcome (D-02/D04 comparison study). The authors compared 12-month VNS+TAU outcomes to those of a comparable TRD group. Admission criteria were similar for those receiving VNS+TAU (n=205) or only TAU (n=124). In the primary analysis, repeated measures of linear regression were used to compare the VNS+TAU group (monthly data) to the TAU group (quarterly data) according to scores of the 30-item Inventory of Depressive Symptomatology Self Report (IDS-SR 30). The two groups had similar baseline demographic data, psychiatric treatment histories, and degrees of treatment resistance, except that more TAU participants had at least 10 prior MDEs, and the VNS+TAU group had more ECT before study entry. VNS plus TAU was associated with greater improvement per month in IDS-SR (30) than treatment as usual (TAU) across 12 months ($p<.001$). Response rates, according to the 24-item Hamilton Rating Scale for Depression (HRSD) (last observation carried forward) at 12 months, were 27% for vagus nerve stimulation (VNS)+TAU and 13% for TAU ($p<.011$). Both groups received similar TAU (drugs and ECT) during follow-up. The authors reported that the comparison of two similar but nonrandomized treatment-resistant depression (TRD) groups showed that VNS+TAU was associated with a greater antidepressant benefit over 12 months.

Neu et al. (2005) reported a randomized controlled trial conducted to investigate if VNS has an influence on cerebral blood flow (CBF) in humans. This investigation was designed as an add-on study (DO1; Rush, 2000). In 10 patients with an implanted stimulator who participated in a multicenter clinical trial to evaluate the efficacy of VNS in depression, CBF was investigated by functional transcranial Doppler at baseline (before the stimulator was turned on for the first time) and during stimulation with three different stimulation intensities in a randomized order. No significant change of CBF above standard deviation could be registered. The authors reported that VNS does not have an influence on CBF velocity in depressive patients.

Carpenter et al. (2004) (partial results DO2 randomized controlled trial) reported that VNS has shown promising antidepressant effects in TRD, but the mechanisms of action are not known. Cerebrospinal fluid (CSF) studies in epilepsy patients show that VNS alters concentrations of monamines and gamma aminobutyric acid (GABA), neurotransmitter systems possibly involved in the pathogenesis of depression. Twenty-one adults with treatment-resistant, recurrent, or chronic major depression underwent standardized lumbar puncture for collection of 12 mL CSF on three separate but identical procedure days during participation in the VNS D-02 clinical trial. All subjects

remained on stable regimens of mood medications. Collections were made at baseline (two weeks after surgical implantation but before device activation), week 12 (end of the acute-phase study), and week 24. Cerebrospinal fluid concentrations of norepinephrine (NE), 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA), and 3-methoxy-4-hydroxyphenylglycol (MHPG) were determined with high-performance liquid chromatography. Concentrations of GABA were assayed with mass spectrometry. Comparison of sham versus active VNS revealed a significant (mean 21%) VNS associated increase in CSF HVA. Mean CSF concentrations of NE, 5-HIAA, MHPG, and GABA did not change significantly. Higher baseline HVA/5-HIAA ratio predicted worse clinical outcome. The authors reported that although several of the CSF neurochemical effects observed in the VNS study were similar to those described in the literature for antidepressants and ECT, the results did not suggest a supposed antidepressant mechanism of action for VNS.

Marangell et al. (2002) reported a nonrandomized, open-label, single-arm study (DO1) of adults in a treatment-resistant major depressive episode (MDE). This open follow-up study was conducted to determine whether the initial promising effects were sustained, and whether changes in function would be observed. Thirty adult outpatients in a treatment-resistant, nonpsychotic MDE received an additional nine months of VNS treatment following exit from the three-month acute study. Changes in psychotropic medications and VNS stimulus parameters were allowed during this longer term follow-up study. A priori definitions were used to define response (≥50% reduction in baseline HDRS) and remission (HDRS ≥10). The response rate was sustained (40%–46%); $p<0.317$) and the remission rate significantly increased (17–29%; $p<0.045$) with an additional nine months of long-term VNS treatment after exit from the acute study (one year total VNS treatment). Significant improvements in function between acute study exit and the one-year follow-up assessment as measured by the Medical Outcomes Study Short Form-36 were observed. The authors reported that longer term VNS treatment was associated with sustained symptomatic benefit and sustained or enhanced functional status in this follow-up study.

Rush et al. (2000) investigated VNS as delivered by the NeuroCybernetic Prosthesis (NCP) System. The open-label nonrandomized, uncontrolled clinical study (D-01) covered 30 adult outpatients with nonpsychotic treatment-resistant major depressive (n=21) or bipolar I (n=4) or bipolar II (n=5) depressed phase disorders, who had failed at least two robust medication trials in the current MDE while on stable medication regimens. The patients completed a baseline period followed by NCP System implantation. A two-week single-blind recovery period (no stimulation) was followed by 10 weeks of VNS. Results indicated that in the current MDEs (median length=4.7 years), patients had not adequately responded to two (n=9), three (n=2), four (n=6) or five or more (n=13) robust antidepressant medication trials or ECT (n=17). Baseline 28 item Hasegawa's Dementia Scale (HDS) scores averaged 38.0. Response rates (≥50% reduction in baseline scores) were 40% for both the HDRS28 and the Clinical Global Impressions-Improvement index (CGI-I) (score of 1 or 2) and 50% for the Montgomery-Asberg Depression Rating Scale (MADRAS). Symptomatic responses (accompanied by substantial functional improvement) have been largely sustained during long-term follow-up to date. The researchers concluded that these open trial results suggest that VNS has antidepressant effects in TRD. This uncontrolled study was small, without long-term outcome and with no comparison group.

In 2012, Martin et al. reported the results of a systematic review and meta-analysis to evaluate the efficacy of VNS for the treatment of depression. Efficacy was evaluated according to severity of illness and percentage of responders. A total of 14 studies met the selection criteria and were included in the review. The results are mainly based on uncontrolled studies, with small or medium sample sizes and intermediate quality levels. The duration of the randomized controlled trial included was 10 weeks The meta-analysis of efficacy for uncontrolled studies showed a significant reduction in scores at the Hamilton Depression Rating Scale endpoint, and the percentage of responders was 31.8% ([23.2%-41.8%], $p< 0.001$). However, the randomized control trial which covered a sample of 235 patients with depression, reported no statistically significant differences between the active intervention and placebo groups. The authors reported that currently, insufficient data are available to describe VNS as effective in the treatment of depression. Additionally, it cannot be ruled out that the positive results observed in the uncontrolled studies might have been mainly due to a placebo effect.

In 2008, Daban et al. reported the results of a systematic review and meta-analysis to evaluate the safety and efficacy of VNS in TRD. A total of 18 studies were included in the review (six short term and 12 long term studies). Some studies included patients who had already been enrolled in previous studies. Only one study was randomized and therefore, a meta-analysis could not be performed. According to the authors, the current

literature suggests that VNS therapy is promising and may have a potential role in the treatment of TRD, but experience and the evidence base are still limited. They also stated that VNS is an invasive treatment involving risk and that although the evidence is weak, it may have a role in the treatment of depressed patients not responding well to medication, particularly those with a chronic, disabling course. The authors reported that large, well-designed studies are needed to confirm the results reported in mainly open studies regarding the efficacy of VNS in major depression.

In 2019, Hayes published a Medical Technology Directory report on vagus nerve stimulation for treatment resistant depression. The evidence evaluation states that low-quality evidence from several observational and uncontrolled studies for treatment with VNS improves depression symptoms in patients with treatment-resistant depression (TRD). There is a lack of consistent supporting evidence of the efficacy of VNS from well-designed randomized controlled trials and a lack of thorough safety data regarding the device, and the substantial burden of TRD. Considering the safety concerns regarding VNS, noninvasive treatments should be exhausted before this option is considered and patients should be specifically informed of the risks and properly followed up. For adults with treatment-resistant rapid-cycling bipolar disorder (BPD) there is a very-low-quality and insufficient evidence base for this patient population. The future outlook section of the report states that the clinical benefit of VNS for TRD remains controversial and it is unclear whether the possible benefits associated with VNS therapy outweigh any risks. Larger, randomized, appropriately controlled studies are necessary to establish VNS as a safe and effective alternative treatment for these patients. The 2020 Hayes annual review identified two new relevant publications that did not change the Hayes conclusion.

Professional Societies/Organizations: The American Psychiatric Association (APA) practice guideline for the treatment of patients with major depressive disorder states that electroconvulsive therapy (ECT) remains the treatment of best established efficacy against which other stimulation treatments (e.g., VNS, deep brain stimulation, transcranial magnetic stimulation, other electromagnetic stimulation therapies) should be compared. VNS may be an additional option for individuals who have not responded to at least four adequate trials of antidepressant treatment, including ECT [III]. For patients whose depressive episodes have not previously responded to acute or continuation treatment with medications or a depression focused psychotherapy but who have shown a response to ECT, maintenance ECT may be considered [III]. Maintenance treatment with VNS is also appropriate for individuals whose symptoms have responded to this treatment modality [III]. According to the APA, relative to other antidepressive treatments, the role of VNS remains a subject of debate. However, it could be considered as an option for patients with substantial symptoms that have not responded to repeated trials of antidepressant treatment. The three APA rating categories represent varying levels of clinical confidence:

- I: Recommended with substantial clinical confidence
- II: Recommended with moderate clinical confidence
- III: May be recommended on the basis of individual circumstances (Gelenberg, et al., 2010).

The 2016 Department of Veterans Affairs and the Department of Defense evidence-based clinical practice guideline for the management of major depressive disorder recommends against offering vagus nerve stimulation (VNS) for patients with major depressive disorder, including patients with severe treatment-resistant depression outside of a research setting.

Stroke Rehabilitation:
Vagus nerve stimulation (VNS) has been proposed as an adjunct to standard rehabilitation therapy in individuals with stroke to improve function. The literature is limited in quantity and by small patient populations and short-term follow-ups with an inability to generalize findings across a broad range of patient populations (Dawson, et al., 2016; Dawson, et al., 2021).

U.S. Food and Drug Administration (FDA): In August 2021, the Vivistim System, also known as the MicroTransponder Vivistim Paired VNS System (MicroTransponder Inc., Austin, TX), received FDA premarket (PMA) approval for the indication of vagus nerve stimulation during chronic ischemic stroke rehabilitation therapy. It is intended to be used during rehabilitation sessions to reduce upper extremity motor deficits and improve motor function in patients with moderate to severe arm impairment. A history of bilateral or left cervical vagotomy is a contraindication to device implantation. According to the manufacturer website, Vivistim delivers stimulation during specific targeted movements to help the brain strengthen or create new neural pathways to

bypass the damaged area (Vivistim, 2021). The device can be used in the home setting or during in-clinic therapy sessions.

Literature Review: Dawson, et al. (2021) conducted a pivotal, triple-blinded, randomized controlled trial (RCT) (n=108) to evaluate the safety and efficacy of vagus nerve stimulation (VNS) paired with rehabilitation on improving arm function after stroke. Participants ranged in age from 22–80 years. Sixty-four percent of participants in the VNS group were male, 79% were white, 17% were African American, and 2% were Asian, Indian, or other. Sixty-five percent of participants in the control group were male, 78% were white, 16% were African American, and 7% were Asian, Indian, or other. Patients were included in the study if they had a history of supratentorial ischemic stroke having occurred between nine months and ten years prior to enrollment and had severe arm impairment defined as a Fugl-Meyer Assessment-Upper Extremity (FMA-UE) score of 20–50 points. All patients were implanted with the Vivistim System VNS device and received six weeks of in-clinic therapy three times per week for six weeks followed by a home exercise program. The intervention consisted of active VNS (i.e., 0.8mA, 100ms, and 30Hz) used in conjunction with stroke rehabilitation timed so that stimulation occurred with each repetition of movement (VNS group) (n=53). The comparator was sham VNS (i.e., 0 MA) paired with stroke rehabilitation (control group) (n=55). Participants in both treatment groups received five active stimulations in reducing strengths at the start of each therapy session in an effort to reduce the participant's ability to infer treatment allocation. In-clinic rehabilitation consisted of high-repetition, task-based, functional, individualized, and progressive upper limb exercises. The change in impairment measured by the FMA-UE score on the first day after completion of in-clinic therapy was the primary outcome measured. The secondary outcome measured was the FMA-UE score at 90 days after completion of in-clinic therapy. Baseline assessments occurred at one week after device implantation. Follow-up occurred at 30 and 90 days after the completion of in-clinic therapy. Compared to baseline, FMA-UE scores were significantly improved in the VNS group compared to the control group at the first day after completion of in-clinic therapy (p=0.0014). At 90 day follow-up, FMA-UE scores remained significantly improved in the VNS group compared to the control group (p=0.0077). Forty percent of participants in the VNS group and 55% of participants in the control group experienced an adverse event deemed "possibly, probably, or definitely" related to device implantation and were mostly due to post-op pain. Twenty-five percent of participants in the VNS group and 16% of participants in the control group experienced an adverse event deemed either "possibly, probably, or definitely" related to device use. Vocal cord paralysis related to surgery occurred in one patient in the control group and resolved after five weeks. There were no significant between-group differences of adverse event reports. Author noted limitations of the study included the fact that results cannot be generalized to individuals who did not meet inclusion criteria or who had experienced different types of stroke or other neurological disorders. The authors also pointed to their small sample size, short-term follow-up, and disproportionate number of male participants as limitations. Additional high quality studies with long-term follow-up and larger and more diverse patient populations are needed to fully evaluate the safety and efficacy of VNS for improving upper extremity function in individuals with stroke.

Other Indications:
Vagus nerve stimulation (VNS) has been proposed for use in a number of other indications including, but not limited to, addiction, alzheimer's disease, anxiety, autism, bulimia, cancer, cerebral palsy, chronic heart failure, coma, craving, essential tremor, fibromyalgia, headache, memory and learning disability, migraine, multiple sclerosis, narcolepsy, obesity, obsessive-compulsive disorder, panic disorder, pain syndromes, posttraumatic stress disorder, sleep disorder, traumatic brain injury, primary sjögren's syndrome, tourette's syndrome. In alzheimer's disease, it has been proposed that stimulation of the vagus nerve may cause surges in norepinephrine in an area of the brain that is involved with memory storage (Adelson, 2004). The peer-reviewed scientific literature regarding the use of VNS for alzheimer's disease or other indications is limited by small sample size and lack of a comparator; therefore conclusions about safety and efficacy cannot be made at this time. VNS devices are not FDA-approved for treatment of these indications (Tarn, et al., 2019; Kimberley, et al., 2018; Kilgard, et al., 2018; Reijmen, et al., 2018; Premchand, et al., 2016; Grazzi, et al., 2016; Gold, et al., 2016; Zannad, et al., 2015; Shi, et al., 2013; McClelland, et al., 2013, Herremans, et al., 2012; Lange, et al., 2011; De Ferrari, et al., 2011; Beekwilder, et al., 2010; Klein; et al., 2010; Levy, et al., 2010; George, et al., 2010; Pardo, et al., 2007; George, et al., 2007; Ansari, et al., 2007; Bodenlos, et al., 2007; Merrill, et al., 2006; Hatton, et al., 2006; Mauskop, et al., 2005; Adelson, 2004; Handforth, et al., 2003; Sjogren, et al., 2002).

Transcutaneous Vagus Nerve Stimulator (tVNS)

Non-implantable or transcutaneous vagus nerve stimulation (tVNS) is being investigated as a noninvasive alternative to surgery for VNS. tVNS using a transcutaneous approach at stimulation of the cervical branch of the vagus nerve in the neck or of the auricular branch at the concha of the outer ear have been developed.

U.S. Food and Drug Administration (FDA): The April 14, 2017 (updated September 1, 2017) FDA De Novo request (DEN150048) states the gammaCore Non-invasive Vagus Nerve Stimulator is indicated for the acute treatment of pain associated with episodic cluster headache in adult patients. On May 30, 2017, gammaCore-S (electroCore® Medical, LLC, Basking Ridge, NJ) received Class II clearance by the FDA through the 510(k) process (K171306). Approval was based on the predicate device gammaCore. The differences between the gammaCore-S and the gammaCore device is a change in the user interface. The indication for use states the gammaCore-S Non-invasive Vagus Nerve Stimulator is intended to provide noninvasive vagus nerve stimulation (nVNS) on the side of the neck. The gammaCore-S device is indicated for the acute treatment of pain associated with episodic cluster headache in adult patients. Each stimulation with gammaCore-S lasts two minutes. The patient controls the stimulation strength.

On November 27, 2018, the gammaCore Sapphire non-invasive Vagus Nerve Stimulator (K182369) expanded FDA 510(k) approval for adjunctive use for the preventive treatment of cluster headache in adult patients. The indications for use state that gammaCore Sapphire (non-invasive vagus nerve stimulator) is intended to provide non-invasive vagus nerve stimulation (nVNS) on the side of the neck. gammaCore is 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."

On February 25, 2020, the gammaCore Sapphire 510(k) approval was expanded to also include the indication of:

- "The preventive treatment of migraine headache in adult patients."

The 510(k) approval of the gammaCore Sapphire device was further expanded on December 2, 2020 to include adolescents (age 12 years and older) and again on June 15, 2021 to include treatment of hemicranias continua in adults and paroxysmal hemicranias in adults.

Literature Review
Evidence in the peer-reviewed literature related to the treatment indications for which the gammaCore device is cleared in the U.S. includes outcomes reported in the PRESTO randomized controlled trial (RCT) for patients with acute treatment of pain associated with migraine headache (Tassorelli, et al., 2018) and outcomes reported in patients with episodic cluster headache who were enrolled in ACT1 (Silberstein, et al., 2016b) or ACT2 RCTs (Goadsby, et al., 2018). Additional PRESTO trial outcomes and a few uncontrolled small open-label studies are also published (Grazzi, et al., 2018; Martelletti, et al., 2018; Barbanti, et al., 2015; Kinfe, et al., 2015; Goadsby, et al., 2014).

Evidence in the peer-reviewed literature related to the preventive treatment of cluster headache consists of the pivotal PREVA study (Gaul, et al., 2016). A published post hoc analysis of PREVA trial outcomes is also available (Gaul, et al., 2017). Also published is a retrospective analysis of data from 30 patients in the United Kingdom (UK) with medically refractory cluster headache who were applying to the National Health Service for individual funding requests for gammaCore therapy (Marin et al., 2018).

Cluster Headache
Silberstein et al. (2016b) conducted a randomized, double-blind, sham-controlled prospective study (ACT1) evaluating tVNS as acute treatment of cluster headache. In this pivotal US study participants were diagnosed with episodic cluster headache or chronic cluster headache ≥ one year before enrollment. The study population was predominantly white (87%) and male (84%). This trial had two design phases: a one-month, double-blind sham-controlled phase, followed by three-month, open-label nVNS therapy phase. A total of 150 participants were randomized (1:1) to receive t-VNS or sham treatment for ≤ one month during a double-blind phase; study completers could enter a three-month t-VNS open-label phase. The primary endpoint was response rate, defined as the proportion of participants who achieved pain relief (pain intensity of 0 or 1) at 15 minutes after treatment initiation for the first cluster headache attack without rescue medication use through 60 minutes. The key

secondary endpoint was sustained treatment response, which was defined as the percentage of patients with a 0 or 1 pain severity score, without rescue medication, 15 through 60 minutes following treatment. A total of 133 participants were included in the intention-to-treat population (ITT): all participants, 60 tVNS-treated and 73 sham-treated; episodic cluster headache cohort: 38 t-VNS-treated, 47 sham-treated; and, chronic cluster headache cohort: 22 t-VNS-treated, 26 sham-treated. There was no significant difference in the primary efficacy endpoint between the two treatment groups. In the total study population, a response was achieved in 26.7% of t-VNS-treated participants and 15.1% of sham-treated participants (p=0.10). On subset analysis, response rates were significantly higher in the episodic cluster headache cohort treated with t-VNS than in the sham-treated cohort (t-VNS, 34.2%; sham, 10.6%; p=0.008), but not the chronic cluster headache cohort (t-VNS, 13.6%; sham, 23.1%; p=0.48. Sustained response rates were significantly higher with t-VNS for the episodic cluster headache cohort (p=0.008) and total population (p=0.04). A total of 35 of 150 participants reported adverse device effects (t-VNS, 11; sham, 24) in the double-blind phase and 18 of 128 participants in the open-label phase. Adverse device effects included application site reactions (e.g., tingling, burning, soreness, stinging or skin irritation, redness, or erythema), lip or facial drooping, pulling, or twitching, and dysgeusia or metallic taste. No serious adverse device effects were reported. The authors state a limitation of this study was inadequate blinding. Investigators reported that a “considerable proportion” of nVNS group patients correctly guessed their treatment assignment after the first treatment. This is noteworthy because the primary efficacy endpoint was measured based on response to the first treatment only. Sample size of individual cohorts lacked statistical power.

To confirm and extend the results from the ACT1 study above, Goadsby et al. (2018) examined additional clinical and patient-related endpoints in a European setting (ACT 2). This RCT compared nVNS with a sham device for acute treatment in patients with episodic or chronic cluster headache (eCH, cCH). After completing a 1-week run-in period, subjects were randomly assigned (1:1) to receive nVNS or sham therapy during a 2-week double-blind period. Some patients dropped out after the run-in period. The primary efficacy endpoint was the proportion of all treated attacks that achieved pain-free status within 15 minutes after treatment initiation, without rescue treatment. The Intention to treat (ITT) population in the double blind period comprised 48 nVNS-treated (14 eCH, 34 cCH) and 44 sham-treated (13 eCH, 31 cCH) subjects. The trial used a 5-point scale to rate pain severity (0=no pain and 4=very severe pain).The primary efficacy endpoint was the proportion of all treated attacks that reported no pain (pain score of 0) within 15 minutes after treatment initiation. This endpoint did not statistically differ in the overall study population or in the subgroup of patients with chronic cluster headache. A statistical difference favoring gammaCore over sham nVNS was seen in the subgroup of patients with episodic cluster headache. For the primary endpoint, nVNS (14%) and sham (12%) treatments were not significantly different for the total cohort. In the eCH subgroup, nVNS (48%) was superior to sham (6%; $p < 0.01$). No significant differences between nVNS (5%) and sham (13%) were seen in the cCH subgroup. Twenty nVNS-treated subjects (40%) and 14 sham treated subjects (27%) had ≥1 AE during the double blind period. The author reported limitations included short-term follow-up, imbalance between CH subtypes, during the open-label period subjects could alter their CH treatment regimens by adding prophylactic therapies, or changing doses of existing treatments, or both.

Marin et al. (2018) conducted a multicenter, retrospective study of the gammaCore tVNS device for individuals with cluster headaches. The researchers reviewed data from 30 subjects (29 with chronic cluster headaches and one with episodic cluster headaches) who used tVNS after an inadequate response and/or intolerable side effects with ≥ 3 current or previous treatments (e.g., medications, deep brain stimulation, occipital nerve stimulation). The subjects were instructed to use tVNS for preventive therapy, acute therapy, or both. The mean duration of the evaluation period was 7.6 months (0.9–27.5). The mean range of attack frequency with standard of care (SoC) alone was 26.6 (3.8–77.0) attacks/week compared to 9.5 (0–38.5) with SoC plus tVNS ($p<0.01$). A total of three subjects, who averaged 42 to 63 attacks/week before tVNS, had no attacks during the evaluation period (range from 1.7 to 13.2 months). For the 25 subjects who reported duration of attacks, the mean decreased from 51.9 minutes with SoC alone to 29.4 minutes with SoC plus tVNS ($p<0.01$). In the 18 subjects who reported severity, the mean decreased from 7.8 with SoC alone to 6.0 with SoC plus tVNS ($p<0.01$). No serious adverse events were reported. The researchers concluded that t-VNS “led to significant decreases in attack frequency, severity, and duration in patients with CH who previously did not benefit from or could not tolerate multiple preventive and/or acute treatments.” The study was limited by a retrospective design, small sample size and inherent inclusion bias. By definition, this was a responder study, and patient responses were

unlikely representative of the cluster headache population as a whole. Furthermore, the current study sample comprising 63% women was unusual considering that cluster headache is more common among men.

Gaul et al. (2016) evaluated non-invasive vagus nerve stimulation (nVNS) as an adjunctive prophylactic treatment of chronic cluster headache (CH) in a pivotal prospective, open-label, randomized study (PREVA Trial) that compared adjunctive prophylactic nVNS (n=48) with standard of care (SoC) alone (control (n=49)). It enrolled adults with chronic cluster headache for ≥ one year prior to enrollment, without pain-free remission lasting at least one month. All trial participants received only SoC treatment during a two-week baseline period. A two-week baseline phase was followed by a four-week randomized phase (SoC plus nVNS vs control) and an optional four-week extension phase (SoC plus nVNS). SoC treatments included verapamil, lithium, topiramate, and/or corticosteroids; use of specific prophylactic agents was similar between treatment groups. Changes in SoC prophylactic medications were not permitted throughout the study. Participants were also given the option of acutely treating attacks with three additional nVNS doses at pain onset but were advised not administer preventive therapy within a two-hour period after acute treatment. The primary end point was the reduction in the mean number of CH attacks per week. Secondary end points were response rate, abortive medication use and safety/tolerability. During the randomized phase, individuals in the intent-to-treat population treated with SoC plus nVNS (n=45) had a significantly greater reduction in the number of attacks per week vs controls (n=48) for a mean therapeutic gain of 3.9 fewer attacks per week. Higher ≥50% response rates were also observed with SoC plus nVNS vs controls (40% (18/45)) vs controls (8.3% (4/48); $p<0.001$). Researchers reported that the optional use of nVNS as abortive therapy for an acute cluster headache attack had no effect on attack duration or pain intensity. No serious treatment-related adverse events occurred. Study limitations include the lack of a placebo or sham device, an open-label study design, the short treatment duration, and the use of patient-reported outcomes.

Migraine

Diener et al. (2019) reported on a randomized controlled trial (PREMIUM trial: NCT02378844) to evaluate the safety, efficacy, and tolerability of non-invasive vagus nerve stimulation (nVNS) for the prevention of migraine headaches. The study began with a four week baseline period during which treatment was not administered. This was followed by a 12 week treatment randomization period and then a 24 week open label period during which the sham patients began receiving nVNS. There were 341 patients aged 18–75 years. Patients were included if they met the following: a previous diagnosis of migraine, experienced between 5-12 migraine days per month over the previous four months, an onset of migraines at age ≤ 50 years, agreed not to use any migraine prevention treatments, and agreed not to change the dosage of any other medication that may have impacted the severity or frequency of migraines. Exclusion criteria included: a history of aneurysm, current use of a steroid, co-morbid condition expected to interfere with the treatment, severe cardiac disease, CVA, abnormal ECG, or were implanted with another electrical device or metal hardware. The intervention (n=169) was the use of the gammaCore-R device three times per day upon awakening, six to eight hours after that, and again six to eight hours after the second treatment. With each treatment, the device delivered a 5 kHz electrical stimulation. Sham stimulation that delivered a 0.1 Hz electrical stimulation (n=172) with each treatment served as the comparator. The primary outcome measure was the change in the number of migraine days during the four-week intervention period compared to the four-week baseline. Secondary outcomes measured included: number of patients with a ≥50% reduction in migraine days, mean change in the number of acute medication days, change in the number of headache days per month, and number of patients with adverse events. Overall follow-up time was 40 weeks to allow for the four week baseline period, the 12 week randomization period, and the 24 week open label period. The authors reported a mean reduction in migraine days per month in the nVNS group of 2.26 days compared to 1.8 days in the sham group ($p=0.15$). The percentage of patients with a ≥ 50% reduction in the number of migraine days per month was 31.9% in the nVNS group compared to 25.0% in the sham group ($p=0.19$). There was a 2.73 day reduction in the number of headache days per month reported in the nVNS group compared to 2.11 days in the sham group ($p=0.10$). Acute medication days were reduced in the nVNS group by 1.90 days per month compared to 1.35 days per month in the sham group ($p=0.11$). Reported adverse events were reported included: rash, pain, erythema, discomfort at the application site, and dizziness. Author noted limitations included: non-adherence to the three times daily treatment protocol, the sham device generated a vagal response, and the use of bilateral stimulations which was thought to have mitigated the overall efficacy reported in the study. Additional limitations included the small patient population. Additional, high quality studies are needed to validate the findings of this review.

Tassoreli, et al., 2018 evaluated non-invasive vagus nerve stimulation (nVNS) in the Prospective Study of nVNS for the Acute Treatment of Migraine (PRESTO). In this pivotal multicenter, double-blind, randomized, sham-controlled study participants were 100% white and 76.5% of participants were female; a majority (approximately 93%) had episodic migraines without aura. Participants were <50 years of age at migraine onset and had an attack frequency of 3–8 attacks per month with <15 headache days per month over the last six months. A total of 248 participants were randomized to receive nVNS (n=122) or sham treatment (n=126) within 20 minutes from pain onset. Participants were to repeat treatment if pain had not improved in 15 minutes. The trial had three design phases, each lasting four weeks: an observational run-in phase, a randomized double-blind phase, and an open-label active-treatment phase. Patients continued taking their usual migraine medications during the run-in phase. After randomization, patients could treat up to five migraine attacks with their allocated device (active or sham nVNS). Migraine medications were allowed as a rescue intervention during this phase. Patients were asked to wait 120 minutes after device treatment before taking a rescue medication. During the open-label phase, patients could treat up to five additional attacks with active nVNS. The primary endpoint was the proportion of participants who were pain free without using rescue medication at 120 minutes after study treatment completion for the first treated migraine attack of the double-blind period. Secondary endpoints were pain-free rates at 30 and 60 minutes, pain relief at 30, 60, and 120 minutes, mean percentage change in pain score from baseline to 30, 60, and 120 minutes, absence of associated symptoms (i.e., nausea, vomiting, photophobia, and phonophobia) at 120 minutes. nVNS (n=120) was superior to sham (n=123) for pain freedom at 30 minutes (12.7% vs 4.2%; p=0.012) and 60 minutes (21.0% vs 10.0%; p=0.023) but not at 120 minutes (30.4% vs 19.7%; p=0.067; primary endpoint; logistic regression) after the first treated attack. The inconsistency between the 120-minute finding and the findings at 30 and 60 minutes prompted a post-hoc repeated measures testing. This unplanned testing found that a significantly greater proportion of nVNS versus sham group patients were pain-free through 120 minutes post treatment (rather than at 120 minutes, as was defined for the primary endpoint). nVNS demonstrated benefits across other endpoints including pain relief at 120 minutes and was safe and well-tolerated. Almost all participants (98%) administered at least one stimulation and were adherent to the treatment instructions, but most participants did not administer repeat stimulations for the first attack at 15 minutes as instructed (nVNS, 60.8%; sham, 60.2%) or optionally at 120 minutes (nVNS, 95.8%; sham, 93.5%). The most common adverse events (AEs) were application site discomfort and nasopharyngitis in the nVNS group and application site erythema and pain, dizziness, flu-like symptoms, and nasopharyngitis among controls. Participants reported no serious adverse events during the study. Only two participants, both controls, discontinued from the study due to AEs. A reported limitation of this study was that the sham device, which delivered an appreciable electrical signal, appears to have had some level of vagal activation. Selection of an appropriate sham device which is a consistent challenge in neuromodulation studies.

Grazzi et al. (2018) examined additional data from the above PRESTO to provide further insights into the practical utility of nVNS by evaluating its ability to consistently deliver clinically meaningful improvements in pain intensity while reducing the need for rescue medication. Patients recorded pain intensity for treated migraine attacks on a four-point scale. Data were examined to compare nVNS and sham with regard to the percentage of patients who benefited by at least one point in pain intensity. The percentage of attacks that required rescue medication and pain-free rates stratified by pain intensity at treatment initiation was assessed. A significantly higher percentage of patients who used acute nVNS treatment (n=120) vs sham (n=123) reported a ≥ 1-point decrease in pain intensity at 30 min (nVNS, 32.2%; sham, 18.5%; p=0.020), 60 min (nVNS, 38.8%; sham, 24.0%; p=0.017), and 120 min (nVNS, 46.8%; sham, 26.2%; p=0.002) after the first attack. Similar significant results were seen when assessing the benefit in all attacks. The proportion of patients who did not require rescue medication was significantly higher with nVNS than with sham for the first attack (nVNS, 59.3%; sham, 41.9%; p=0.013) and all attacks (nVNS, 52.3%; sham, 37.3%; p=0.008). When initial pain intensity was mild, the percentage of patients with no pain after treatment was significantly higher with nVNS than with sham at 60 min (all attacks: nVNS, 37.0%; sham, 21.2%; p=0.025) and 120 min (first attack: nVNS, 50.0%; sham, 25.0%; p=0.018; all attacks: nVNS, 46.7%; sham, 30.1%; p=0.037). The researchers concluded that nVNS “has the flexibility to be used alone or as adjunctive therapy for multiple attacks without risk of pharmacologic interactions and adverse events”.

Martelletti, et al., 2018) reported additional pre-defined secondary and other end-points from the above PRESTO Study. The nVNS group (n=120) had a significantly greater percentage of attacks treated during the double-blind period that were pain-free at 60 (p= 0.005) and 120 mins (p= 0.026) than the sham group (n= 123) did. Similar results were seen for attacks with pain relief at 60 (p= 0.025) and 120 mins (p= 0.018). For the first attack and all

attacks, the nVNS group had significantly greater decreases (versus sham) in pain score from baseline to 60 mins (p=0.029); the decrease was also significantly greater for nVNS at 120 mins for the first attack (p= 0.011). Results during the open-label period were consistent with those of the nVNS group during the double-blind period. The incidence of adverse events and adverse device effects was low across all study periods, and no serious adverse events occurred. The authors concluded that these results further demonstrated that nVNS is an effective and reliable acute treatment for multiple migraine attacks, which can be used safely while preserving the patient's option to use traditional acute medications as rescue therapy, possibly decreasing the risk of medication overuse. The authors stated that this study had several limitations. The selection of an appropriate sham device in neuromodulation studies was challenging. In accordance with previous recommendations to ensure maintenance of the study blind, the sham device used in PRESTO produced an active signal that could be perceived by the user but was not designed to stimulate the vagus nerve; recent data suggest that the strength of the sham device's signal may have inadvertently activated the vagus nerve and could have inflated the responses to sham treatment across all end points. This phenomenon, which merited further investigation, may have been related to a psychobiological placebo effect; but more likely resulted from the unanticipated physiologically active signal that may have decreased the difference in therapeutic gain seen between the nVNS and sham groups. During both the double-blind and open-label periods, the mean number of acute medications used per migraine attack was substantially lower than that seen during the observational period. Such a decrease in medication use could be interpreted as evidence of treatment efficacy; however, these results must be interpreted with caution, as patients were encouraged to refrain from using acute medications for 120 mins after stimulation with the study device. This study limitation most likely contributed to decreases in acute medication use in both the nVNS and sham groups during the double-blind period and may partially explain the lack of significance between treatment groups for this end-point.

Silberstein et al. (2016a) evaluated the feasibility, safety, and tolerability of noninvasive vagus nerve stimulation (nVNS) for the prevention of chronic migraine (CM) attacks (EVENT Study). In this prospective, multicenter, double-blind, sham-controlled pilot study of nVNS in CM prophylaxis, adults with CM (≥15 headache d/mo) entered the baseline phase (one month) and were subsequently randomized to nVNS or sham treatment (two months) before receiving open-label nVNS treatment (six months). The primary endpoints were safety and tolerability. Efficacy endpoints in the intent-to-treat population included change in the number of headache days per 28 days and acute medication use. Fifty-nine participants (mean age, 39.2 years; mean headache frequency, 21.5 d/mo) were enrolled. During the randomized phase, tolerability was similar for nVNS (n = 30) and sham treatment (n=29). Most adverse events were mild/moderate and transient. Mean changes in the number of headache days were -1.4 (nVNS) and -0.2 (sham). Twenty-seven participants completed the open-label phase. For the 15 completers initially assigned to nVNS, the mean change from baseline in headache days after eight months of treatment was -7.9. The authors concluded that therapy with nVNS was well-tolerated with no safety issues. Study limitations included the small sample size, blinding challenges, and high discontinuation rate. The authors reported that larger sham-controlled studies are needed.

Lendavi et al. (2018) conducted a systematic review for randomized controlled trials (RCTs) and prospective cohort clinical studies assessing the safety and efficacy of noninvasive peripheral nerve stimulation of the cervical branch of the vagal nerve (afferent properties) for primary headache disorders (episodic/chronic migraine [EM/CM] and cluster headache [ECH/CCH]). Three RCTs were identified for ECH/CCH (ACT-1, ACT-2 and PREVA), one RCT for migraine (EVENT) and several prospective cohort studies and retrospective analyses for both headache disorders. The authors concluded that cervical nVNS represents a novel, safe and efficient adjunctive treatment option for primary headache disorders. In particular, preliminary observations suggest enhanced nVNS responsiveness in favor of episodic subtypes (EM and ECH). However, preclinical studies are urgently warranted to dissect the mechanism of action. Comparative and reproducible conclusions are limited by the different stimulation protocols and/or outcome parameter measures.

Other Indications

Transcutaneous vagus nerve stimulation (tVNS) has been proposed for use in a number of indications including, but not limited schizophrenia (Hasan, et al., 2015); tinnitus (Lehtimäki, et al., 2013), intractable epilepsy (Aihua, et al., 2014; He, et al., 2013; Stefan, et al., 2012), depression (Fang, et al., 2016; Hein, et al., 2013; Rong, et al., 2016, 2012), pain (Busch, et al., 2013), cardiac function (Kreuzer, et al., 2012), postoperative cognitive dysfunction in elderly patients (Xiong, et al., 2009, central sleep apnea (Forde, et al., 2017). Most of the evidence in the peer-reviewed literature for tVNS consists of pilot studies or case series for a variety of indications. The

studies are limited by lack of a comparator and small sample size therefore conclusions about safety and efficacy cannot be made at this time.

Professional Societies/Organizations:

The American Headache Society has published evidenced-based guidelines on the treatment of cluster headache. The guideline, reviewing outcomes of the PREVA study, states that “future studies that are blinded with a sham control are warranted to elucidate the efficacy and safety of noninvasive vagus nerve stimulation for treatment of cluster headache” (Robbins, et al., 2016).

Use Outside of the US
Per the manufacturer website, the tVNS device NEMOS® tVNS Technologies GmbH (Erlangen, Germany) received the European market (CE mark) for the treatment of epilepsies. This device is not FDA-approved in the United States. In October 2018 Ceromed was taken over by tVNS Technologies GmbH.

gammaCore has regulatory approval in the European Union, South Africa, India, Colombia, New Zealand, Canada, and Malaysia for the acute and/or prophylactic treatment of cluster headache. CE Marking has been granted for primary headache, epilepsy, bronchoconstriction, gastric motility disorders, and depression and anxiety. In January 2016, ElectroCore LLC announced the commercial launch of gammaCore in Germany for the treatment of migraine and cluster headache.

In May of 2021, the Scottish Intercollegiate Guidelines Network (SIGN) stated in a national clinical guideline on the management of and investigative procedures for epilepsy in children that, “Vagus nerve stimulation could be considered as an adjunctive treatment for children with drug-resistant epilepsy who are not candidates for surgery, under the specialist guidance of a consultant pediatric neurologist.” This recommendation was given based upon expert opinion, a high quality systematic review of five randomized controlled trials, and a single randomized controlled trial.

In December 2019, the National Institute for Clinical Excellence (NICE) (United Kingdom) published a guidance document on non-invasive vagus nerve stimulation with the gammaCore device for cluster headaches that states gammaCore is recommended as an adjunct to standard care for reducing the frequency and intensity of cluster headaches. It should only be continued for people whose symptoms reduce in the first three months of use. Three randomized controlled trials (RCT), one post-hoc analysis of an RCT, one pooled analysis of two RCTs, and three non-comparative cohort studies were used to make this recommendation. The evidence included a total of 410 patients. It was noted that the degree of benefit, however, is uncertain.

In March 2016, the National Institute for Clinical Excellence (NICE) (United Kingdom) published a guidance document addressing transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine that states evidence on the safety of transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine raises no major concerns. The evidence on efficacy is limited in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research (NICE, 2016).

In December 2020, NICE (United Kingdom) published a guidance document addressing implanted vagus nerve stimulation (VNS) for treatment-resistant depression that states current evidence on the efficacy of VNS for treatment-resistant depression is limited in quality. Therefore this procedure should be used only with special arrangements for clinical governance, consent and audit or research (NICE, 2020).

In January 2012 (updated 2020), NICE (United Kingdom) published a clinical guideline addressing the diagnosis and management of epilepsy. The guideline states that vagus nerve stimulation is indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults who are refractory to antiepileptic medication but who are not suitable for resective surgery. This includes adults whose epileptic disorder is dominated by focal seizures (with or without secondary generalization) or generalized seizures. Vagus nerve stimulation is indicated for use as an adjunctive therapy in reducing the frequency of seizures in children and young people who are refractory to antiepileptic medication but who are not suitable for resective surgery. This includes

children and young people whose epileptic disorder is dominated by focal seizures (with or without secondary generalization) or generalized seizures.

The Canadian Network for Mood and Anxiety Treatments (CANMAT) published an evidence-based clinical guideline for the management of adults with major depressive disorder. The authors concluded that VNS is a third line treatment for treatment resistant depression after repetitive transcranial magnetic stimulation and electroconvulsive therapy. (Milev, et al., 2016).

In a 2015 national clinical guideline (revised 2018) for the diagnosis and management of epilepsy in adults, the Scottish Intercollegiate Guidelines Network stated that in adult patients who have been found to be unsuitable for resective surgery for epilepsy, vagus nerve stimulation may be considered.

In a 2015 evidence based guideline for the treatment of depressive disorders, the British Association for Psychopharmacology (Britain) stated that due to a limited evidence of efficacy, VNS may be considered for patients with treatment resistant chronic depression but not as a first-line treatment (Cleare, et al., 2015).

Medicare Coverage Determinations

	Contractor	Policy Name/Number	Revision Effective Date
NCD	National	Vagus Nerve Stimulation (VNS) (160.18)	7/22/2020
LCD		No Local Coverage Determination found	

Note: Please review the current Medicare Policy for the most up-to-date information.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
61886	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to 2 or more electrode arrays
61888	Revision or removal of cranial neurostimulator pulse generator or receiver
64553	Percutaneous implantation of neurostimulator electrode array; cranial nerve
64568	Open implantation of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator
64569	Revision or replacement of cranial nerve (eg, vagus nerve) neurostimulator electrode array, including connection to existing pulse generator

HCPCS Codes	Description
C1767	Generator, neurostimulator (implantable), non-rechargeable
C1778	Lead, neurostimulator (implantable)
C1816	Receiver and/or transmitter, neurostimulator (implantable)
C1820	Generator, neurostimulator (implantable), non-high-frequency with rechargeable battery and charging system
C1883	Adapter/extension, pacing lead or neurostimulator lead (implantable)
L8679	Implantable neurostimulator, pulse generator, any type

HCPCS Codes	Description
L8680	Implantable neurostimulator electrode, each
L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
L8682	Implantable neurostimulator radiofrequency receiver
L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
L8686	Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension
L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension

Considered Experimental/Investigational/Unproven:

HCPCS Codes	Description
C1822	Generator, neurostimulator (implantable), high frequency, with rechargeable battery and charging system

Considered Experimental/Investigational/Unproven when used to report Transcutaneous Vagus Nerve Stimulation (tVNS):

CPT®* Codes	Description
97014	Application of a modality to 1 or more areas; electrical stimulation (unattended)
97032	Application of a modality to 1 or more areas; electrical stimulation (manual), each 15 minutes

HCPCS Codes	Description
E0720	Transcutaneous electrical nerve stimulation (tens) device, two lead, localized stimulation
K1020	Non-invasive vagus nerve stimulator

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