Transcutaneous (Non-implantable) Vagus Nerve Stimulation (e.g. gammaCore-S®)

Policy MP-036

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Disclaimer:
1. Policies are subject to change without notice.
2. Policies outline coverage determinations for U of U Health Plans Commercial, and Healthy U (Medicaid) plans. Refer to the “Policy” section for more information.

Description:
The vagus nerve, a large nerve that runs down the neck, into the chest and down into the gut which connects the lower part of the brain to the heart, lungs and intestines. Vagus nerve stimulation (VNS) uses short bursts of electrical energy directed into the brain via the vagus nerve. Stimulating this nerve has been studied as a way to treat several different types of conditions such as: seizures that don't respond to medication, depression, headaches, epilepsy, tinnitus and pain.

Historically, stimulation of the vagus nerve is performed using a pulsed electrical stimulator implanted within the carotid artery sheath. There are also devices available that are implanted at different areas of the vagus nerve to treat conditions like obesity. More recently, non-implantable VNS devices (also referred to as n-VNS or transcutaneous VNS [t-VNS]) have been developed to treat migraine and cluster headaches. An example of this type of device is gammaCore-S® (ElectroCore™, LLC) which is a noninvasive handheld prescription device intended to deliver transcutaneous vagus nerve stimulation for the acute treatment of pain associated with episodic cluster headaches and migraines in adults.

GammaCore-S initially received 510(k) clearance for treatment of both acute migraine and episodic cluster headache with expansion of its FDA clearance to include cluster headache prevention. Therapy using the gammaCore device is self-administered, and for cluster headache prevention consists of two daily treatments, each of which is comprised of three consecutive two-minute stimulations. To do so, patients apply a conductive gel to the side of their neck, and then hold the gammaCore to the same area while it dispenses a mild electrical stimulation through the skin and to the vagus nerve. Acute migraine therapy involves 6 stimulations encompassing 3 two minutes stimulations the first two separated by 20 minutes and the second and third by 2 hours. For acute cluster headaches, the patient uses three 2 minute
stimulations separated by 3 minutes. For use in cluster headache prevention, the three 2 minute stimulations are administered twice a day.

The gammaCore-S device is not available for purchase. It is preloaded with a specific number of stimulations and requires a monthly “prescription”. If prescription not ‘refilled’ the device will automatically lock out and become nonfunctional.

**Policy Statement and Criteria**

1. **Commercial Plans**

   U of U Health Plans does NOT cover non-implantable (transcutaneous) vagus nerve stimulation devices (e.g. gammaCore-S®) as they are considered investigational for all indications.

2. **Medicaid Plans**

   Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website at [http://health.utah.gov/medicaid/manuals/directory.php](http://health.utah.gov/medicaid/manuals/directory.php) or the [Utah Medicaid code Look-Up tool](http://health.utah.gov/medicaid/manuals/directory.php).

**Clinical Rationale**

No systematic reviews have been published on noninvasive vagal nerve stimulation. A Hayes Search and Summary published on April 16, 2019 concluded current evidence demonstrates conflicting findings regarding the use of gammaCore-S® for the treatment of headaches (migraine and cluster).

In support of the Hayes findings, Nesbitt et al. (2015), in an open-label observational study of 19 patients (11 chronic, 8 episodic) described the initial experience with a noninvasive vagus nerve stimulator (nVNS), designed to provide portable, non-invasive, transcutaneous stimulation of the vagus nerve, both acutely and preventively, as a treatment for cluster headaches (CH). The authors concluded their findings suggested that nVNS may be practical and effective as an acute and preventive treatment in chronic cluster headaches. Yet, they acknowledge the size and design of their study did not allow for definitive conclusions related to efficacy and safety and, further evaluation of this treatment using randomized sham-controlled trials are needed.

Silberstein et al. evaluated non-invasive vagus nerve stimulation (nVNS) as an acute cluster headache (CH) treatment in a 2016 randomized, double-blind, sham-controlled (ACT1) study. They studied one hundred fifty patients aged 18 Years to 75 Years, randomized to receive either sham control or nVNS treatment for less than or equal to one month; completers could enter a 3-month nVNS open-label phase. The primary end point was response rate, defined as the proportion of subjects who achieved pain relief (pain intensity of 0 or 1) at 15 minutes after treatment initiation for the first CH attack without rescue medication use through 60 minutes. The authors concluded that nVNS provided significant, clinically meaningful, rapid, and sustained benefits for episodic cluster headache but not for chronic cluster headache, which affected results in the total population. However, in one of the largest
randomized sham-controlled studies for acute CH treatment, the response rate was not significantly different (vs sham) for the total population.

In another 2016 open-label study of 56 patients Grazzi et al. assessed noninvasive vagus nerve stimulation (nVNS) for the prophylactic treatment of menstrual migraine/menstrually related migraine (MM/MRM). There were no safety/tolerability concerns. Even though the findings suggested that nVNS may be an effective treatment to reduce the number of MM/MRM and analgesic use without safety or tolerability concerns in patients, the authors concluded that more RCTs are needed to validate these findings.

Furthermore, in studies focusing on acute migraine pain, Tassorelli et al. in 2018 assessed 248 patients using noninvasive vagus nerve stimulation (nVNS) for the treatment of migraines. The purpose of this multicenter, double-blind, sham-controlled trial was to determine the safety, efficacy, and tolerability of nVNS. Patients were randomized to receive nVNS or sham within 20 minutes of the onset of pain of episodic migraines with or without aura, then repeat treatment if the pain had not improved within 15 minutes. nVNS (n = 120) was superior to sham (n = 123) for pain freedom at 30 minutes (12.7% vs 4.2%) and 60 minutes (21.0% vs 10.0%) but not at 120 minutes (30.4% vs 19.7%) after the first treated attack. A post hoc repeated-measures test provided further insight into the therapeutic benefit of nVNS through 30, 60, and 120 minutes. nVNS demonstrated benefits across other endpoints including pain relief at 120 minutes and was safe and well tolerated. They concluded, the findings of this trial suggested effective pain relief, tolerability, and practicality of nVNS for the treatment of acute episodic migraines in as early as 30 minutes and up to 60 minutes after an attack. However, the role of nVNS in migraine therapy needs further exploration in long term follow-up with ongoing large-scale, randomized, sham-controlled trials.

In a 2018 double-blind cohort (ACT2) study, Goadsby et al. compared randomly assigned patients, with cluster headaches (CH) (episodic [eCH] or chronic [cCH]), for acute treatment with either non-invasive vagus nerve stimulation (nVNS) or a sham device during a 2 week 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 full analysis set comprised 48 nVNS-treated (14 eCH, 34 cCH) and 44 sham-treated (13 eCH, 31 cCH) subjects. 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%). No significant differences between nVNS (5%) and sham (13%) were seen in the cCH subgroup. After combining both eCH and cCH patients, the study found nVNS was no different to sham. The authors concluded that for the treatment of CH with nVNS was superior to sham therapy in eCH but not in cCH attacks. However, this study had limitations, such as its short duration, which did not allow for evaluation of continued/change in response with long-term nVNS therapy, the imbalance between CH subtypes, and the eCH subgroup comprised <30% of subjects by letting them alter their CH treatment regimens, which confounded the study results. It was felt these limitations made it impossible to discern if the changes in outcomes were attributable to nVNS therapy or other changes in treatment.

Lastly, a 2019 UpToDate review on “Cluster headache: Treatment and prognosis” concluded that “When chronic cluster headache is unresponsive to medical treatments, various surgical interventions and neurostimulation techniques are potential treatment options, though none are clearly established as effective. In such cases, it is particularly important to exclude potential causes of secondary cluster headache. Neurostimulation techniques, including sphenopalatine ganglion stimulation and vagus nerve stimulation, appear promising but remain investigational. Destructive surgical procedures are unproven and should be viewed with great caution.”
Applicable Coding

CPT Codes
No applicable codes

HCPCS Codes
E0770 Functional electrical stimulator, transcutaneous stimulation of nerve and/or muscle groups, any type, complete system, not otherwise specified
E1399 Durable medical equipment, miscellaneous

References:

1. Food and Drug Administration. 510(k) premarket notification: gammaCore-S (K171306). 2017;
2. Food and Drug Administration. 510(k) premarket notification: gammaCore-S (K173442). 2018;
5. Hayes, Inc. (2019) Search and Summary “gammaCore Transcutaneous Vagus Nerve Stimulator (electroCore*, Inc.) for the Treatment of Headaches”. Available at:
   https://www.hayesinc.com/subscribers/displaySubscriberArticle.do?articleUid=hss.gammacore4685
   Available at: https://www.uptodate.com/contents/cluster-headache-treatment-and-prognosis?search=cluster%20headache%20treatment&source=search_result&selectedTitle=1~67&usage_type=default&display_rank=1

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