



Louisiana

Baroreflex Stimulation Devices

Policy # 00315

Original Effective Date: 09/14/2011

Current Effective Date: 12/20/2017

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Radiofrequency Ablation of the Renal Sympathetic Nerves as a Treatment for Resistant Hypertension is addressed separately in medical policy 00465.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of baroreflex stimulation implanted devices in all situations including but not limited to treatment of hypertension and heart failure to be **investigational**.*

Background/Overview

Baroreceptors are pressure sensors contained within the walls of the carotid arteries. They are part of the autonomic nervous system that regulates basic physiologic functions such as heart rate and blood pressure (BP). When these receptors are stretched, as occurs with increases in BP, the baroreflex is activated. Activation of the baroreflex signals the brain, which responds by inhibiting sympathetic nervous system output and increasing parasympathetic nervous system output. The effect of this activation is to reduce heart rate and BP, thereby helping to maintain homeostasis of the circulatory system.

The use of baroreflex stimulation devices (also known as baroreflex activation therapy) is a potential alternative treatment for resistant hypertension and heart failure. Both hypertension and heart failure are relatively common conditions, and are initially treated with medications and lifestyle changes. A substantial portion of patients are unresponsive to conventional therapy and treating these patients is often challenging, expensive, and can lead to adverse effects. As a result, there is a large unmet need for additional treatments.

One device is approved for sale in Europe for hypertension and heart failure patients. This second-generation system consists of a unilateral electrode and lead attached to the carotid sinus and a pulse generator implanted subcutaneously in the chest wall. Programming is performed using radiofrequency telemetry with an external laptop computer and software. The first-generation system had bilateral leads attached to each carotid sinus and a larger pulse generator.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

In 2014, the Barostim neo^{®‡} Legacy System (CVRx, Minneapolis, MN) received a humanitarian device exemption from the FDA for use in patients with treatment-resistant hypertension who received Rheos^{®‡} Carotid Sinus leads as part of the Rheos pivotal trial and were considered responders in that trial.

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In November 2015, CVRx received expedited access pathway (EAP) designation from FDA for Barostim Therapy^{®†} to treat heart failure. EAP designation does not guarantee that an application to FDA will ultimately be approved.

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

The literature review focused on identifying controlled trials, particularly randomized controlled trials (RCTs). RCTs are important in determining the efficacy of baroreflex stimulation devices due to the natural variability in BP, the heterogeneity of the patient populations with high BP, and the presence of many potential outcome confounders. Case series have limited utility for determining efficacy. They can be useful for demonstrating potential of the technique, to determine the rate of short- and long-term adverse effects of treatment, and to evaluate the durability of treatment response.

HYPERTENSION

One published RCT, the Rheos pivotal trial, evaluated the efficacy of baroreflex stimulation for lowering BP. The trial, published in 2011, was double-blind and included patients with treatment-resistant hypertension defined as at least 1 systolic blood pressure (SBP) measurement of 160 mm Hg or more with diastolic blood pressure (DBP) of 80 mm Hg or more after at least 1 month of maximally tolerated medical therapy. A total of 322 patients had the Rheos system implanted, and 265 patients underwent randomization. Participants were randomized in a 2:1 fashion to the device turned on or off for a 6-month period. After 6 months, all patients had the device turned on. The primary efficacy end points were the percentage of patients achieving at least a 10 mm Hg decrease in SBP at the 6-month time point (acute efficacy) and the percentage of patients who maintained their BP response over the 6- to 12-month time period (sustained efficacy). Primary safety outcomes were defined thresholds for procedural safety (at least 82% of patients free from procedural adverse events at 30 days), therapy safety (not more than 15% excess treatment-related adverse events in the experimental group), and device safety (at least 72% of patients free from procedural or therapy-related adverse events at 12 months).

At 6 months, 54% of patients in the stimulation group had an SBP decrease of 10 mm Hg or more compared with 46% of patients in the control group ($p=0.97$), indicating that the primary acute efficacy outcome was not met. The primary sustained efficacy outcome was met, with 88% of patients who responded at 6 months maintaining a response at 12 months. A secondary efficacy outcome (the percentage of patients reaching target SBP) showed a significant between-group difference. A total of 42% of the patients in the active treatment group reached a target SBP of 140 mm Hg compared with 24% in the control group ($p=0.005$). For the primary procedural safety end point, the predefined threshold of 82% was not met. At 30 days, the percentage of patients free of procedural adverse events was 74.8%. The primary safety end point for therapy safety was met, with a similar percentage of patients free of treatment-related adverse effects at 6 months (91.7% vs 89.3%, $p<0.001$ for noninferiority). The primary safety end point for

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device safety was also met, with 87.2% of patients free of device-related adverse events at 12 months, exceeding the predefined threshold of 72%.

Patients who actively participated in the Rheos pivotal trial were followed after 12 months, and additional data were reported in a 2012 extension trial by Bakris et al. A total of 276 (86%) of the 322 implanted patients consented to long-term open-label follow-up. After a mean follow-up of 28 months, 244 (88%) of 276 were considered to be clinically significant responders. Response was defined as sustained achievement of the target SBP (≤ 140 mm Hg, or ≤ 130 mm Hg for patients with diabetes or renal disease), or a reduction in SBP of 20 mm Hg or more from device activation. Alternatively, patients could qualify as responders if their implanted device was deactivated and if they had an increase in SBP of at least 20 mm Hg in the 30 days after device deactivation. In the extension study, there was no comparison group.

Several uncontrolled observational studies have also been published. The largest of these, the DEBut-HT trial, was a multicenter, single-arm feasibility study of the Rheos baroreflex activation therapy system published in 2010. This study enrolled 45 patients with treatment-resistant hypertension defined as a BP greater than 160/90 mm Hg, despite treatment with at least 3 antihypertensive drugs, including a diuretic. The planned follow-up was 3 months, with a smaller number of patients followed up to 2 years. In 37 patients completing the 3-month protocol, office SBP was reduced by 21 mm Hg (SD=4; $p < 0.001$) and DBP was reduced by 12 mm Hg (SD=2; $p < 0.001$). There was a smaller reduction in 24-hour ambulatory BP (n=26), with a decrease of 6 mm Hg (SD=3) in SBP ($p = 0.10$) and a decrease of 4 mm Hg (SD=2) in DBP ($p = 0.04$). In 26 patients followed for 1 year, the declines in office BP were 30 mm Hg (SD=6) for systolic ($p < 0.001$) and 20 mm Hg (SD=4) for diastolic ($p < 0.001$). For ambulatory BP (n=15), the 1-year declines were 13 mm Hg (SD=3) for systolic ($p < 0.001$) and 8 mm Hg (SD=2) for diastolic ($p = 0.001$). A total of 7 (16.7%) of 42 patients experienced adverse events. Three patients required device removal due to infection, 1 patient experienced perioperative stroke, 1 patient experienced tongue paresis due to hypoglossal nerve injury, 1 patient had postoperative pulmonary edema, and 1 patient required reintervention for device explantation.

A single-arm study using the second-generation Neo device to treat uncontrolled hypertension was published in 2016 by Wallbach et al. The study reported on 44 patients with resistant hypertension, defined as an office BP at least 140 mm Hg or 130 mm Hg for patients with chronic kidney disease and proteinuria, despite treatment with at least 3 antihypertensive medications including a diuretic. Mean baseline office BP was 171/91 mm Hg. After 6 months of baroreflex activation therapy, mean office BP decreased to 151 ± 26 mm Hg over 82 ± 17 mm Hg (pre to post, $p < 0.001$). At 6 months, the mean number of BP medications used per patient decreased from 6.5 ± 1.5 at baseline to 6.0 ± 1.8 ($p < 0.03$). One procedure-related major adverse event occurred, a contralateral stroke. Ten (23%) of the 44 patients experienced a minor procedure-related complication. The most common minor adverse events were disturbance of wound healing (n=5 [11%]) and postoperative hematoma (n=4 [9%]). One patient had revision surgery but explantation was not needed.

Section Summary: Hypertension

One RCT has evaluated baroreflex stimulation devices. This trial, which compared the first-generation Rheos device plus medical management to medical management alone, met some but not all of its efficacy

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end points. Baroreflex stimulation–treated patients were no more likely to achieve at least a 10 mm Hg decrease in SBP at 6 months, but were more likely to reach the target SBP of 140 mm Hg or less at 6 months. The trial met 2 of its 3 predefined safety end points (therapy safety and device safety but not procedural safety). In addition, several uncontrolled studies have reported short-term reductions in BP, together with adverse events such as infection, hypoglossal nerve injury, and wound complications. Additional RCTs—particularly those using the second-generation device—are needed to draw conclusions about safety and efficacy.

HEART FAILURE

One RCT has evaluated baroreflex stimulation for the treatment of heart failure. This trial, published by Abraham et al (2015), was nonblinded and included 146 patients with New York Heart Association (NYHA) class III heart failure and an ejection fraction of 35% or less despite guideline-directed medical therapy. Patients were randomized to baroreflex stimulation (Barostim Neo system) plus medical therapy (n=76) or to continued medical therapy alone (n=70) for 6 months. The primary safety outcome was the proportion of patients free from major adverse neurologic and cardiovascular events (MANCE). The trialists specified 3 primary efficacy end points: changes in NYHA functional class, quality of life (QOL) score, and 6-minute walk distance (6MWD).

The overall MANCE-free rate was 97.2%; rates were not reported separately for the baroreflex stimulation and control groups. In terms of the efficacy outcomes, there was significant improvement in the baroreflex stimulation group versus the control group on each of the 3 outcomes. Significantly more patients in the treatment group (55%) had improvement of at least 1 level in NYHA functional class than in the control group (24%; $p<0.002$). Mean QOL scores, as assessed by the Minnesota Living with Heart Failure Questionnaire, improved significantly more in the treatment group (-17.4 points) than in the control group (2.1 points; $p<0.001$). Similarly, mean 6MWD improved significantly more in the treatment group (59.6 meters) than in the control group (1.5 meters; $p=0.004$).

Twelve-month results for 101 (69%) of 146 patients were reported by Weaver et al (2016). No additional system- or procedure-related MANCE occurred between 6 and 12 months. Moreover, outcomes for NYHA functional class improvement, QOL score, and 6MWD were all significantly better in the treatment group than in the control group at 12 months. This analysis had a substantial amount of missing data. Overall, the limitations of this RCT included a relatively small sample size for a common condition, relatively short intervention period, and lack of blinding; some of the positive findings on the subjective patient-reported outcomes may be due at least in part to a placebo effect. Additional RCTs with larger sample sizes and longer follow-up are needed to confirm these positive findings.

Another RCT evaluating baroreflex stimulation for heart failure is underway (see Table 1). The Baroreflex Activation Therapy for Heart Failure Clinical Trial (BeAT-HR), which as of April 2017 is recruiting patients, will have a much larger sample size (estimated enrollment, 800) than the Abraham et al trial and will assess cardiovascular mortality and heart failure morbidity as well as safety, functional, and QOL outcomes. This trial is being conducted as part of the data plan for FDA approval under an EAP designation.

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Section Summary: Heart Failure

One RCT has compared baroreflex stimulation plus medical therapy to medical therapy alone in patients with heart failure. This RCT found a low rate of major adverse events and met all 3 efficacy end points (improvements in NYHA functional class, QOL, and 6MWD). However, the study had methodologic limitations, including lack of blinding, a relatively small sample size for a common condition, and relatively short intervention period. A second RCT, with a much larger sample size that will assess mortality rates, is underway.

SUMMARY OF EVIDENCE

For individuals who have treatment-resistant hypertension who receive baroreflex stimulation therapy, the evidence includes 1 RCT and several small uncontrolled studies. Relevant outcomes are overall survival, functional outcomes, QOL, hospitalizations, medication use, and treatment-resistant morbidity. The uncontrolled studies have reported short-term reductions in BP in patients treated with baroreflex stimulation devices, as well as adverse events such as infection, hypoglossal nerve injury, and wound complications. The RCT comparing baroreflex stimulation with continued medical management met some of the efficacy end points but not others and 2 of its 3 predefined safety end points. Additional RCTs are needed to permit conclusions on the efficacy and safety. In addition, baroreflex stimulation currently has a very narrow FDA approval (i.e., for patients who previously participated in a pivotal trial) and broader approval or clearance is needed for wider application. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have treatment-resistant heart failure who receive baroreflex stimulation therapy, the evidence includes 1 RCT. Relevant outcomes are overall survival, functional outcomes, QOL, hospitalizations, medication use, and treatment-resistant morbidity. The RCT met all 3 efficacy end points but had methodologic limitations, including lack of blinding, a relatively small sample size for a common condition and a relatively short intervention period. A second, larger, RCT designed to assess the effects of the intervention on mortality, safety, functional, and QOL outcomes, is underway. In addition, the 1 baroreflex stimulation device with humanitarian device exemption approval currently has only a very narrow FDA approval (i.e., for patients who previously participated in a pivotal trial) and broader approval or clearance is needed for wider application. The evidence is insufficient to determine the effect of the technology on health outcomes.

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Policy History

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09/01/2011	Medical Policy Committee review
09/14/2011	Medical Policy Implementation Committee approval. New policy.
09/06/2012	Medical Policy Committee review
09/19/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/19/2013	Coding revised
09/05/2013	Medical Policy Committee review
09/18/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/06/2014	Medical Policy Committee review
11/21/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015	Medical Policy Committee review
11/16/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Added situations of hypertension and heart failure to existing INV policy statement.
12/01/2016	Medical Policy Committee review
12/21/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017	Medical Policy Committee review
12/20/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date:	12/2018

Coding

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Code Type	Code
CPT	0266T, 0267T, 0268T, 0269T, 0270T, 0271T, 0272T, 0273T
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
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