Molina Clinical Policy
Implantable Neurostimulator (remedē System) for Central Sleep Apnea: Policy No. 340

Last Approval: 10/13/2021
Next Review Due By: October 2022

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members.[1] References included were accurate at the time of policy approval and publication.

OVERVIEW

Central Sleep Apnea (CSA) refers to a heterogeneous group of sleep-related breathing disorders characterized by diminished or absent central respiratory drive. Central apneas occur through two pathophysiologic patterns, either post-hyperventilation or post-hypoventilation. CSA may be primary (e.g., idiopathic) or secondary (i.e., associated with an underlying medical cause). The International Classification of Sleep Disorders (3rd ed.) (ICSD-3) describes several different entities grouped under CSA with varying signs, symptoms, and clinical and polysomnographic features. Those that affect adults include primary central sleep apnea, Cheyne-Stokes breathing-central sleep apnea (CSB-CSA) pattern, high-altitude periodic breathing, central sleep apnea due to medical conditions other than Cheyne-Stokes, and central sleep apnea due to drugs or substances.[5,17]

The prevalence of CSA is not high in the general population however, prevalence is higher among older adults, males, and those with certain comorbid conditions, such as heart failure or stroke. Diagnosis of central sleep apnea generally requires a full-night polysomnographic (PSG) evaluation, which includes both sleep measures and respiration measures. An overnight, in-laboratory PSG is recommended in patients with daytime sleepiness plus risk factors for CSA (e.g., heart failure, stroke, use of a long-acting opioid) or more than one symptom or sign of CSA (e.g., daytime sleepiness, insomnia, morning headaches, nocturnal angina, witnessed pauses in breathing during sleep). PSG also differentiates CSA from the more common obstructive sleep apnea (OSA), which can have a very similar presentation; however, are differentiated depending on the presence (OSA) or absence (CSA) of the respiratory effort. On PSG recording, CSA syndrome diagnosis requires the presence of five or more central apneas per hour of sleep and symptoms of insomnia, excessive daytime sleepiness or frequent arousals, and/or hypersomnolence during the day. A common measure of the severity of CSA is the apnea-hypopnea index (AHI), defined as the mean number of apnea and/or hypopnea episodes that occur during sleep divided by the number of hours of sleep, and is expressed in events per hour (Germany et al., 2014). In general, an AHI of < 5 events per hour is categorized as normal, 5 to 14 events per hour as mild, 15 to 30 events per hour as moderate, and > 30 events per hour as severe.

The goals of therapy in patients with CSA are to normalize sleep-related breathing patterns (i.e., abolish central apneas, decrease or eliminate oxygen desaturations) and thereby improve both the quality of sleep and daytime symptoms and function (Badr, MS). CSA treatments include positive airway pressure (PAP) therapies, such as continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP), adaptive servo ventilation (ASV), supplemental oxygen, and medications including acetazolamide, theophylline, and sedative-hypnotic agents. Phrenic nerve stimulation (PNS) is a potential treatment option for adults with CSA who do not respond to currently available apnea therapies.[5,6]

Phrenic nerve stimulation (PNS) by implantable remedē System (Respicardia, Inc, Minnetonka, MN) causes diaphragmatic contraction like normal breathing and produces improvement in sleep in patients with CSA of different etiologies. The remedē System was FDA approved in October 6, 2017 for adult patients who have been diagnosed with moderate-to-severe CSA. The implantable device which transvenously stimulates the phrenic a nerve causing diaphragmatic contraction similar to normal breathing (Aurora, 2016) [8] and is described by the

manufacturer as: “An implantable pacemaker-like device that was designed for improving central sleep apnea (CSA) using Respidrive™, a Respiratory Rhythm Management™ algorithm. The remedē System delivers electrical pulses via a proprietary, novel transvenous implantable lead to one of the body’s two phrenic nerves. The remedē System therapy is intended to stimulate the diaphragm to restore a more natural, less disrupted, breathing pattern.” The system consists of a battery pack and small, thin wires placed under the skin in the upper chest area, monitors respiratory signals and causes normal breathing to be restored by stimulating the phrenic nerve to communicate with the diaphragm. The system is programmed using an external System Programmer and Programming Wand. It monitors the patient’s respiratory signals during sleep and stimulates the nerve to move the diaphragm and restore normal breathing. This device is not intended for use in patients with obstructive sleep apnea (OSA).[5]

The remedē System is classified by the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) as an implanted phrenic nerve stimulation devices for central sleep apnea (CSA) and regulated as a Class III device, classified under the Product Code PSR.[2-4]

COVERAGE POLICY [1,7]

Implantable neurostimulators including, but not limited to, the remedē System and **are considered experimental and investigational** due to insufficient evidence supporting the safety and efficacy for treating central sleep apnea.

Implantable neurostimulator for the treatment of central sleep apnea **is considered experimental or investigational** based upon insufficient evidence to:

- Permit conclusions concerning the effect on health outcomes;
- Support improvement of the net health outcome; and
- Support improvement of the net health outcome as much as, or more than, established alternatives.

Limitations and Exclusions

Implantable neurostimulator including, but not limited to the remedē System, **are considered experimental and investigational** due to insufficient evidence supporting the safety and efficacy for treating central sleep apnea.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE [8-19]

Overall, the quality of evidence evaluating the clinical impact of the phrenic nerve stimulation (PNS) with the remedē System in adults with central sleep apnea (CSA) is low. While the device has been approved by the FDA and indicated for the treatment of moderate to severe CSA in adults, available evidence of only 12 months of outcome data from a single randomized controlled sham study is insufficient to conclude the long-term safety and efficacy of the device. The small sample size and a lack of diverse patient population in the studies also limits conclusions to a selected group of patients, as studies enrolled primarily older males with HF. The physiologic determinants of central breathing instability in populations of different age groups, gender and racial descent, were not adequately represented in the study population and thus optimal patient selection criteria for the remedē System is inconclusive. In addition, results from trials suggest a statistically significant reduction in AHI events. However, it should be noted that average AHI scores did not achieve normal-to-mild disease severity (< 15 apnea events per hour) thus the clinical significance of this reduction needs further evaluation. Moreover, there were no measures of cardiovascular outcomes as the clinical impact for patients with CSA, especially those with HF. Furthermore, there were no trials that directly compared PNS to other non-invasive therapies for CSA, such as positive airway pressure (PAP) therapies, to establish comparative efficacy and its place in therapy. In summary, the evidence is insufficient to determine the effects of this technology on net health outcomes and there is insufficient evidence to show

transvenous phrenic neurostimulation is reasonable and necessary for the treatment of CSA. Further large, randomized, comparative, controlled studies are needed to determine the safety and efficacy, define optimal patient selection and assess long-term effect of PNS on CSA-related morbidity and mortality.

The FDA approval of the remedē System is based on an industry-supported, multicenter, prospective, randomized controlled sham study that aimed to determine the safety and assess the effectiveness of the remedē System in reducing apnea-hypopnea index (AHI) in moderate to severe CSA (AHI of least 20 events/hour shown on PSG). Central apneas needed to be > 50% of the apneas, happen at least 30 times per night, and the obstructive apnea index apnea index (OAI) needed to be < 20%.[9]

A total of 151 adult participants (at least 18 years, mean age 65 years, 89% male; 95% Caucasian) who have been stable for at least 30 days and have had appropriate guideline-based therapy underwent device implantation in the pectoral region. Participants were randomly assigned (1:1) by a computer-generated method stratified by site to either stimulation [treatment; 73 of 151 (52%) subjects having the device activated] or no stimulation (78 serving as controls with no activation; n=78) for 6 months, then all patients received neurostimulation for additional 6 months. Treatment assignment was known to both patients and clinicians. The system was activated one month after insertion and activation gradually increased in the treatment group until diaphragmatic capture without disrupting sleep was accomplished. [9]

- 64% had heart failure, but patients with stage D heart failure were excluded
- Other exclusion criteria included phrenic nerve palsy, cerebrovascular event in previous 12 months, central sleep apnea secondary to opioids, and advanced renal disease

The primary effectiveness endpoint was the proportion of the treatment patients versus controls who achieved a 50% or greater reduction in AHIs measured in a PSG lab. The primary safety endpoint was freedom from adverse events during the 12 months. Subjects were evaluated regularly until the end of the trial. After 6 months, the remedē System was activated in the sham group. Effectiveness was based on modified intention to treat (ITT) data at 6 months (n=141). A significant higher number of subjects in the active remedē System group had a 50% or better reduction in AHI from baseline to 6 months post-procedure ($p<0.0001$).[9]

- Baseline AHIs were 48.8 + 19.3 in the treatment and 43.7 + 16.8 in the control group
- After 6 months, results showed that 51% of the patients with the active implant (35/68 or 51%) had at least a 50% reduction in their AHI from baseline. The control group (subjects with an inactive implant) had an 11% decrease in their AHI (8/73 or 11%). However, the mean AHI still remained elevated at a mean of 25 although 26 of the 35 had an AHI < 20.
- Other statistically significant improvements between the groups were the arousal events per hour, the percent of REM sleep, the oxygen desaturation > 4%, and the Epworth Sleepiness Scale. Treatment patients also had higher scores on the patient global assessment.
- A total of 76% of subjects in the remedē System group reported improvement in quality of life. Safety results were based on intention to treat (ITT) data for 12 months (n=151). There were seven deaths but none found to be related to the device or treatment.

The most common adverse events (AEs) reported included concomitant device interaction, implant site infection, and swelling and local tissue damage or pocket erosion. The number of subjects free from serious AEs was 91% (95% CI, 86% to 95%); however, 13 subjects had serious AEs including impending pocket erosion, implant site infection, lead dislodgement, concomitant device interaction, elevated transaminase, extra-respiratory stimulation, implant site hematoma, lad component failure, lead displacement, and non-cardiac chest pain. The remedē System should not be used by patients with an active infection or by patients who are known to require magnetic resonance imaging (MRI). Transvenous neurostimulation could provide a treatment option for central sleep apnea. Limitations of the study included a low percentage of female subjects, potential referral bias, and a loss to follow-up.[9]

A summary of a pivotal trial found the following:[9]

- 87% completed trial, 93% included in analyses (exclusions decreased the numbers to 68 in the treatment and 73 in the control group).
- Comparing neurostimulation vs. no stimulation
  - ≥ 50% improvement in apnea-hypopnea index at 6 months in 51% vs. 11% ($p < 0.0001$, NNT 3)

  - Treatment-related serious adverse events at 12 months in 8% vs. 9% (no p value reported)
- Neurostimulation associated with improved central apnea index, arousal index, oxygen desaturation, sleepiness score, and health-related quality of life at 6 months ($p < 0.0001$ for each).
- Subjects who experienced non-serious AEs were 48%. Implants were unsuccessful in 5 subjects, and the rate of explants was 5.3% (8/151).
- 7 patients died (unrelated to implant, system, or treatment), of whom 4 died in first 6 months (2 deaths in each group, treatment group and control group); 3 additional deaths occurred in the second six months but considered not related to the device.

Abraham, et al. evaluated transvenous unilateral phrenic nerve stimulation to treat central sleep apnea (CSA) in a prospective, multicenter, non-randomized study to determine feasibility, safety and efficacy. Central apnea was defined as the absence of airflow and respiratory effort for >10 sec and mixed apnea was considered a minimum of three respiratory efforts with absent inspiratory effort at the beginning of the episode. Eligible patients had an AHI of at least 20 and at least one-half of the events were of central origin. Patients with obstructive events > 20% were excluded. Fifty-seven (n=57) patients with CSA underwent baseline polysomnography followed by transvenous phrenic nerve stimulation system implantation and follow-up. Feasibility was assessed by implantation success rate and therapy delivery. Safety was evaluated by monitoring of device- and procedure-related adverse events. Efficacy was evaluated by changes in the apnea-hypopnea index at 3 months. Quality of life at 6 months was evaluated using a sleepiness questionnaire, patient global assessment, and, in patients with heart failure at baseline, the Minnesota Living with Heart Failure Questionnaire. The study met its primary end point, demonstrating a 55% reduction in apnea-hypopnea index from baseline to 3 months (49.5 ± 14.6 episodes/h vs. 22.4 ± 13.6 episodes/h of sleep; $p < 0.0001$; 95% confidence interval for change: -32.3 to -21.9). Central apnea index, oxygenation, and arousals significantly improved. Favorable effects on quality of life and sleepiness were noted. Epworth Sleepiness Scores (EPS) were improved at six months and 36 patients with HF showed improvement by an average of 10 points in the Minnesota Living With Heart Failure Questionnaire (MLWHF) ($p=0.0009$). Device- or procedure-related serious adverse events occurred in 26% of patients through 6 months post therapy initiation, predominantly due to lead repositioning early in the study. Therapy was well tolerated. Efficacy was maintained at 6 months. The authors concluded, transvenous unilateral phrenic nerve stimulation appears safe and effective for CSA, however these findings should be confirmed in a large, prospective randomized, controlled trial (NCT01124370). Limitations of the study included small sample size, lack of a control arm, short follow-up duration, and potential for referral bias.[10]

Jagielski, et al. evaluated 2-month outcomes of the study by Abraham and colleagues (2015). A total of 47 patients with CSA were treated with the remedē System for a minimum of 3 months. Sleep-disordered breathing parameters were evaluated by polysomnography (PSG) at 3, 6, and 12-month follow-up. Sleep symptoms and QOL were also evaluated; 41 patients completed all follow-up PSGs and were included in the analysis. At 12 months, there was sustained improvement compared with baseline in the apnea-hypopnea index (AHI), central apnea index and there was sustained improvement in the oxygen desaturation index, rapid eye movement (REM) sleep and sleep efficiency: AHI (49.9 ± 15.1 versus 27.5 ± 18.3 events/hour, $p < 0.001$); central apnea index (28.2 ± 15.0 versus 6.0 ± 9.2 events/hour, $p < 0.001$); oxygen desaturation index (46.1 ± 19.1 versus 26.9 ± 18.0 events/hour, $p < 0.001$), rapid eye movement (REM) sleep (11.4 ± 6.1 % versus 17.1 ± 8.0 %, $p < 0.001$), and sleep efficiency (69.3 ± 16.9 % versus 75.6 ± 17.1 %, $p = 0.024$). There were also continued favorable effects on sleepiness and QOL; 3 deaths unrelated to remade System therapy and 5 serious AEs occurred over 12 months of follow-up. The authors noted the main limitations of the study were the non-randomized (lack of a control group), open-label nature of the trial, the small sample size and small number of female subjects enrolled in the study, and the loss to follow-up. The researchers recommended larger, randomized, controlled trials to confirm their results.[11]

Costanzo, et al. reported on the 12-month outcomes of the 2016 Costanzo study. At 12 months post remedē System implantation, the treatment group had an active device for 12 months (n=54), and the control group had an active device for 6 months (n=65). After 12 months, 67% of the treatment group had a ≥ 50% reduction in AHI from baseline (36 of 54; 95% CI, 53% to 78%). Subjects continued to have improvements in sleep metrics, oxygenation, and quality of life. For the control group with an active device for 6 months, 55% of subjects had a ≥ 50% reduction in AHI from baseline (36 of 65; 95% CI, 43% to 67%). At 12 months follow-up, there were 7 reported deaths, but they were not related to the procedure or device. The freedom from serious adverse events at 12 months for the intent-to-treat population was 91% (138 of 151; 95% CI, 86% to 95%). The authors concluded that the remedē System improves sleep metrics and quality of life for at least 12 months without safety concerns. However, the evidence to date remains insufficient to demonstrate the safety and efficacy of this new implantable device, with 12-

month safety outcomes data available from a single randomized controlled sham study. Large, randomized, controlled studies are needed to assess long-term outcomes.[12]

Costanzo, et al. evaluated the remedē System, a new physiologic treatment that uses transvenous PNS to contract the diaphragm, thereby stabilizing gas exchange and restoring normal breathing throughout the sleep period. This was a prospective multi-center randomized trial with blinded endpoints evaluating the safety and effectiveness of the remedē System. Up to 173 patients with CSA will be randomized 1:1 to remedē System therapy initiated at 1 month after implantation (treatment) or to an implanted remedē System that will remain inactive for 6 months (control). Primary effectiveness endpoint is the percentage of patients who experience a reduction in AHI by a greater than or equal to 50 % at 6 months (responder analysis). Primary safety endpoint is freedom from serious AEs through 12 months. Secondary endpoints include sleep-disordered breathing parameters, sleep architecture, Epworth Sleepiness Scale score, and Patient Global Assessment. The authors concluded that this study is the first RCT of the safety and effectiveness of the remedē System for the treatment of CSA.[13]

Ponikowski, et al. conducted a prospective, non-randomized trial to determine the feasibility of using unilateral transvenous phrenic nerve stimulation for the treatment of CSA in patients with heart failure (HF). Thirty-one patients from six centers were selected; 16 were able to undergo two nights of polysomnography (PSG) and were enrolled in the study. Measurements of apnea-hypopnea index (AHI), central apnea index (CAI), obstructive apnea index (OAI), hypopnea index, arousal index, and 4% oxygen index (ODI 4%) were performed prior to and after phrenic nerve stimulation of 271 + 71 minutes. The AHI, CAI, arousal index and ODI 4% significantly improved although there were no significant changes in the hypopnea index or OAI. The AHI remained elevated at 23 (12-27) events/hour. There were two adverse events of a lead thrombus and an episode of ventricular tachycardia, neither of which was considered directly related to the phrenic nerve stimulation therapy. The authors stated the study provided a strong proof of concept and that large-scale, long-term randomized controlled trials using an implanted system were needed. The study was supported by Respicardia, Inc. and six of the authors were paid consultants and one an employee of this company.[14]

National and Professional Organizations

The **American Academy of Sleep Medicine (AASM)** issued an updated guideline in 2016 on adaptive servo-ventilation (ASV) in patients with central sleep apnea (CSA). The guideline does not include diaphragmatic/phrenic nerve stimulation or diaphragm pacing as a recommended treatment for this condition.[18]

The AASM also published the *Practice Parameters with an Evidence-Based Literature Review and Meta-Analyses* recommends the following:[19]

- Optimize treatment of heart failure
- CPAP indicated as initial treatment to normalize the apnea-hypopnea index (< 15)*
- Nocturnal oxygen therapy is indicated*
  - may be given as supplement to CPAP or for patients intolerant of CPAP
  - consider repeat sleep study with oxygen to evaluate resolution of central sleep apnea events
- Second-line options to consider, based on limited evidence
- Bilevel positive airway pressure (BPAP) in a spontaneous timed (ST) mode targeted to normalize the apnea hypopnea index, only if no response to CPAP, oxygen therapy, and ASV**
- Acetazolamide and theophylline** should be considered only if
  - Standard medical therapy is optimized
  - Positive airway pressure therapy not tolerated
  - Close clinical follow-up provided for adverse effects

* AASM Standard, **AASM Option

A 2017 update to the guidelines published in 2015 was published by the **American College of Cardiology (ACC), American Heart Association (AHA),** and the **Heart Failure Society of America (HFSA).** The update focused on the management of heart failure. The guideline does not include diaphragmatic/phrenic nerve stimulation or diaphragm pacing as a recommended treatment for heart failure management. The guideline includes the following recommendations regarding sleep disordered breathing:[20]

- In patients with NYHA class II-IV heart failure and suspicious of sleep disordered breathing or excessive daytime sleepiness, a formal sleep assessment is reasonable.
- In patients with cardiovascular disease and obstructive sleep apnea, CPAP may be reasonable to improve sleep quality and daytime sleepiness.
- In patients with NYHA class II-IV heart failure with reduced ejection faction (HFrEF) and central sleep apnea, adoptive servo-ventilation causes harm.

SUPPLEMENTAL INFORMATION

Definitions

Apnea: cessation of airflow for > 10 seconds

Central Apnea Index (CAI): the number of central sleep apnea episodes per hour of sleep

Apnea-Hypopnea Index (AHI): the number of apneas and hypopneas (reduction airflow to < 50% of normal rate) per hour of sleep.

- The results of polysomnogram (PSG) testing are reported in terms of the apnea-hypopnea index (AHI), or respiratory disturbance index (RDI).
- The AHI is determined by adding the total number of apneas and hypopneas during the sleep time and dividing that number by the total hours of sleep.

CODING & BILLING INFORMATION

CPT Codes

CPT	Description
0424T	Phrenic nerve neurostimulation (e.g., remedē implantable system) for treatment of central sleep apnea; insertion or replacement of complete system (transvenous placement of right or left stimulation lead, sensing lead, implantable pulse generator)
0425T	Insertion or replacement of neurostimulator system for treatment of central sleep apnea; sensing lead only
0426T	Insertion or replacement of neurostimulator system for treatment of central sleep apnea; stimulation lead only
0427T	Insertion or replacement of neurostimulator system for treatment of central sleepapnea; pulse generator only

HCPCS Code

HCPCS	Description
E1399	Durable medical equipment, miscellaneous (when used for Expiratory Positive Airway Pressure device)

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

10/13/2021	Policy reviewed, no changes, updated references. Added CPT codes 0425T, 0426T and 0427T.
4/23/2020, 2/8/2021	Policy reviewed, no changes.
03/11/2019	New policy.

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APPENDIX

Reserved for State specific information *(to be provided by the individual States, not Corporate). Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*