APPENDIX to Vagus Nerve Stimulation Policy

Prior Authorization Requirements

This service (or procedure) is considered **medically necessary** in certain instances and **investigational** in others (refer to policy for details).

For instances when the indication is **medically necessary**, clinical evidence is required to determine **medical necessity**.

For instances when the indication is **investigational**, you may submit additional information to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

Evidence Basis for the Policy

Rationale

While the mechanisms for the therapeutic effects of vagus nerve stimulation (VNS) are not fully understood, the basic premise of VNS in the treatment of various conditions is that vagus visceral afferents have a diffuse central nervous system projection, and activation of these pathways has a widespread effect on neuronal excitability. Surgery for implantation of a vagus nerve stimulator involves wrapping two spiral electrodes around the left vagus nerve within the carotid sheath. The electrodes are connected to an infraclavicular generator pack. The programmable stimulator may be adjusted in advance to stimulate at regular times or on demand by patients or family by placing a magnet against the subclavicular implant site. In 1997, the United States Food and Drug Administration (FDA) approved a VNS device called the NeuroCybernetic Prosthesis (NCP®) (Cyberonics Inc, Houston, TX) system 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.”

Since 1997, it has been reported that recipients of a vagus nerve stimulator have experienced improvements in mood. Therefore, there has been research interest in VNS as a treatment for refractory depression. On July 15, 2005, Cyberonics Inc., received PMA supplement approval

by the FDA for the VNS Therapy™ System "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."

Seizures

In 1998 the Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment offered the following conclusions regarding treatment of seizures:

- Published evidence from two large, well-designed multicenter trials involving over 300 patients demonstrated the use of VNS as an adjunct to optimal use of antiepileptic drugs in the treatment of medically refractory patients with at least six partial-onset seizures per month reduced seizure frequency by approximately 25% after three months of treatment. In patients who achieved an initial reduction in seizure frequency, the beneficial treatment effect appeared to be maintained and may have increased with time
- Adverse effects were mild and consisted primarily of hoarseness or voice change during "on" periods of stimulation
- There was limited information about the use of VNS in patients with other types of seizure disorders

In addition to adults, there has been interest in expanding the use of VNS to younger patients. Several studies have reported results that support the safety of the device in children with refractory seizures (Amar et al., 2001). Sixty pediatric patients were treated as part of the double-blind clinical trials conducted to support the FDA application (Murphy, 1999). At 18 months, the median reduction in seizure frequency was 50%, similar to the results achieved in adults. Patwardhan and colleagues (2000) reported that among 38 patients aged 11 months to 16 years, 29% had a greater than 90% reduction in seizure frequency, while 39% had 50% to 90% reduction. The major limitations of VNS are the facts that stimulation generally does not completely eliminate seizures, and it is not possible to predict which patients will optimally respond. Therefore, some authors suggest that VNS may be most appropriately used in patients with refractory seizures who are not candidates for surgery (i.e., bilateral or unresectable foci or no identified structural abnormality).

Since approval of VNS for partial seizures, Tecoma and Iragui (2006) observed that a number of case series including patients with generalized seizures have been published. These series report seizure reduction rates similar to or greater than those reported in partial epilepsy, and note that "this body of evidence suggests that VNS has broad antiepileptic efficacy." The authors suggest these results may be particularly important since resective epilepsy surgery is generally not feasible in these patients. More recent reports are consistent with their observations. In a French study of 50 consecutive refractory adolescents and adults who were not eligible for surgery and of whom 11 had generalized epilepsy, 58% were classified as responders at three years' follow-up (Montavont et al., 2007). Generalized epilepsy was predictive of a better outcome than partial epilepsy seizures. The authors concluded VNS was a useful palliative procedure in severe generalized epilepsies with atonic or tonic-clonic seizures resulting in frequent falls and entailed less risk than callosotomy. In a multicenter study of 28 children with refractory seizures, You et al., (2007) reported that 15 children (53.6%) showed a greater than 50% reduction in seizure

frequency and nine (32%) had a greater than 75% reduction. In addition, there were no significant differences when groups were compared by seizure type or etiology. Tecoma and Iragui (2006) cited a multicenter retrospective analysis of 50 children with Lennox-Gestaut syndrome (LGS) treated with VNS. Median seizure reduction at six months was 88% for tonic seizures and 81% for atypical absence. You et al., (2008) compared VNS and total corpus callosotomy for LGS. Of the 14 patients who underwent a corpus callosotomy, nine (64%) had a greater than 50% reduction in seizure frequency and five (36%) had a greater than 75% reduction. Of the 10 patients who underwent VNS implantation, seven (70%) had a greater than 50% reduction in seizure frequency and two (20%) had a greater than 75% reduction. Seizure reduction of 61% was also reported in a case series of 12 patients with drug-resistant idiopathic generalized epilepsy (Kostov et al., 2007). Based on these data one can conclude that VNS is an effective treatment for refractory seizures other than partial epilepsy.

Refractory 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 (Elger et al., 2000). However, studies examining VNS for the treatment of depression are limited, and all published and unpublished data concerning clinical outcomes of VNS therapy for the indication of treatment-resistant depression come from company-sponsored clinical studies.

Technology Evaluation Center Assessments written in 2005 and updated in 2006 concluded 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 Inc.), and have since been reported on in various publications (Rush et al., 2005; George et al., 2005). Analyses from these study groups were presented for FDA review and consisted of a case series of 60 patients receiving VNS (Study D-01), a short-term (i.e., three-month) randomized sham-controlled clinical trial of 221 patients (Study D-02), and an observational study comparing 205 patients on VNS therapy compared to 124 patients receiving ongoing treatment for depression (Study D-04) (FDA, 2005). Patients who responded to sham treatment in the short-term randomized, controlled trial (approximately 10%) were excluded from the long-term observational study.

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 were some losses to follow-up (Rush et al., 2000; Sackeim et al., 2001; Marangell et al., 2002). 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 to a sham control (implanted but inactivated VNS) showed a non-statistically significant result for the principal outcome (Rush et al., 2005; FDA, 2005). Fifteen percent of VNS subjects responded, versus 10% of control subjects ($p = 0.31$). The Inventory of Depressive Symptomatology - Self-Report was considered a secondary outcome, and showed a difference in outcome that was statistically significant in favor of VNS (17.4% versus 7.5%, $p = 0.04$).

The observational study comparing patients participating in the randomized clinical trial and a separately recruited control group (D-04 versus D-02) evaluated VNS therapy out to one year

and showed a statistically significant difference in the rate of change of depression score (George et al., 2005; FDA, 2005). 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 (FDA, 2005). Given these concerns about the quality of the observational data, these results did not provide strong evidence for the effectiveness of VNS therapy.

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.

Data from the case series and clinical trials have been reanalyzed in subsequent publications to show what proportions of patients who respond at one time are still responders at a subsequent time point. Among those who achieved a response at three or 12 months, 60% to 75% of such patients were judged to remain a responder after one year. However, this information by itself does not provide evidence of the efficacy of VNS beyond that provided by the original comparative trials. Overall, the available scientific evidence does not demonstrate efficacy of VNS for treatment-resistant depression.

A systematic review of the literature for VNS of treatment-resistant depression identified the randomized trial described above in the 18 studies that met the study's inclusion criteria (Daban et al., 2008). Vagus nerve stimulation was found to be associated with a reduction in depressive symptoms in the open studies. A preliminary report from an ongoing European multicenter open-label efficacy and safety study of VNS for treatment-resistant depression described one responder (of 11) at three months, two responders at six months, and six responders (55%) at one year; three patients (27%) were considered to be in remission (Corcoran et al., 2006). However, results from the only double-blind trial were considered to be inconclusive (Rush et al., 2005; FDA, 2005). Daban et al., (2008) concluded further clinical trials are needed to confirm efficacy of VNS in treatment-resistant depression.

Fitzgerald and Daskalakis (2008) stated “given the invasive nature of vagus nerve stimulation and potential side effects, further research is urgently required.” A guideline statement from the Canadian Network for Mood and Anxiety Treatments included a review of the literature on VNS for depression in 2009 and concluded that there is a lack of substantial evidence for short-term and long-term efficacy in acute severe depression, and the appropriate place of VNS remains to be determined (Kennedy et al., 2009). Given the limitations of prior literature as described in the 2006 TEC Assessment, combined with the lack of substantial literature, the scientific evidence is considered to be insufficient to permit conclusions concerning the effect of VNS on major depression.

Essential Tremor

Handforth and colleagues (2003) studied VNS in nine patients with essential tremor. Four weeks after implantation of the VNS device, tremor assessment using a masked videotape of patients was performed. Raters found no improvement in upper extremity tremors. Therefore, the authors of the study concluded that VNS is not likely to have any clinically meaningful effect in essential tremor treatment.

Headaches

Drawing on the analgesic effects noted with VNS in the treatment of depression, Mauskop (2005) evaluated VNS in five patients with severe, refractory chronic cluster and migraine headaches. The author reported excellent results in one patient who was able to return to work and significant improvement in two patients. Cecchini et al., (2009) evaluated VNS in four patients suffering from daily headache and chronic migraine. However, these studies are too small to draw conclusions on the effects of VNS for the treatment of headache, and further study is needed.

Obesity

Unintended weight loss has been observed in participants in studies of VNS, prompting interest in use of the technology to prevent or treat obesity. Bodenlos et al., (2007) investigated whether VNS might affect food cravings in patients with chronic, treatment-resistant depression. They recruited 33 participants and divided them into three groups; 11 subjects receiving VNS for depression, 11 patients with depression but not receiving VNS, and 11 healthy controls. Most participants (42%) had a Body Mass Index (BMI) in the normal range. Participants viewed food images on a computer in random order and then a second time in the same order. They were asked after each viewing how much they would like to eat each food if it were available and how well they would be able to resist tasting each one. Vagus nerve stimulation devices were turned on for one viewing and off for the other. The depression VNS group had greater differences in food cravings between viewings in the sweet food category than the other two groups. No significant differences between groups were found for foods in proteins and vegetables/fruits categories. A significant proportion of the variability in VNS-related changes in cravings for sweet foods was attributed to clinical VNS device settings, depression scores, and BMI. A number of limitations in the study prevent drawing conclusions about the impact of VNS on eating behavior including small study size, selection and lack of randomization, heterogeneity of groups with respect to depression, BMI, and age. Comorbidities including anxiety and medical conditions and drugs that might influence food intake and cravings were not considered. Large, well-designed and executed controlled studies are needed to evaluate the impact of VNS on eating behavior and obesity.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of

service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

Type	Number	Description
CPT	43651	Laparoscopy, surgical; transection of vagus nerves, truncal
	43652	Laparoscopy, surgical; transection of vagus nerves, selective or highly selective
	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 electrodes; cranial nerve
	64573	Incision for implantation of neurostimulator electrodes; cranial nerve
	64585	Revision or removal of peripheral neurostimulator electrodes
	95970	Electronic analysis of implanted neurostimulator pulse generator system (eg, rate, pulse amplitude and duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient compliance measurements); simple or complex brain, spinal cord, or peripheral (ie, cranial nerve, peripheral nerve, autonomic nerve, neuromuscular) neurostimulator pulse generator/transmitter, without reprogramming

Type	Number	Description
	95971	Electronic analysis of implanted neurostimulator pulse generator system (eg, rate, pulse amplitude and duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient compliance measurements); simple spinal cord, or peripheral (ie, peripheral nerve, autonomic nerve, neuromuscular) neurostimulator pulse generator/transmitter, with intraoperative or subsequent programming
	95974	Electronic analysis of implanted neurostimulator pulse generator system (eg, rate, pulse amplitude and 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	Electronic analysis of implanted neurostimulator pulse generator system (eg, rate, pulse amplitude and 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, each additional 30 minutes after first hour (List separately in addition to code for primary procedure)
	L8695	
HCPC	C1767	Generator, neurostimulator (implantable), nonrechargeable
	C1778	Lead, neurostimulator (implantable)
	C1787	Patient programmer, neurostimulator
	C1816	Receiver and/or transmitter, neurostimulator (implantable)
	C1820	Generator, neurostimulator (implantable), with rechargeable battery and charging system
	C1897	Lead, neurostimulator test kit (implantable)
	L8680	Implantable neurostimulator electrode (with any number of contact points), each

Type	Number	Description
	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, nonrechargeable, includes extension
	L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
	L8688	Implantable neurostimulator pulse generator, dual array, nonrechargeable, includes extension
	L8689	External recharging system for battery (internal) for use with implantable neurostimulator, replacement only
	L8695	External recharging system for battery (external) for use with implantable neurostimulator, replacement only
ICD9 Procedure	02.93	Implantation or replacement of intracranial neurostimulator lead(s)
	04.92	Implantation or replacement of peripheral neurostimulator lead(s)
	86.94	Insertion or replacement of single array neurostimulator pulse generator, not specified as rechargeable
	86.95	Insertion or replacement of dual array neurostimulator pulse generator, not specified as rechargeable
	86.96	Insertion or replacement of other neurostimulator pulse generator
	86.97	Insertion or replacement of single array rechargeable neurostimulator pulse generator
	86.98	Insertion or replacement of dual array rechargeable neurostimulator pulse generator
ICD9 Diagnosis	All Diagnoses	

Type	Number	Description
Place of Service	All Places of Service	

Tables

N/A

Definitions

N/A

Index / Cross Reference of Related BSC Medical Policies

The following Medical Policies share diagnoses and/or are equivalent BSC Medical Policies:

- Deep Brain Stimulation
- Electrical Stimulation for Pain
- Gastric Electrical Stimulation
- Neuromuscular and Functional Electrical Stimulation
- Sacral Nerve Neuromodulation/Stimulation
- Spinal Cord Stimulation
- Urinary Incontinence Outpatient Treatment
- Occipital Nerve Stimulation

Key / Related Searchable Words

N/A

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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
12/1/2005	Medical Policy Committee accepted CTAF as consent BCBSA TEC review Vol.20 No.8. New Policy	Medical Policy Committee
3/1/2006	MPC accepted CTAF February technology review: VNS. Policy updated; Policy statement unchanged.	Medical Policy Committee
8/1/2006	MPC accepted BCBSA TEC Vol.21, No. 7; Policy unchanged regarding treatment resistant depression.	Medical Policy Committee
12/1/2006	Policy Updated - adopted BCBSA MPP	Medical Policy Committee
1/7/2011	Policy title change from Vagus Nerve Stimulation Therapy (VNS). Policy revision with position change	Medical Policy Committee

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.

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