Policy Replaced with LCD L34555
Effective February 26, 2018

BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Vagus Nerve Blocking Therapy for Treatment of Obesity

Policy #:	598	Latest Review Date:	February 2017
Category:	Surgery	Policy Grade:	B

Background:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*

    - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
    - *Furnished in a setting appropriate to the patient's medical needs and condition;*
    - *Ordered and furnished by qualified personnel;*
    - *One that meets, but does not exceed, the patient's medical need; and*
    - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

Vagus nerve blocking therapy for obesity consists of an implantable device that delivers electrical stimulation to branches of the vagus nerve on the anterior abdominal wall. The intent is to cause intermittent blocking of signals to the intra-abdominal vagus nerve to disrupt hunger sensations and induce feelings of satiety.

Obesity is a common condition in the United States. A large nationally representative survey conducted in 2009 to 2010 found that 36% of American adults age 20 and older were obese, defined as body mass index (BMI) of 30 kg/m^2 or more. Fifteen percent of adults had a BMI of 35 kg/m^2 or more and 6% had a BMI of 40 kg/m^2 or more. Among children age 2 to 19 years, 17% were obese, defined in the population as being at or above the 95% percentile in sex-specific BMI for corresponding age (based on the U.S. Centers for Disease Control and Prevention age growth charts).

Obesity is a major cause of premature death and is linked to serious illnesses including heart disease, Type 2 diabetes, sleep apnea, osteoarthritis, and certain types of cancer. In a 2013 systematic review, being obese has been associated with higher all-cause mortality and death from cardiovascular disease. In that same year, the American Medical Association officially recognized obesity itself as a disease.

Lifestyle interventions, specifically changes to diet and exercise, are the first-line treatment of obesity. These interventions can be enhanced by participation in a structured weight loss program and/or by psychological interventions such as cognitive behavioral therapy. There are also prescription weight loss medications available, most notably orlistat (which blocks digestion and absorption of fat) and lorcaserin (which decreases appetite and promotes satiety). Weight loss medications have limited evidence of efficacy and there are adverse effects (e.g., oily stool, nausea, dizziness) associated with their use.

Weight loss (bariatric) surgery is a potential option for obese patients who have failed conservative treatments. Common procedures include gastric bypass surgery (open or laparoscopic approaches), sleeve gastrectomy, and laparoscopic adjustable gastric banding. Certain types of bariatric surgery have been found to improve outcomes in selected patients who choose that treatment. (**Refer to medical policy *#053 Surgical Management of Morbid Obesity* for additional information**.)

Vagus nerve blocking therapy is another potential treatment option for obese patients. The vagus nerve consists of two long cranial nerves that extend from the brain stem to the viscera. The term *vagus* is Latin for wandering and the vagus nerve winds through the abdomen and has branches that come in contact with the heart, lung, stomach and other body parts. The vagus nerve plays a major role in autonomic and sympathetic nervous system functioning, including regulation of heartbeat and breathing. It is also involved in regulation of the digestive system, although its exact role in controlling appetite and feelings of satiety is unknown. Vagus nerve blocking therapy involves intermittent blocking of signals to the intra-abdominal vagus nerve, with the intent disrupting hunger sensations and inducing feelings of satiety.

In January 2015, FDA approved a medical device specifically designed to provide vagal nerve blocking therapy for weight regulation in obese patients. This device, the Maestro® Rechargeable System, includes a neuro-blocking pulse generator that is implanted subcutaneously on the thoracic sidewall, and flexible leads approximately 47 cm in length that are placed on the abdominal anterior and posterior vagal nerve trunks. External components include a mobile charger, a transmit coil, a programmable microprocessor and customized software. The system delivers high-frequency pulses of electrical current to vagal nerve trunks; therapy parameters and the treatment schedule can be customized by a clinician. Like other surgical interventions, there is the potential for adverse effects. In addition, there may be other unintended consequences of disrupting signals to a particular portion of the vagus nerve.

(Stimulation of the vagus nerve via a device implanted within the carotid artery sheath has also been evaluated as a treatment for obesity. **Refer to medical policy *#260 Vagus Nerve Stimulation* for additional information**. Vagus nerve stimulation is FDA-approved to treat epilepsy and depression, not for obesity treatment.)

Policy:

Effective for dates of service on or after February 26, 2018 refer to LCD L34555

Effective for dates of service prior to February 26, 2018:

Blue Advantage will treat **intra-abdominal vagus nerve blocking therapy** in all situations, including but not limited to the treatment of obesity as a **non-covered benefit** and as **investigational.**

Blue Advantage 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 Advantage administers benefits based on the members' contract and 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:

The most recent literature review was updated through December 20, 2016.

Assessment of efficacy for therapeutic intervention involves a determination of whether the intervention improves health outcomes compared with available alternatives.

In the case of interventions to treat obesity, a double-blind RCT is optimal because these interventions require changes to patient behavior (diet and exercise) which are subject to the placebo effect. Health outcomes such as mortality, cardiovascular events, and rates of Type 2 diabetes would be optimal, but are difficult to use as study end points due to the need for a large sample size and long follow-up period. Cardiovascular risk factors, such as changes in blood

pressure, glucose, and lipid levels, are good intermediate measures because they have been linked with these health outcomes, and would require smaller sample sizes. Weight loss outcomes, reported as absolute change in weight or body mass index (BMI), or as percent excess weight loss (EWL) or percent BMI are acceptable intermediate outcome measures and are commonly used in obesity studies. Weight loss has been linked to improvements in cardiovascular risk factors. While there is no generally accepted threshold of percent EWL that is considered clinically significant, bariatric surgery trials generally define clinical success as loss of at least 50% EWL. The amount of weight loss is expected to be lower for other, less dramatic weight loss interventions.

Sham controls are useful for establishing the efficacy of an intervention beyond the placebo effect and for controlling for other nonspecific effects of interventions including disease natural history and regression to the mean. Because there are so many existing treatment options for weight loss, if sham-controlled weight loss intervention studies are positive, trials using an active comparator, such as medication or other types of surgery, are desirable.

Vagus Nerve Blocking Therapy for Obesity

The published literature on vagus nerve blockade for obesity consists of two RCTs, both of which were industry-sponsored, multicenter, double-blind and sham controlled. Although both trials included a sham treatment group, protocols differed. In the 2012 EMPOWER trial, all participants had devices implanted and leads placed. However, external controllers were programmed differently such that if the controllers were worn for 10 hours per day, the total charge delivered was 3.9 Coulombs (C) to patients in the treatment group and a negligible amount, 0.0014 C, to the sham group. In the 2014 ReCharge trial, all participants had devices implanted but no leads were placed in the sham group.

Study characteristics and results of the two trials are summarized in Table 1.

Table 1: RCTs Evaluating Vagus Nerve Blocking for Treatment of Morbid Obesity: Characteristics

Variables	EMPOWER (Sarr et al, 2012)	ReCharge (Ikramuddin et al, 2014)
No. patients randomized	294	239
Age range, y	18-65	18-65
Key eligibility criteria	• BMI 40-45 kg/m^2 or 35-39.9 kg/m^2 with ≥1 obesity-related comorbid conditions • Failed to respond to supervised diet/exercise program (timeframe not specified)	• BMI 40-45 kg/m^2 or 35-40 kg/m^2 with ≥1 obesity-related comorbid conditions • Failed to respond to supervised diet/exercise program within past 5 y
Intervention	Maestro device plus 15 weight management counseling sessions (n=192)	Maestro device plus 17 weight management counseling sessions (n=162)
Comparator	Sham with Maestro device plus 15 weight management counseling sessions (n=102)	Sham with Maestro device plus 17 weight management counseling sessions (n=77)
Outcome measures		
Primary	Difference in mean percent EWL at 12 mo (superiority margin: 10%)	Difference in mean percent EWL at 12 mo (superiority margin: 10%) ≥55% of patients in active treatment group achieved 20% EWL; ≥45% achieved 25% EWL
Secondary	Difference in percent of patients who achieved ≥25% EWL	

Safety	Rate of SAEs	SAEs <15% in active treatment group
Follow-up, mo	12	12

BMI: body mass index; EWL: excess weight loss (calculated as difference between pre- and posttreatment weights divided by difference between pretreatment weight and ideal body weight. BMI of 25 kg/m^2 was considered ideal); RCT: randomized controlled trial; SAE: serious adverse event.

Table 2: RCTs Evaluating Vagus Nerve Blocking for Treatment of Morbid Obesity: Results

	EMPOWER (Sarr et al, 2012)			ReCharge (Ikramuddin et al, 2014)		
Outcomes	**Active**	**Sham**	**Difference**	**Active**	**Sham**	**Difference**
	Mean Percent EWL			**Mean Percent EWL**		
Primary efficacy	17%	16%	1% (p=NS)	24.4%	15.9%	8.5% (p=0.71[a])
	≥25% EWL					
Secondary efficacy	22%	25%	NS			
	No. of SAEs			**Percentage of SAEs**		
Safety	23	12		3.7%[b]	NR	

EWL: excess weight loss (calculated as difference between pre- and posttreatment weights divided by difference between pretreatment weight and ideal body weight. BMI of 25 kg/m^2 was considered ideal); NR: not reported; RCT: randomized controlled trial; SAE: serious adverse event.

[a] For a >10% difference.

[b] Met objective of <15%.

The primary efficacy outcomes were not met in either of the two RCTs. The difference in mean percent EWL was the sole primary efficacy outcome in the EMPOWER study and a coprimary outcome in the ReCharge study. This outcome was evaluated in both trials using a superiority margin of 10%, i.e., the efficacy objective would only be met if there was more than a 10% difference between groups in EWL. U.S. Food and Drug Administration (FDA) documents state that the unattained 10% margin was considered to indicate a clinically meaningful difference in weight loss between active and sham treatment groups.

For the ReCharge trial, however, in addition to the primary efficacy analysis, the authors also conducted a post hoc analysis that evaluated the difference in EWL between groups using a two-sided *t* test with no superiority margin. In this post hoc analysis, the difference between groups, (8.5% EWL; 95% CI, 3.1% to 13.9%) was statistically significant. (The difference between groups in percent EWL in the EMPOWER study was 1%).

The outcome used in these studies was percent EWL, and modest changes in this outcome may translate to a relatively small amount of weight loss relative to total weight for patients with morbid obesity. Mean initial body weight in the ReCharge trial was 113 kilograms (249 pounds) in the active treatment group and 116 kilograms (255 pounds) in the sham group. Mean excess body weight was 44 kilograms (97 pounds) in the treatment group and 45 kilograms (99 pounds) in the sham group. Thus, a difference of 10% EWL, used in the primary analyses, represents only about a 5 kilograms (10 pounds) difference in absolute weight loss and a 4% difference in absolute body weight.

The ReCharge study had a second primary outcome which was met if at least 55% patients in the active treatment group achieved at least 20% EWL and at least 45% achieved at least 25% EWL. This outcome was not achieved; the data showed that 52% of patients in the active treatment group achieved at least 20% EWL and 38% achieved at least 25% EWL. In the EMPOWER

study, groups did not differ significantly on the secondary outcome measure (percent of patients achieving at least 25% EWL).

In a post hoc subgroup analysis of the EMPOWER trial, longer duration of device use per day was related to a larger percentage of EWL. However, this improvement occurred in the sham group, as well as the active treatment group. For example, percent EWL among patients who used the device fewer than six hours was 5% in the active treatment group and 6% in the sham group whereas EWL among patients who used the device at least 12 h/d was 30% and 22%, respectively. This finding suggests a substantial placebo effect associated with device use.

Both trials met their primary safety end points which related to SAEs. However, there were nonserious adverse events that occurred frequently. Rates of key adverse events (all severity levels) in the ReCharge trial are shown in Table 2. Most of these were of mild or moderate severity. The authors of the EMPOWER trial did not report individual adverse events.

Table 3: Most Common Adverse Events, ReCharge Trial

Adverse Event	Treatment Group No. (%) Patients	Sham Group No. (%) Patients
Pain, neuroregulator site	61 (38%)	32 (42%)
Dyspepsia	38 (23%)	3 (4%)
Pain, other	37 (23%)	0
Pain, abdominal	20 (12%)	2 (3%)
Nausea	11 (7%)	0
Dysphagia	13 (8%)	0
Belching	13 (8%)	0

Additional information on ReCharge trial design and findings was reported in FDA documents. The study was designed to evaluate primary end points at 12 months and then to continue following patients until five years post-implant. Patients were blinded until 12 months and unblinding began once all patients had completed the 12-month follow-up. After the 12-month follow-up, sham patients had the option of crossing over into the active treatment group. At 18 months, follow-up data (n=159) were reported for 117 patients (72%) initially assigned to the active treatment group and 42 (55%) assigned to the sham treatment group. The number of patients in the sham group who crossed over to active treatment and the timing of unblinding were not reported. At 18 months, the mean percent EWL was 25.3% in the active treatment group and 11.7% in the sham group. There was a mean between-group difference of 13.5% (95% confidence interval, 5.7% to 21.3%). In this analysis, the treatment group sustained the weight loss they achieved at 12 months, and the control group gained weight. Nearly half of the patients initially randomized to the sham group were not included in the 18-month analysis, which limits ability to draw conclusions about these data. In addition, the 18-month analysis could be biased by unblinding, which occurred after all patients completed the 12-month follow-up. In the 12-month sham intervention phase of the trial, patients in both groups experienced decreased hunger, increased cognitive restraint and decreased food intake. It is likely that unblinding could have an impact on these factors. FDA documents also report longer term safety data. Analyses of data up to 48 months from the EMPOWER trial and 18 month data from the ReCharge trial did not identify any deaths or unanticipated SAEs. There were 13 surgical explants though 12 months (five in active treatment group, eight in sham group) and an additional 16 explants

between 12 and 18 months (14 in active treatment group, seven in sham group). Reasons for explant included patient decision, pain and need for magnetic resonance imaging.

Eighteen-month follow-up data from the ReCharge trial were published by Shikora et al in 2015. The authors reported on a larger proportion of the patient population than discussed in FDA documents. In addition to the 159 (67%) of 239 randomized patients who completed the 18-month follow-up, the 2015 analysis included 30 patients who missed the 18-month analysis but had a visit at 16 or 17 months. The additional patients included 11 from the active treatment group and 19 from the sham group, for a total sample size of 188 patients (79% of those originally randomized). At 18 months, the mean percent EWL was 23.5% (95% CI: 20.8% to 26.3%) in the active treatment group and 10.2% (95% CI: 6.0% to 14.4%) in the sham group. The mean between-group difference in percent EWL was 13.4% (95% CI, 8.4% to 18.4%). The authors also evaluated the potential impact of blinding and found no statistically significant impact of blinding on their findings; findings were also similar when the analysis was restricted to patients who remained blinded at 18 months. The percentages of EWL at 18 months in this 2015 analysis of ReCharge trial data are similar to those previously published in FDA documents although sample size is larger, reducing potential bias from missing data. However, this was a post hoc analysis which incorporates 16- and 17-month data in addition to 18-month data and results are considered preliminary or hypothesis-generating.

Twenty-four-month outcomes from the ReCharge trial were published by Apovian et al in 2016. The investigators noted that the sham arm was no longer a valid comparator at 24 months due to crossover and dropout; moreover, patients were unblinded at 12 months. There was no prespecified statistical analysis plan for analyses that occurred after the 12-month primary outcome assessment, including the analysis in this 2016 article. A total of 103 (43%) patients of 239 randomized patients completed the 24-month follow-up. Their mean EWL was 21% (95% CI, 16% to 26%) and the mean total weight loss was 8% (95% CI, 6% to 10%). No serious treatment-related adverse events were reported in the 18- to 24-month time period. The analysis lacked a blinded comparison group, and, like the 18-month data, was post hoc.

Section Summary: Vagus Nerve Blocking Therapy for Obesity

Two sham-controlled RCTs have been published. The primary efficacy outcome, at least a 10% difference between groups, was not met for either trial. In the first trial (EMPOWER), the observed difference in excess weight loss (EWL) between groups at 12 months was 1%. In the more recent trial (ReCharge), the observed difference in EWL between groups at 12 months was 8.5%, a post hoc analysis found this difference statistically significant, but the magnitude of change may not be viewed as clinically significant according to the investigators'original trial design decisions. Additional analyses of data from ReCharge found a difference in EWL at 18 months of approximately 13% in 79% of randomized patients and a mean EWL of 21% at 24 months in 43% of randomized patients. However, analyses beyond 12 months are post hoc analyses considered preliminary and need to be replicated in other appropriately designed randomized controlled trials (RCTs). In addition, the 18- and 24-month data have potential biases, including missing data and the impact of unblinding. Moreover, the 18 month analysis combined data from different follow-up visits and the 24-month analysis lacked a control group. The 2 RCTs found that vagal nerve blocking was reasonably safe in terms of serious adverse

events during follow-up, although a substantial number of mild and moderate adverse events were reported.

Summary of Evidence
The evidence for vagus nerve blocking therapy in individuals who have obesity includes 2 sham-controlled randomized controlled trials (RCTs). Relevant outcomes are change in disease status, morbid events, quality of life and treatment-related morbidity. The primary efficacy outcome, at least a 10% difference between groups at 12 months, was not met for either trial. In the first trial (EMPOWER), the observed difference in EWL between groups at 12 months was 1%. In the more recent trial (ReCharge), the observed difference in EWL between groups at 12 months was 8.5%. In a post hoc analysis, the 8.5% EWL was statistically significant, but this magnitude of change may not be clinically significant according to the investigators' original trial design decisions. Post hoc analyses of longer-term data have been published and are subject to various biases including missing data and unblinding at 12 months. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements
American Society for Metabolic and Bariatric Surgery
A position statement published in 2016 by the American Society for Metabolic and Bariatric Surgery includes the following conclusions and recommendations on vagus nerve blocking therapy for treatment of obesity:

> "1. Reversible vagal nerve blockade has been shown to result in statistically significant EWL at 1 year compared with a control group in one of 2 prospective randomized trials.
>
> 2. Reversible vagal nerve blockage has been shown to have a reasonable safety profile with a low incidence of severe adverse events and a low revisional rate in the short term. More studies are needed to determine long-term reoperation and explantation rates.
>
> 3. The prospective collection of VBLOC outcomes as part of the national center of excellence databases is encouraged to establish the long-term efficacy of this new technology."

U.S. Preventive Services Task Force Recommendations
The U.S. Preventive Services Task Force (USPSTF) published recommendations for screening and management of obesity in adults in 2012. USPSTF recommends screening all adults for obesity and referring those with a BMI of 30 kg/m^2 or higher to intensive, multicomponent behavioral interventions. Vagus nerve blocking therapy and other surgical interventions were not addressed in the recommendations or literature review. As of December 30, 2016, the recommendations are in the process of being updated; no release date for the updated recommendations was provided.

Key Words:
Vagus nerve blocking therapy, Maestro, obesity, neurostimulator

Approved by Governing Bodies:

FDA approved the Maestro Rechargeable System, (Enteromedics, St. Paul, MN) through the premarket approval process on January 14, 2015. The device is indicated for use in adults age 18 years and older who have a BMI of 40 to 45 kg/m^2 or a BMI of 35 to 39.9 kg/m^2 with one or more obesity-related conditions such as high blood pressure or high cholesterol and have failed at least one supervised weight management program within the past five years. Implantable components are incompatible with magnetic resonance imaging (MRI). Additional contraindications to use of the device include conditions such as cirrhosis of the liver, portal hypertension and clinically significant hiatal hernia, and the presence of a previously implanted medical device.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:

CPT Codes:

0312T	Vagus nerve blocking therapy (morbid obesity); laparoscopic implantation of neurostimulator electrode array, anterior and posterior vagal trunks adjacent to esophagogastric junction (EGJ), with implantation of pulse generator, includes programming
0313T	laparoscopic revision or replacement of vagal trunk neurostimulator electrode array, including connection to existing pulse generator
0314T	laparoscopic removal of vagal trunk neurostimulator electrode array and pulse generator
0315T	removal of pulse generator
0316T	replacement of pulse generator
0317T	neurostimulator pulse generator electronic analysis, includes reprogramming when performed

References:

1. Apovian CM, Shah SN, Wolfe BM, et al. Two-year outcomes of vagal nerve blocking (vBloc) for the treatment of obesity in the ReCharge trial. Obes Surg. Aug 10 2016.
2. Flegal KM, Kit BK, Orpana H, et al. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA. Jan 2 2013; 309(1):71-82.
3. Ikramuddin S, Blackstone RP, Brancatisano A, et al. Effect of reversible intermittent intra-abdominal vagal nerve blockade on morbid obesity: the ReCharge randomized clinical trial. JAMA. Sep 3 2014; 312(9):915-922.

4. Ogden CL, Carroll MD, Kit BK, et al. Prevalence of childhood and adult obesity in the United States, 2011-2012. JAMA. Feb 26 2014; 311(8):806-814.
5. Papasavas P, El Chaar M, Kothari SN, et al. American Society for Metabolic and Bariatric Surgery position statement on vagal blocking therapy for obesity. Surg Obes Relat Dis. Mar-Apr 2016; 12(3):460-461.
6. Sarr MG, Billington CJ, Brancatisano R, et al. The EMPOWER study: randomized, prospective, double-blind, multicenter trial of vagal blockade to induce weight loss in morbid obesity. Obes Surg. Nov 2012; 22(11):1771-1782.
7. Shikora SA, Wolfe BM, Apovian CM, et al. Sustained weight loss with vagal nerve blockade but not with sham: 18-month results of the ReCharge trial. J Obes. 2015; 2015:365604.
8. Summary of Safety and Effectiveness Data (SSED): Maestro Rechargeable System. www.accessdata.fda.gov/scripts/cdrh/cfdocs/cftopic/pma/pma.cfm?num=p130019.
9. U.S. Preventive Services Task Force. Obesity in Adults: Screening and Management. 2012; www.uspreventiveservicestaskforce.org/Page/Topic/recommendation-summary/obesity-in-adults-screening-and-management. Accessed December 30, 2016.

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