BlueCross BlueShield of Alabama

Name of Policy:
Vagus Nerve Stimulation

Policy #: 260
Category: Surgery

Latest Review Date: April 2018
Policy Grade: D

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

Stimulation of the vagus nerve can be performed by means of 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 policy also addresses devices that stimulate the vagus nerve transcutaneously.

Vagus Nerve Stimulation

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 generalized seizures, and it has been investigated for a range of other conditions.

While the mechanisms for the antiepileptic effects of vagal nerve stimulation are not fully understood, the basic premise of VNS in the treatment of epilepsy is that vagal visceral afferents have a diffuse central nervous system projection, and activation of these pathways has a widespread effect on neuronal excitability. 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. There are also vagal efferent pathways that innervate the heart, vocal cords, and other laryngeal and pharyngeal muscles, and provide parasympathetic innervation to the gastrointestinal tract that may also be stimulated by VNS.

The type of VNS device addressed in this policy consists of an implantable, programmable electronic pulse generator that delivers stimulation to the left vagus nerve at the carotid sheath. The pulse generator is connected to the vagus nerve via a bipolar electrical lead. Surgery for implantation of a vagal nerve stimulator involves implantation of the pulse generator in the infraclavicular region and wrapping two spiral electrodes around the left vagus nerve within the carotid sheath. The programmable stimulator may be programmed in advance to stimulate at regular times or on demand by patients or family by placing a magnet against the subclavicular implant site.

Various types of devices which stimulate the vagus nerve transcutaneously have been developed as well. The FDA has not approved any transcutaneous vagus nerve stimulation devices.

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

Indications

VNS was originally approved for the treatment of medically-refractory epilepsy. Significant advances have occurred in surgical treatment for epilepsy and in medical treatment of epilepsy with newly developed and approved medications. Despite these advances, however, 25% to 50% of patients with epilepsy experience breakthrough seizures or suffer from debilitating adverse effects of antiepileptic drugs. VNS has been used as an alternative to or adjunct to epilepsy surgery or medications as a therapy for refractory seizures.

Based on observations that patients treated with VNS experienced improvements in mood, VNS has been evaluated for the treatment of refractory depression. VNS has been investigated for

multiple other conditions which may be affected by either the afferent or efferent stimulation of the vagus nerve, including headaches, tremor, obesity, heart failure, fibromyalgia, tinnitus, and traumatic brain injury.

Policy:

Effective for dates of service on or after May 2, 2014:

Vagus Nerve stimulation (VNS) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage as a treatment of **medically refractory seizures**.

Vagus Nerve stimulation (VNS) does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage as a treatment of other conditions including but not limited to: essential tremor, headaches, depression, obesity, Alzheimer's disease, chronic heart failure, upper-limb impairment due to stroke, fibromyalgia, tinnitus and traumatic brain injury and is considered **investigational**.

Non-implantable Vagus Nerve stimulation does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

This policy was created in 2000 and updated periodically with literature review. The most recent update covered the period through December 11, 2017.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is

preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice. The following is a summary of the key literature to date.

Vagus Nerve Stimulation

Clinical Context and Test Purpose

The purpose of implantable vagus nerve stimulation (VNS) is to apply pulsed electrical energy via the vagus nerve to alter aberrant neural activity resulting in seizures.

The question addressed in this evidence review is: Does the use of VNS as a treatment for medically refractory seizures result in changes in management and improvement in health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients
One relevant population of interest is patients with medically refractory seizures.

Interventions
The test being considered is implantable VNS.

Comparators
Comparators are conventional antiepileptic drugs and/or resective surgery.

Outcomes
Outcomes of interest are technical reliability, clinical validity or diagnostic accuracy (test accuracy, test validity [e.g., sensitivity, specificity]), and clinical utility that includes consideration of avoidance of harms.

Timing
VNS is typically used when a patient has had unsuccessful medical therapy, been intolerant of medical therapy, or had failed resective surgery.

Setting
VNS is initiated with surgical implantation and subsequently administered in outpatient and home care settings.

Systematic Reviews

Reports on the use of VNS to treat medication resistant seizure disorders date to the decade beginning with 1990 and were coincident with preapproval and early post-approval study of the device.

VNS for Adult Partial-Onset Seizures
In 2011, Englot et al published a meta-analysis of the literature through November 2010 on efficacy and predictors of response of VNS. Table 2 summarizes the 15 RCTs or prospective observational studies. Overall, VNS did predict a 50% or greater reduction in seizure frequency

at last follow-up, the main effect, with an odd ratio (OR) of 1.83 (95% confidence interval [CI], 1.80 to 1.86; p>0.001). Table 2 summarizes the meta-analysis

Table 2. Summary of Trials and Studies Included in Meta-Analysis

Study (year)	N	Duration (FU)	No. of Sites	Design	Seizure Type	Seizure Frequency Reduction >50%
Ben-Menachem (1994)	114	3 mo.	Multisite	Blinded RCT	Partial	31%
Handforth (1998)	196	3 mo.	Multisite	Blinded RCT	Partial	23%
Amar (1998)	17	3 mo.	Single	Blinded RCT	Partial	57%
Scherrmann (2001)	29	NR	Single	Non-Blinded RCT	Mixed	45%
DeGiorgio (2015)	61	3 mo.	Multisite	Non-Blinded RCT	Partial	29%
Ben-Menachem (1999)	64	3-64mo.	Single	Prospective OBS	Mixed	45%
Parker (1999)	15[a]	1y	Single	Prospective OBS	Mixed	27%
Labar (1999)	24	3 mo.	Single	Prospective OBS	Generalized	46%
Degiorgio (2000)	195	12 mo.	Multisite	Prospective OBS	Mixed	35%
Chavel (2003)	29	1-2y	Single	Prospective OBS	Partial	54%
Vonck (1999, 2004)	118	>6mo.	Multisite	Prospective OBS	Mixed	50%
Majoie (2001, 2005)	19[a]	2y	Single	Prospective OBS	Mixed	21%
Huf (2005)	40[c]	2y	Single	Prospective OBS	NR	28%
Kang (2006)	16[d]	>1y	Multisite	Prospective OBS	Mixed	50%
Ardesch (2007)	19	>2y	Single	Prospective OBS	Partial	33%

FU: follow-up; NR: not reported: OBS: observational; RCT: randomized controlled trial.
a Children with encephalopathy.
b Rate at 1 year of follow-up.
c Adults with low IQ.
d Children.
e Rate at 2 years.

The evidence review on treatment of seizures was originally informed, in part, by a 1998 TEC Assessment that offered the following conclusions:

- For patients 12 years of age and older with medically refractory partial-onset seizures, for whom surgery is not recommended or for whom surgery has failed evidence is available from 2 multicenter, randomized, blinded, active control studies submitted for device registration. The trials, which were limited to patients with partial-onset seizures, and included outcomes for 314 patients, present sufficient data to demonstrate that VNS is a beneficial adjunct to optimal antiepileptic drug therapy for the treatment of these

seizures. In patients with at least 6 partial-onset seizures/month, VNS reduces seizure frequency by approximately 25% after 3 months of treatment. In patients who achieve an initial reduction in seizure frequency, the beneficial treatment effect appears to be maintained and may increase with time. The results of these studies are included in Table 2.

- Adverse effects are mild and consist primarily of hoarseness or voice change during "on" periods of stimulation.

Based on this TEC Assessment, earlier versions of this evidence review supported the use of VNS for partial-onset seizures for patients older than 12 years of age in individuals for whom surgery is not recommended or whom surgery has failed.

In 2015, Panebianco, et al updated a Cochrane systematic review and meta-analysis of vagus nerve stimulation to treat partial seizures. This review specifically evaluated randomized, double-blind, parallel or crossover, controlled trials of VNS as add-on treatment comparing high- and low-stimulation paradigms and VNS stimulation vs no stimulation or a different intervention. Five trials with a total of 439 participants compared high-frequency stimulation to low-frequency stimulation in participants aged 12 to 60 years and another trial examined high-frequency stimulation vs low-frequency stimulation in children. The overall relative risk (RR) for a response to high stimulation compared with low stimulation using the fixed-effect model was calculated to be 1.73 (95% Cl, 1.13 to 2.64; p=0.01), showing that patients receiving high stimulation are more likely to show a 50% or greater reduction in seizure frequency.

Randomized Controlled Trials
In 2014, Ryvlin et al reported a randomized controlled trial (RCT) on long-term quality of life outcomes for 112 patients with medication-resistant focal seizures, which supported the beneficial effects of VNS for this group.

VNS for Adult Generalized Seizures
Resective surgery is generally less of an option for individuals with generalized treatment resistant seizures that may be multifocal or involve an eloquent area are less likely candidates for respective surgery. Vagus nerve stimulation has been evaluated as alternative to disconnection procedures such as surgical division of the corpus callosum.

The evidence for the efficacy of VNS for generalized seizures in adults is primarily from observational data; registries and small cohort studies.

In 2016, Englot et al examined freedom from seizure rates and predictors across 5554 patients enrolled in the VNS Therapy Patient Outcomes Registry. The registry was established in 1999, after the 1997 FDA approval of VNS and is maintained by the manufacturer of the device, Cyberonics (Houston, TX). Data were prospectively collected by 1285 prescribing physicians from 978 centers (911 in the United States and Canada and 67 internationally) at patients' preoperative baselines and at various intervals during therapy. During active data collection, participation in the registry included approximately 18% of all implanted VNS devices. The database was queried in January 2015, and all seizure outcomes reported with the 0- to 4-, 4- to 12-, 12- to 24-, and 24- to 48-month time ranges after VNS device implantation were extracted and compared with patient preoperative baseline. Available information on patient demographics, epilepsy etiology and syndrome, historical seizure types and frequencies, quality

of life, physician global assessment, current antiepileptic drugs, medication changes, malfunctions, battery changes, and changes in therapy were tracked at each time point of data submission. At each observation time point, responders were defined as having 50% or greater decrease in seizure frequency compared with baseline and non-responders as less than 50% decrease.

A localized epilepsy syndrome such as partial-onset seizures was recorded in 59% of the registry participants; generalized epilepsy in 27%, and 11% had a syndromic etiology such as Lennox-Gastaut.

The outcomes for the approximately 1500 registry enrollees with generalized seizures are summarized in Table 3. These rates were not statistically different from participants with predominantly partial seizures.

Table 3. Summary of VNS Registry Outcome Results

Generalized Seizures	Responder Rate %	Seizure Freedom Rate %
0-4 mo.	50	7
4-12 mo.	55	8
12-24 mo.	55	8
24-48 mo.	Approximately 60[a]	Approximately 9[a]

Responder rate: ≥50% decrease in seizure frequency.
a Approximation based on publication Figure 1 and narrative.

VNS for Pediatric Seizures

The evidence for VNS for pediatric seizures consists of a variety of small non-comparator trials, prospective observational studies and retrospective case series. As in the adult studies there is heterogeneity of seizure etiologies; mixed, syndromic and, idiopathic generalized and limited information on concomitant antiepileptic drug requirement. Some studies have defined pediatric as less than 12 years of age and others as less than 18 years and may have included patients as young as 2 to 3 years of age. Study subpopulations may have had prior failed resective surgery. Complete freedom from seizures is the exception and the primary reported end point is 50% or more reduction is seizure frequency determined over varying lengths of follow-up. There is overlap of authors for multiple studies suggesting utilization of VNS in specialized clinical care environments. Multiple studies have some form of innovator device company sponsorship.

Table 4 summarizes the evaluable literature on VNS in pediatric populations of all seizure types

Table 4. Summary of VNS Pediatric Study

Author (year)	Study Type	Sample	Seizure Disorder	Duration of FU	Seizure Frequency Reduction ≥50% or Median Reduction, n (%)[a]	Notes
Hornig (1997)	Case Series	19	Mixed	2-30 mo.	10(53)	Prior failed resective surgery, n=3
Murphy (1999)	Prospective OBS	60	Mixed	18 mo.	42% (n=46)[a]	Age: 26% <12 y
Patwardhan (2000)	Case series	38	Mixed	12 mo.	26 (68)	Age: 11 mo. to 16y

Frost (2001)	Retrospective case review	50	LGS	6 mo.	57.9%[a]	Age: 13y (median)
You (2007)	Prospective OBS	28	Mixed	31.4 mo.	15(53.6)	Age range: 2-17y
Klinkenberg (2012)	RCT[b]	41	Mixed	19 wk.	High stim 3/21 (14.2) Low Stim 4/20 (20)	Age range: 3-17y
Cukiert (2013)	Case Series	24	LGS	24 mo.	Unknown[c]	Age: <12y
Healy (2013)	Retrospective case review	16	Unknown	3y review period	9(56)	Age:<12y
Terra (2014)	Retrospective case-control[d]	36	Mixed	3y review period	20 (55.4) VNS group	Age <18y Difference from baseline seizure frequency[e]
Yu (2014)	Retrospective case review	69/252[f]	Mixed	12 mo.	44% (n=28)[a]	Age <12 y=28

FU: follow-up; LGS: Lennox-Gastaut syndrome; OBS: observational; RCT: randomized controlled trial; VNS: vagus nerve stimulation.
a Median reduction in total seizure frequency.
b RCT comparing high- (n=21) with low-stimulation (n=20) VNS.
c Seizure reduction not reported but 10 (41.6%) experienced transient seizure frequency worsening.
d Age-matched 31 VNS with 72 non-VNS controls.
e Baseline seizure frequency; VNS: 346.64 (SD=134.11) vs control group: 83.63 (SD=41.43).
f Sixty-nine of 252 of identified cases had evaluable pre- and post-implantation data.

Section Summary: Treatment of Treatment-Resistant Seizures

The evidence on the efficacy of VNS for treatment of medically refractory seizures consists of 2 RCTs reported at the time of initial FDA approval of the marketed device, a recent meta-analysis and numerous uncontrolled studies. The RCTs both reported a significant reduction in seizure frequency with VNS for patients with partial-onset seizures. The uncontrolled studies as well as case series have consistently reported reductions of clinical significance defined as 50% or more reduction in seizure frequency in both adults and children over almost 2 decades history of publication. Interpretation of all outcomes and results is limited by the variety of comparators (when used), variability in length of follow-up, limited published data on antiepileptic medication requirements, mixed seizure etiologies and, history of prior failed resective surgery. There is overlap of authors for multiple studies suggesting utilization of VNS in specialized clinical care environments. Multiple studies have some form of innovator device company sponsorship.

Treatment Resistant Depression

Interest in the application of VNS for treatment of refractory depression is related to reports of improvement in depressed mood among epileptic patients undergoing VNS. TEC Assessments written in 2005 and updated in 2006 concluded that evidence was insufficient to permit conclusions of the effect of VNS therapy on health outcomes. The available evidence for these TEC Assessments included study groups assembled by the manufacturer of the device (Cyberonics) and have since been reported on in various publications. Analyses from these study groups were presented for U.S. Food and Drug Administration (FDA) review and consisted of a case series of 60 patients receiving VNS (Study D-01), a short-term (i.e., 3-month) sham-controlled RCT of 221 patients (Study D-02), and an observational study comparing 205 patients on VNS therapy with 124 patients receiving ongoing treatment for depression (Study D-04).

Patients who responded to sham treatment in the short-term RCT (approximately 10%) were excluded from the long-term observational study.

The primary outcome evaluated was the relief of depression symptoms that can usually be assessed by any one of many different depression symptom rating scales. A 50% reduction from baseline score is considered to be a reasonable measure of treatment response. An improvement in depression symptoms may allow reduction of pharmacologic therapy for depression, with a reduction in side effects related to that form of treatment. In the studies evaluating VNS therapy, the 4 most common instruments used were the Hamilton Rating Scale for Depression, Clinical Global Impression, Montgomery and Asberg Depression Rating Scale, and the Inventory of Depressive Symptomatology (IDS).

Several case series studies published before the randomized trial showed rates of improvement, as measured by a 50% improvement in depression score of 31% at 10 weeks to greater than 40% at one to two years, but there are some losses to follow-up. Natural history, placebo effects, and patient and provider expectations make it difficult to infer efficacy from case series data.

The randomized study (D-02) that compared VNS therapy with a sham control (implanted but inactivated VNS) showed a nonstatistically significant result for the principal outcome.(22,23) Fifteen percent of VNS subjects responded versus 10% of control subjects (p=0.31). The Inventory for Depressive Symptomatology Systems Review (IDS-SR) score was considered a secondary outcome and showed a difference in outcome that was statistically significant in favor of VNS (17.4% vs 7.5%, respectively, p=0.04).

The observational study that compared patients participating in the RCT and a separately recruited control group (D-04 vs D-02, respectively) evaluated VNS therapy out to one year and showed a statistically significant difference in the rate of change of depression score. However, issues such as unmeasured differences between patients, non-concurrent controls, differences in sites of care between VNS therapy patients and controls, and differences on concomitant therapy changes raise concern about this observational study. Analyses performed on subsets of patients cared for in the same sites, and censoring observations after treatment changes, generally showed diminished differences in apparent treatment effectiveness of VNS and almost no statistically significant differences. Patient selection for the randomized trial and the observational comparison trial may be of concern. VNS is intended for treatment-refractory depression, but the entry criteria of failure of two drugs and a six-week trial of therapy may not be a strict enough definition of treatment resistance. Treatment-refractory depression should be defined by thorough psychiatric evaluation and comprehensive management. It is important to note that patients with clinically significant suicide risk were excluded from all VNS studies. Given these concerns about the quality of the observational data, these results did not provide strong evidence for the effectiveness of VNS therapy.

In addition to the results of the TEC Assessment, several systematic reviews and meta-analyses have addressed the role of VNS in treatment resistant depression. A systematic review of the literature for VNS of treatment-resistant depression identified the randomized trial previously described among the 18 studies that met the study's inclusion criteria. VNS was found to be associated with a reduction in depressive symptoms in the open studies. However, results from the only double-blind trial were considered to be inconclusive. Daban et al concluded that further clinical trials are needed to confirm efficacy of VNS in treatment-resistant depression.

In a meta-analysis that included 14 studies, Martin and Martin-Sanchez reported that among the uncontrolled studies in their analysis, 31.8% of subjects responded to VNS treatment. However, results from a meta-regression to predict each study's effect size suggested that 84% of the observed variation across studies was explained by baseline depression severity. Berry et al reported results from a meta-analysis of six industry-sponsored studies of safety and efficacy for VNS in treatment-resistant depression, which included the D-01, D-02, Bajbouj et al (D-03), D-04, and Aaronson et al (D-21) study results. In addition, the meta-analysis used data from a registry of patients with treatment-resistant depression (335 patients receiving VNS and treatment as usual and 301 patients receiving treatment as usual) that were unpublished at the time of the meta-analysis publication (online site, ClinicalTrials.gov identifier: NCT00320372). The authors report that adjunctive VNS was associated with a greater likelihood of treatment response (odds ratio, 3.19; 95% confidence interval [CI], 2.12 to 4.66). However, the meta-analysis did not have systematic study selection criteria, limiting the conclusions that can be drawn from it.

In 2014, Liu et al conducted a systematic review of brain stimulation treatments, including deep brain stimulation, electroconvulsive therapy, transcranial magnetic stimulation, and VNS, for mental illnesses other than nonpsychotic unipolar depression in adults 65 years-old or older. The authors identified two small studies which evaluated the effect of VNS on cognition in patients with Alzheimer disease, one with 10 subjects and one with 17 subjects, which were mixed in demonstrating clinical improvements.

In 2013, Aaronson et al reported results from an active-controlled trial in which 331 patients with a history of chronic or recurrent bipolar disorder or major depressive disorder, with a current diagnosis of a major depressive episode, were randomized to one of three VNS current doses (high, medium, low). Patients had a history of failure to respond to at least four adequate dose/duration of antidepressant treatment trials from at least two different treatment categories. After 22 weeks, the current dose could be adjusted in any of the groups. At follow-up visits at weeks 10, 14, 18, and 22 after enrollment, there was no statistically significant difference between the dose groups for the study's primary outcome, change in IDS score from baseline. However, the mean IDS score improved significantly for each of the groups from baseline to the 22-week follow-up. At 50 weeks of follow-up, there were no significant differences between the treatment doses groups for any of the depression scores used. Most patients completed the study; however, there was a high rate of reported adverse events, including voice alteration in 72.2%, dyspnea in 32.3%, and pain in 31.7%. Interpretation of the IDS improvement over time is limited by the lack of a no treatment control group. Approximately 20% of the patients included had a history of bipolar disorder; as such, the results may not be representative of most patients with treatment resistant unipolar depression.

Other case series do not substantially strengthen the evidence supporting VNS. A case series study by Bajbouj et al that followed patients for two years showed that 53.1% (26/49) patients met criteria for a treatment response and 38.9% (19/49) met criteria for remission. A small study of nine patients with rapid-cycling bipolar disorder showed improvements in several depression rating scales over 40 weeks of observation. Another case series by Cristancho et al that followed patients for one year showed that 4/15 responded and 1/15 remitted according to the principal response criteria. In a 2014 case series which included 27 patients with treatment resistant

depression, five patients' demonstrated complete remission after one year and six patients were considered responders.

Adverse effects of VNS therapy included voice alteration, headache, neck pain, and cough, which are known from prior experience with VNS therapy for seizures. Regarding specific concerns for depressed patients such as mania, hypomania, suicide, and worsening depression, there does not appear to be a greater risk of these events during VNS therapy.

Section Summary: Treatment- Resistant Depression

There is one RCT evaluating the efficacy of VNS for resistant depression. This study reported only short-term results and found no significant improvement for the primary outcome with VNS. Other available studies, which include nonrandomized comparative studies and case series, are limited by relatively small sizes and the potential for bias in selection; the case series are further limited by the lack of a control group .Given the limitations of this literature, combined with the lack of substantial new clinical trials, the scientific evidence is considered to be insufficient to permit conclusions concerning the effect of this technology on major depression. Another neuromodulation technique for the treatment of depression is evaluated in evidence review (Transcranial Magnetic Stimulation as a Treatment of Depression and Other Psychiatric Disorders Policy #170).

Other Conditions

Treatment of Chronic Heart Failure

VNS has been investigated for treatment of congestive heart failure in some case series studies. A case series Phase 2 trial of VNS therapy for chronic heart failure was reported with improvements in New York Heart Association class quality of life, 6-minute walk test, and LV ejection fraction. The ANTHEM-HF study is also a case series study, but patients were randomized to either right- or left-sided vagus nerve implantation (but there is no control group). Overall, from baseline to 6-month follow-up, LV ejection fraction improved by 4.5% (95% CI, 2.4 to 6.6), left ventricular and systolic volume (LVESV) improved by 4.1 ml (95% CI, -9.0 to 0.8), LVESD improved by -1.7 mm (95% CI, -2.8 to -0.7), heart rate variability improved by 17 ms (95% CI, 6.5 to 28), and 6-minute walk distance improved by 56 m (95% CI, 37 to 75).

In 2015, Zannand et al reported results from the NECTAR-HF trial, a randomized, sham-controlled trial, with outcomes from VNS in patients with severe left ventricular (LV) dysfunction, despite optimal medical therapy. Ninety-six patients were implanted with VNS and randomized in a 2:1 manner to VNS ON or VNS OFF for six months. Programming of the generator was performed by a physician unblinded to treatment assignment, while all other investigators and site study staff involved in end point data collection were blinded to randomization. Sixty-three patients were randomized to the intervention, of which 59 had paired pre-post data available, while 32 were randomized to control, of which 28 had paired data available. The analysis was a modified intention-to-treat. For the primary end point of change in left ventricular end systolic diameter (LVESD) from baseline to 6 months, there were no significant differences between groups (p=0.60 between-group difference in LVESD change). Other secondary efficacy end points related to LV remodeling parameters, LV function, and circulating biomarkers of heart failure, did not differ between groups, with the exception of SF-60 physical component score, which showed greater improvement in the VNS ON group than in the control group (from 36.3 to 41.2 in the VNS ON group vs from 37.7 to 38.4 in the control

group; p=0.02). Subject blinding was found to be imperfect, which may have biased the subjective outcome data reporting.

Treatment of Upper Limb Impairment after Stroke
Dawson et al conducted a pilot randomized trial of VNS in patients with upper-limb dysfunction after ischemic stroke. Twenty-one subjects were randomized to VNS plus rehabilitation or rehabilitation alone. The mean change in the outcome as assessed by a functional assessment score was +8.7 in the VNS group versus +3.0 in the control group (p=0.064). Six patients in the VNS group achieved clinically meaningful response versus four in the control group (p=0.17).

Essential Tremor, Headache, Fibromyalgia, and Tinnitus
VNS has been investigated with small pilot studies or studies evaluating mechanism of disease for several conditions. These conditions include essential tremor, fibromyalgia, headache, and tinnitus. The utility of VNS added to behavioral management of autism and autism spectrum disorders has been posited but there are no randomized controlled trials. None of these studies are sufficient to make conclusions on the effect of VNS on these conditions. Only conditions for which at least 1 randomized trial has been reported will be detailed.

Section Summary: Other Conditions
In other conditions evaluated with randomized controlled trials (heart failure and upper limb impairment), the trials did not show efficacy of VNS for the primary outcome. Other conditions have only been investigated with case series studies, which are not sufficient to make conclusions regarding the effect of VNS.

Transcutaneous VNS
Only conditions for which there is at least 1 RCT will be discussed, as case series are inadequate to determine the effect of the technology.

Episodic Cluster Headaches
Goadsby et al (2017) reported on the results of randomized, double-blind, sham-controlled study (ACT2) for the treatment of cluster headache attacks. Ninety-two patients with cluster headaches were randomized to t-VNS (described in this response as noninvasive VNS) or sham treatment. Patients were further identified as having episodic cluster headaches or chronic cluster headaches and randomized at approximately 1:1 to the t-VNS and sham treatment groups. The primary efficacy end point was the ability to achieve pain-free status within 15 minutes of initiation of treatment without use of rescue treatment. There was no difference between t-VNS-treated and sham-treated patients in the overall cluster headache study population. Subgroup analysis of the chronic cluster headache population showed no differences between t-VNS-treated and sham-treated patients. For the episodic cluster headaches subgroup, t-VNS demonstrated a 48% response rate compared with 6% response rate for sham-treated (p<0.01).

Silberstein et al (2016) reported on the results of a randomized, double-blind, sham-controlled study (ACT1) of cluster headache attacks. One hundred fifty patients with cluster headaches were randomized to t-VNS or sham treatment. Patients were further identified as having episodic cluster headaches or chronic cluster headaches and randomized at approximately 1:1 to the t-VNS and sham treatment groups. The primary end point was response rate defined as the ability to achieve pain-free status within 15 minutes of initiation of treatment without rescue medication use through 60 minutes. There were no differences between t-VNS-treated and sham-treated

patients in the overall cluster headache study population. Subgroup analysis of the chronic cluster headache population showed no differences between t-VNS-treated and sham-treated patients. For the episodic cluster headache subgroup, t-VNS demonstrated a 34.2% response rate compared with 10.6% response rate for sham-treated (p=0.008).

Gaul et al (2016) reported on the results of a randomized open-label study of t-VNS for the treatment of chronic cluster headache. Forty-eight patients with chronic cluster headache were randomized to t-VNS or individualized standard of care. Transcutaneous VNS was to be used twice daily with the option of additional treatment during headaches. At 4 weeks, the t-VNS group had a greater reduction in the number of headaches than the control group, resulting in a mean therapeutic gain of 3.9 fewer headaches per week (p=0.02). Regarding response rate, defined as a 50% or more reduction in headaches, the t-VNS group had a 40% response rate, and the control group had an 8.3% response rate (p<0.001). The study lacked a sham placebo control group, which might have resulted in placebo response in the t-VNS group.

Subsection Summary: Transcutaneous VNS for Episodic Cluster Headaches
Transcutaneous (or noninvasive) VNS has been investigated for episodic cluster headaches in 3 RCTs. One RCT assessing cluster headache showed a reduction in headache frequency but did not have a sham treatment group. Two randomized, double-blind, sham-controlled studies (ACT1 and ACT2) showed efficacy in achieving pain-free status within 15 minutes of treatment with t-VNS. However, the ACT1 and ACT2 studies had small episodic cluster headache subgroups of 85 (38 treated, 45 sham) and 27 (14 treated, 13 sham) respectively. Additional studies with larger cohorts of patients with episodic cluster headache are required given the small sample sizes evaluated in these trials.

Other Neurologic, Psychiatric, or Metabolic Disorders
Epilepsy
Aihua et al (2014) reported results from a series of 60 patients with pharmaco-resistant epilepsy treated with a transcutaneous VNS (t-VNS) device, who were randomly assigned to receive stimulation over the earlobe (control group) or the Ramsay-Hunt zone, which includes the external auditory canal and the conchal cavity and is considered to be the somatic sensory territory of the vagus nerve. Thirty patients were randomized to each group; 4 subjects from the treatment group were excluded from analysis due to loss to follow-up (n=3) or adverse effects (n=1), while 9 subjects from the control group were excluded from analysis due to loss to follow-up (n=2) or increase or lack of decrease in seizures or other reasons (n=7). In the treatment group, compared with baseline, the median monthly seizure frequency was significantly reduced after 6 months (5.5 vs 6.0; p<0.001) and 12 months (4.0 vs 6.0; p<0.001) of t-VNS therapy. At 12-month follow-up, t-VNS group subjects had a significantly lower median monthly seizure frequency compared with the control group (4.0 vs 8.0; p<0.001).

Two small case series were identified that used a transcutaneous stimulator (t-VNS device) for treatment of medication refractory seizures. In a small case series of ten patients with treatment resistant epilepsy, Stefan et al reported that 3 patients withdrew from the study, while 5 of 7 patients reported a reduction in seizure frequency. In another small case series, He et al reported that among 14 pediatric patients with intractable epilepsy who were treated with bilateral t-VNS stimulation, of the 13 patients who completed follow-up, mean reduction in self-reported seizure frequency was 31.8% after 8 weeks, 54.1% from week 9 to 16, and 54.2% from week 17 to 24.

Psychiatric Disorders

Hein et al (2013) reported results of 2 pilot RCTs of a t-VNS device for the treatment of depression, one which included 22 subjects and one with 15 subjects. In the first study, 11 subjects each were randomized to active or sham t-VNS. At 2 weeks follow-up, Beck Depression Inventory (BDI) self-rating scores in the active-stimulation group decreased from 27.0 to 14.0 ($p< 0.000$), while the sham-stimulated patients did not show significant reductions in the BDI (31.0–25.8 points). In the second study, 7 patients were randomized to active t-VNS and 8 patients were randomized to sham t-VNS. In this study, BDI self-rating scores in the active stimulation group decreased from 29.4 to 17.4 ($p<0.05$) after two weeks, while the sham-stimulated patients did not show significant change in BDI (28.6 to 25.4). The authors do not report direct comparisons in BDI change between the sham- and active-stimulation groups.

Hasan et al (2015) reported a randomized trial of t-VNS for the treatment of schizophrenia. Twenty patients were assigned either to t-VNS or to sham for 12 weeks. There was no statistically significant difference in the improvement of schizophrenia status during the observation period.

Shiozawa et al (2014) conducted a systematic review of studies evaluating the evidence related to transcutaneous trigeminal or VNS for psychiatric disorders. In the article text, the authors state that they reviewed studies, 4 of which addressed t-VNS for psychiatric disorders and included a total of 84 subjects. Of those 4, 3 of the studies evaluated physiologic parameters in healthy patients, and one evaluated pharmaco-resistant epilepsy (Stefan et al, previously described). The authors also include a fifth study in one data table, although not in their text or reference list (Hein et al, previously described) Overall, the studies included were limited by small size and poor generalizability.

Transcutaneous VNS for Headache

Gaul et al (2015) reported the results of a randomized open-label study of t-VNS for the treatment of chronic cluster headache. Forty-eight patients with chronic headache were randomized to either t-VNS or to individualized standard of care. t-VNS was to be used twice daily with the option of acutely treating headaches with additional treatments. At four weeks, the t-VNS group had a greater reduction in the number of headaches than the control group resulting in a mean therapeutic gain of 3.9 fewer headaches per week ($p=0.02$). In terms of response rate, defined as a >50% reduction in headaches, the t-VNS had a 40% response rate versus 8.3% in the control group ($p<0.001$). Limitations of the study include the lack of a sham control which may result in placebo response in the t-VNS group.

Other Headaches

Goadsby et al (2014) reported results from an open-label pilot study of t-VNS for the treatment of migraine with or without aura. Eighty migraine attacks were self-treated by 27 patients, of an initial sample of 30 patients (two patients treated no migraine attacks with the device, and one patient treated only an aura). Of 54 moderate or severe attacks treated, 12 subjects (22%) were pain-free at 2-hours post-treatment. Thirteen subjects reported adverse events, which were all considered mild or moderate.

Tso et al (2017) evaluated the records of 15 patients treated with a t-VNS device (gammaCore) for paroxysmal hemicrania (n=6) or hemicrania continua (n=9) as primary treatment or as an adjunct to indomethacin. Symptom-related outcomes included reduction of pain severity and reduced frequency of attacks: for the first, 7 hemicrania continua patients saw improvement with

t-VNS therapy, as did 3 patients with paroxysmal hemicranias. The frequency of attacks was reduced for 2 hemicrania continua patients and 2 paroxysmal hemicranias patients. Some adverse events were reported in all patients, although not detailed.

Impaired Glucose Tolerance

Huang et al (2014) reported results of a pilot RCT of a t-VNS device that provides stimulation to the auricle for the treatment of impaired glucose tolerance. The study included 70 patients with impaired glucose tolerance that were randomized to active or sham t-VNS, along with 30 controls who received no t-VNS treatment. After 12 weeks of treatment, patients who received active t-VNS were reported to have significantly lower two-hour glucose tolerance test results than those who received sham t-VNS (7.5 vs 8 mmol/L; p=0.004).

Section Summary: Transcutaneous VNS for Other Neurologic, Psychiatric, or Metabolic Disorders

Transcutaneous VNS has been investigated with small randomized trials for several conditions. Some evidence for the efficacy of t-VNS for epilepsy comes one small RCT, which reported lower seizure rates for active t-VNS-treated patients compared with sham controls; however, the high dropout rates in this study limit conclusions that may be drawn. One small RCT which compared t-VNS with sham stimulation for the treatment of depression demonstrated some improvements in depression scores with t-VNS; however, the lack of comparisons between groups limits conclusions that may be drawn. A sham-controlled RCT for impaired glucose tolerance showed some effect on glucose tolerance tests. None of the trials show definitive evidence of the efficacy of t-VNS.

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 a significant reduction in seizure frequency for patients with partial-onset seizures. The uncontrolled studies have consistently reported large reductions for 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 and other 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 for 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 or upper-limb impairment due to stroke who receive VNS, the evidence includes RCTs and case series. Relevant outcomes are symptoms, change in disease status, and functional outcomes. The RCTs for both conditions 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 essential tremor, headache, fibromyalgia, autism, or tinnitus who receive VNS, the evidence includes case series. Relevant outcomes are symptoms, change in disease status, and functional outcomes. Case series are insufficient to make 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 3 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 who have epilepsy, depression, schizophrenia, noncluster headache, or 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 outcomes among patients. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

American Academy of Neurology

In 1999, the American Academy of Neurology (AAN) released a consensus statement on the use of VNS in adults that stated, "VNS is indicated for adults and adolescents over 12 years of age with medically intractable partial seizures who are not candidates for potentially curative surgical resections, such as lesionectomies or mesial temporal lobectomies." The AAN released an update to these guidelines in 2013 that stated, "VNS may be considered for seizures in children, for LGS [Lennox-Gastaut-syndrome]-associated seizures, and for improving mood in adults with epilepsy (Level C). VNS may be considered to have improved efficacy over time (Level C)." An update is reported to be in progress at the time of this review update.

American Psychiatric Association

The American Psychiatric Association guidelines on the treatment of major depressive disorder in adults, updated in November 2010, includes the following statement on the use of VNS: "Vagus nerve stimulation (VNS) may be an additional option for individuals who have not responded to at least four adequate trials of antidepressant treatment, including ECT [Electroconvulsive therapy]," with a level of evidence III (May be recommended on the basis of individual circumstances).

European Headache Federation

In 2013, the European Headache Federation issued a consensus statement on neuromodulation treatments for chronic headaches, which makes the following statement about the use of VNS:

"Due to the lack of evidence, VNS should only be employed in chronic headache sufferers using a randomized, placebo controlled trial design."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Key Words:

Vagus nerve stimulation (VNS), partial-onset seizures, depression, headaches, essential tremor, Alzheimer's disease, VNS (t-VNS®), VNS (gammaCore®) Non-implantable Vagus Nerve stimulation, Maestro® System, transcutaneous vagus nerve stimulation, AspireSR®, NeuroCybernetic Prosthesis (NCP®)

Approved by Governing Bodies:

In 1997, the NeuroCybernetic Prosthesis (NCP®) System, a vagus nerve stimulation (VNS) device, was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval (PMA) process. The device was approved for use in conjunction with drugs or surgery "as an adjunctive treatment of adults and adolescents over 12 years of age with medically refractory partial onset seizures." There have been subsequent expanded approvals.

In May 2015, a related VNS therapy, AspireSR® (LivaNova), received supplemental premarketing approval from FDA, although the device was recalled in August 2017. The AspireSR® device detects high heart rates associated with seizures and responds with stimulation. Adjunctive use of the AspireSR® for the treatment of epileptic seizures was indicated for patients over 4 years of age who suffer from partial-onset seizures that do not respond to antiepileptic medication.

On May 30, 2017, the gammaCore-S (electroCore® LLC), a noninvasive vagus nerve stimulation device, was cleared for marketing through the 510(K) process (K171306) for the acute treatment of adults with episodic cluster headaches. When the device is applied to the side of the neck by the patient, a mild electrical stimulation of the vagus nerve is carried to the central nervous system. Each stimulation using gammaCore-S lasts 2 minutes. The patient controls the stimulation strength.

Cerbomed has developed a transcutaneous VNS (t-VNS®) system that uses a combined stimulation unit and ear electrode to stimulate the auricular branch of the vagus nerve, which supplies the skin over the concha of the ear. Patients self-administer electric stimulation for several hours a day; no surgical procedure is required. The device received the CE mark in Europe in 2011, but has not been FDA approved for use in the United States. Electrocore has developed a noninvasive VNS (gammaCore®) that is currently being investigated for headache; the device does not have FDA approval.

Table 1 includes the updates pertinent to this evidence review.

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

Device Name	Manufacture	Date Cleared	MPA/510 (k)	Indications
NeuroCybernetic Prosthesis (NCP®)	Cyberonics	1997	P970003	Indicated or adjunctive treatment of adults and adolescents >12 years of age with medically refractory partial onset seizures
		July 2005	P970003/S50	Expanded indication for adjunctive long-term treatment of chronic or recurrent depression for patients ≥18 years of age experiencing a major depressive episode and have not had an adequate response to ≥4 adequate antidepressant treatments
		June 2017	P970003/S207	Expanded indicated use as adjunctive therapy for seizures in patients ≥4 years of age with partial onset seizures that are refractory to antiepileptic medications.
gammaCore®	ElectroCore	May 2017	K171306	Indicated for acute treatment of pain associated with episodic cluster headache in adults using noninvasive vagus nerve stimulation on the side of the neck.

FDA: Food and Drug Administration

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP contracts: FEP does not consider investigational if FDA approved and will be reviewed for medical necessity. Special benefit consideration may apply. Refer to member's benefit plan.

Current Coding:

CPT Codes:

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 two or more electrode arrays
64553	Percutaneous implantation of neurostimulator electrodes array; cranial nerve
64568	Incision for implantation of cranial nerve (e.g., vagus nerve) Neurostimulator electrode array and pulse generator
64569	Revision or replacement of cranial nerve (e.g., Vagus nerve) neurostimulator electrode array. Including connection to pulse generator
64570	Removal of cranial nerve (e.g., vagus nerve) Neurostimulator electrode array and pulse generator
95974	Electronic analysis of implanted neurostimulator pulse generator system (e.g., rate, pulse amplitude, pulse duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient compliance measurements); complex cranial nerve neurostimulator pulse generator/transmitter, with intraoperative or subsequent programming, with or without nerve interface testing, first hour
95975	; with intraoperative or subsequent programming each additional 30 minutes after the first hour (list separately in addition to code for primary procedure)

HCPCS:

L8680	Implantable neurostimulator electrode (with any number of contact points), 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
L8684	Radiofrequency transmitter (external) for use with implantable sacral root neurostimulator receiver for bowel and bladder management, replacement
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
L8689	External recharging system for battery (internal) for use with implantable neurostimulator, replacement only

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Policy History:

Medical Policy Group, March 2006 **(3)**
Medical Policy Administration Committee, March 2006
Available for comment March 14-April 27, 2006
Medical Policy Group, September 2006 **(1)**
Medical Policy Group, October 2007 **(1)**
Medical Policy Group, March 2009 **(4)**
Medical Policy Group, March 2010 **(3)**
Medical Policy Administration Committee, April 2010
Available for comment April 8-May 23, 2010
Medical Policy Group, December 2010 – code updates
Medical Policy Group, March 2011 **(3):** Description, Policy, Key Points, References updated

Medical Policy Group, December 2011 **(3):** 2012 Code Updates – verbiage change to codes 64553. 95974 & 95975
Medical Policy Group, March 2012 **(3):** 2012 Update – Key Points & References
Medical Policy Panel, March 2013
Medical Policy Group, April 2013 **(3):** 2013 Updates to Key Points; no change in policy statement
Medical Policy Panel March 2014
Medical Policy Group March 2014 **(4):** Updated Description, updated policy section by adding that VNS for tinnitus and traumatic brain injury also added non-implantable vagus nerve stimulation devices are investigational. Reworked Key Points Updated Key Words and References.
Available for comment May 2 through July 5, 2014
Medical Policy Group, May 2014 **(5):** 2014 Coding Update: Deleted code L8680 effective July 1, 2014.
Medical Policy Group, June 2014 **(5):** Quarterly 2014 Coding Update: Code L8680 did not delete; Removed delete date and moved code up under active codes.
Medical Policy Panel, March 2015
Medical Policy Group, March 2015 **(6):** Updates to Description, Key Points, Key Words, Codes and References; no change to policy statement.
Medical Policy Panel, February 2016
Medical Policy Group, February 2016 **(6):** Updates to Description, Key Points, Approved by Governing Bodies and References; no changes to policy statement.
Medical Policy Panel, October 2017
Medical Policy Group, October 2017 (**6**): Updates to Description, Key Points, Governing Bodies, Practice Guidelines and References. Added "upper-limb impairment due to stroke"to policy statement.
Medical Policy Panel March 2018
Medical Policy Group, April 2018 **(6):** Updates to Description, Key Points, Key Words, Governing Bodies and References.
