BlueCross BlueShield of Louisiana

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Baroreflex Stimulation Devices

Policy # 00315
Original Effective Date: 09/14/2011
Current Effective Date: 09/18/2013

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.

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 to be **investigational.***

Background/Overview

Baroreflex stimulation devices are used to provide baroreflex activation therapy®‡† (BAT®)‡† which refers to electrical stimulation of the baroreceptors in the carotid arteries by means of an implanted device. Activation of the baroreflex causes inhibition of the sympathetic nervous system, resulting in a variety of physiologic changes including slowed heart rate and decreased blood pressure. Use of baroreflex stimulation devices has therefore been proposed as a treatment for hypertension that is resistant to standard medications, as well as related conditions which are associated with high sympathetic tone.

The 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 blood pressure, the baroreflex is activated. Activation of the baroreflex sends signals to 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 blood pressure, thereby helping to maintain homeostasis of the circulatory system.

Resistant hypertension.Hypertension is a widely prevalent condition, which is estimated to affect approximately 30% of the population in the United States. It accounts for a high burden of morbidity related to strokes, ischemic heart disease, kidney disease, and peripheral arterial disease. Resistant hypertension is defined as elevated blood pressure despite treatment with at least 3 antihypertensive agents at optimal doses. Resistant hypertension is a relatively common condition, given the large number of individuals with hypertension. In large clinical trials of hypertension treatment, up to 20-30% of participants meet the definition for resistant hypertension, and in tertiary care hypertension clinics, the prevalence has been estimated to be 11-18%. Resistant hypertension is associated with a higher risk for adverse outcomes such as stroke, myocardial infarction (MI), heart failure, and kidney failure.

There are a number of factors that may contribute to uncontrolled hypertension, and these should be considered and addressed in all patients with hypertension prior to labeling a patient as resistant. These include non-adherence to medications, excessive salt intake, inadequate doses of medications, excess alcohol intake, volume overload, drug-induced hypertension, and other forms of secondary hypertension. Also, sometimes it is necessary to address comorbid conditions, i.e., obstructive sleep apnea, in order to adequately control BP.

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Treatment for resistant hypertension is mainly intensified drug therapy, sometimes with the use of non-traditional antihypertensive medications such as spironolactone and/or minoxidil. However, control of resistant hypertension with additional medications is often challenging and can lead to high costs and frequent adverse effects of treatment. As a result, there is a large unmet need for additional treatments that can control resistant hypertension. Non-pharmacologic interventions for resistant hypertension include modulation of the baroreflex receptor, and/or radiofrequency denervation of the renal nerves.

Baroreflex activation devices. Devices that activate the baroreflex are implantable devices that provide electrical stimulation to the baroreceptors. The Rheos®‡† Hypertension system has been developed for this purpose. It consists of 3 components:

1) Implantable pulse generator, which controls and delivers the electrical energy. It is implanted subcutaneously beneath the collarbone by minimally invasive surgery.
2) Carotid sinus leads, which are thin wires with electrical contacts that are placed in contact with the carotid baroreceptors. They conduct the electrical energy from the pulse generator to the baroreceptors.
3) The programmer system, which is an external device that allows clinicians to turn the system on and off and regulate the electrical signal delivered to the baroreceptors.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
There are no baroreflex activation therapy devices that have received U.S. FDA approval.

Centers for Medicare and Medicaid Services (CMS)
None

Rationale/Source

Literature review focused on identification of controlled trials, particularly randomized controlled trials (RCTs). Randomized controlled trials are crucial in determining efficacy of this treatment due to the natural variability in BP, the heterogeneity of the patient populations with increased BP, and the presence of many potential confounders of outcome. Case series have limited utility for determining efficacy. They can be useful for demonstrating potential of the technique, for determining the rate of short- and long-term adverse effects of treatment, and to evaluate the durability of the treatment response.

The published evidence that was identified consists of several small, single-arm feasibility trials and preliminary results from a RCT presented at a scientific meeting. All of the available trials enrolled patients with resistant hypertension.

Clinical question: *Is baroreflex stimulation effective in lowering blood pressure in patients with resistant hypertension?*

Results of a randomized controlled trial, the Rheos† pivotal trial, were reported in 2011. This trial is a double-blind, randomized trial of 265 patients with resistant hypertension. All patients had the Rheos system implanted, and patients were randomized to the device turned on or off in a 2:1 fashion for a 6-month

period. After 6 months, all patients had the device turned on. The primary efficacy endpoints were the percent of patients achieving at least 10 mm Hg decrease in systolic blood pressure (SBP) at the 6- month time point (acute efficacy) and the percent of patients who maintained their BP response over the 6-12 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 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 to 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 percent of patients reaching target SBP, did show a significant 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, the predefined threshold of 82% was not met. At 30 days, the percent of patients free of procedural adverse events was 74.8%. The primary safety endpoint of therapy safety was met, with a similar percent of patients free of treatment-related side effects at 6 months (91.7% vs. 89.3%, $p < 0.001$ for non-inferiority). The primary safety endpoint of 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%.

The DEBut-HT trial, was a multicenter, single-arm feasibility trial of the Rheos BAT system published in 2010. This trial enrolled 45 subjects, from 9 clinical centers in Europe, with resistant hypertension defined as a blood pressure of greater than 160/90 despite treatment with at least 3 antihypertensive drugs, including a diuretic. The planned follow-up period was 3 months, with a smaller number of patients followed for up to 2 years. In 37 patients completing the 3-month protocol, systolic office BP was reduced by 21+4 mm Hg ($p < 0.0001$) and diastolic BP was reduced by 12+2 mm Hg ($p < 0.001$). There was a smaller reduction in 24-hour ambulatory BP ($n = 26$), with a decrease of 6+3 mm Hg in systolic BP ($p = 0.10$) and a decrease of 4+2 mm Hg in diastolic BP ($p = 0.04$). In 26 patients followed for 1 year, the declines in office BP were 30+6 mm Hg systolic ($p < 0.001$) and 20+4 mm Hg diastolic ($p < 0.001$). For ambulatory BP ($n = 15$), the 1-year declines were 13+3 mm Hg systolic ($p < 0.001$) and 8+2 mm Hg diastolic ($p = 0.001$). A total of 7/42 patients (16.7%) 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 movement of the device.

Several other smaller feasibility trials have been reported. For example, Heusser et al. treated 12 individuals who had treatment-resistant hypertension with the Rheos system. The mean baseline BP was 193/94 mm Hg, and at 1 month following implantation, there were decreases in systolic BP of 32+10 mm Hg ($p = 0.01$). The decrease in diastolic BP was not reported. Tordoir et al. treated 21 patients with the Rheos system and reported acute decreases in BP at 1 to 3 days post-implantation. The mean baseline BP was 189.6/110.7 mm Hg, with a reduction post-treatment of 28+22 mm Hg systolic, and 16+11 diastolic.

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Adverse events reported included infection necessitating removal (n = 1), hypoglossal nerve injury (n = 1), wound complications (n = 3); intraoperative bradycardia (n = 2); and pain (n = 5).

In 2012, Hoppe et al. published the results of a single-arm series of patients treated with a "second-generation" device, called the Barostim *neo*™‡ † (CVRx™‡, Minneapolis, MN)†. This system consists of a unilateral electrode and lead that is attached to the carotid sinus and a pulse generator that is implanted subcutaneously in the chest wall. Programming is performed via radiofrequency telemetry using an external laptop computer and software. Thirty patients from 7 centers in Europe and Canada with resistant hypertension were treated with this device and followed for a 6-month period. The mean baseline BP was 172/100. At 6 months, there was a decrease in BP of 26.0 mmHg systolic and 12.4 mmHg diastolic. The percent of patients achieving adequate BP control, defined as a systolic BP or 140 or less, was 43%. There were 3 perioperative complications, 1 device pocket hematoma, 1 wound complication, and 1 intermittent pain at the insertion site. One additional patient had longer term intermittent pain at the device site.

Summary
The use of baroreflex stimulation devices is a potential alternative treatment for resistant hypertension. Specific devices for baroreflex stimulation have been developed, but none have received FDA-approval for any indication. Small, uncontrolled feasibility studies report short-term reductions in BP, together with adverse events such as infection, hypoglossal nerve injury, and wound complications. Results of an RCT comparing baroreflex stimulation with continued medical therapy were published in 2011. This trial met some efficacy endpoints but not others. There was not a significant increase in the percent of patients achieving at least a 10 mm Hg decrease in SBP at 6 months, but more patients in the treatment group did reach a target systolic BP of 140 mm Hg or less at 6 months. The trial met 2 of 3 predefined safety endpoints. Further research from RCTs is needed to determine whether baroreflex activation therapy is effective in reducing BP for patients with resistant hypertension. Because of limited evidence showing benefit, and the lack of FDA approval, this treatment is considered investigational.

Ongoing Clinical Trials
A search of online site ClinicalTrials.Gov revealed the following ongoing randomized, controlled trials of baroreflex stimulation therapy:

NCT01471834. The Barostim Neo System in the Treatment of Resistant Hypertension trial is an RCT comparing baroreflex stimulation to conventional therapy in patients with resistant hypertension. The primary outcome measure is change in systolic BP at 6 months' follow-up. Enrollment is planned for 160 participants. The status of this trial is listed as "not yet open for participant recruitment", and an estimated completion date is not given.

The Rheos HOPE4HF Trial (NCT00957073): This randomized trial of 540 patients is intended to assess the safety and efficacy of the Rheos system in patients with heart failure and preserved ejection fraction. Primary outcomes include a composite of cardiovascular death/heart failure events and procedure-related complications; secondary outcomes include cardiovascular events, changes in left ventricular mass, and changes in quality of life. The current status is listed as currently recruiting participants. The estimated completion date is December, 2014.

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NCT01471860. The Barostim Neo System in the Treatment of Heart Failure trial is an RCT comparing baroreflex stimulation with medical management in patients with symptomatic heart failure despite a stable pharmacologic regimen. The primary outcome measure is change in left ventricular (LV) ejection fraction at 6 months' follow-up. The planned enrollment is for 150 participants, with estimated completion date of February 2013. The current status of this trial is given as "not yet open for participant recruitment".

NCT00718939. The Rheos Diastolic Heart Failure trial is an RCT that compares baroreflex stimulation with usual care in patients with clinical heart failure and an ejection fraction of 45% or greater. The primary outcome measure is change in LV mass at 6 months' follow-up. Enrollment is planned for 60 patients, with an estimated completion date of January 2011. Although this estimated completion date has passed, there is no record of publications from this trial and current status is listed as "unknown because the information has not been verified recently."

References

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8. Hoppe UC, Brandt MC, Wachter R et al. Minimally invasive system for baroreflex activation therapy chronically lowers blood pressure with pacemaker-like safety profile: results from the Barostim neo trial. J Am Soc Hypertens 2012; 6(4):270-6..

Coding

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0266T, 0267T, 0268T, 0269T, 0270T, 0271T, 0272T, 0273T
HCPCS	No code
ICD-9 Diagnosis	All diagnoses
ICD-9 Procedure	39.81 thru 39.88

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.
Next Scheduled Review Date: 09/2014

*****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);
    2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. reference to federal regulations.

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