

Subject: Diaphragmatic/Phrenic Nerve Stimulation and Diaphragm Pacing Systems
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Description

This document addresses diaphragmatic/phrenic (D/P) nerve stimulation and diaphragm pacing systems with devices that have obtained clearance from the U.S. Food and Drug Administration (FDA), such as the NeuRx DPS™ RA/4 Respiratory Stimulation System (Synapse Biomedical, Inc., Oberlin, OH), which is an implantable electrical device that stimulates the diaphragm. Diaphragmatic/phrenic nerve stimulator devices and diaphragm pacing systems are indicated for certain ventilator-dependent individuals who lack voluntary control of their diaphragm muscles to enable independent breathing without the assistance of a mechanical ventilator for at least 4 continuous hours a day. A new diaphragmatic nerve stimulator, the Remedē® System (Respocardia®, Inc., Minneapolis, MN), has been cleared by the FDA for the treatment of moderate to severe central sleep apnea (CSA).

Clinical Indications

Medically Necessary:

I. Diaphragmatic/Phrenic Stimulation

Diaphragmatic/phrenic nerve stimulation with an FDA-approved device is considered **medically necessary** as an alternative to invasive mechanical ventilation for individuals who are 18 years of age or older when ALL of the following criteria are met:

- A. The individual has ventilatory failure from stable, high spinal cord injury **or** ventilatory failure from central alveolar hypoventilation syndrome; **and**
- B. The individual cannot breathe spontaneously for 4 continuous hours or more without use of a mechanical ventilator; **and**
- C. Diaphragm movement with stimulation is visible under fluoroscopy; **and**
- D. Stimulation of the diaphragm either directly or through the phrenic nerve results in sufficient muscle activity to accommodate independent breathing without the support of a ventilator for at least 4 continuous hours a day; **and**
- E. Individual has normal chest anatomy, a normal level of consciousness, and has the ability to participate in and complete the training and rehabilitation associated with the use of the device; **and**
- F. Bilateral clinically acceptable phrenic nerve function is demonstrated with electromyography recordings and nerve conduction times.

II. Diaphragmatic Stimulation

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Diaphragmatic/Phrenic Nerve Stimulation and Diaphragm Pacing Systems

Diaphragm stimulation with an FDA approved diaphragm pacing system is considered **medically necessary** as an alternative to invasive mechanical ventilation in individuals who are 18 years of age or older when ALL of the following criteria are met:

- A. The individual has ventilatory failure from stable, high spinal cord injury **or** ventilatory failure from central alveolar hypoventilation syndrome **or** ventilatory failure from motor neuron disease, for example amyotrophic lateral sclerosis; **and**
- B. The individual cannot breathe spontaneously for 4 continuous hours or more without use of a mechanical ventilator; **and**
- C. Diaphragm movement with stimulation is visible under fluoroscopy; **and**
- D. Stimulation of the diaphragm directly results in sufficient muscle activity to accommodate independent breathing without the support of a ventilator for at least 4 continuous hours a day; **and**
- E. Individual has normal chest anatomy, a normal level of consciousness, and has the ability to participate in and complete the training and rehabilitation associated with the use of the device.

Not Medically Necessary:

Diaphragmatic/phrenic nerve stimulation devices and Diaphragm Pacing Systems are considered **not medically necessary** when:

- The individual can breathe spontaneously for 4 continuous hours or more without use of a mechanical ventilator; **or**
- The respiratory insufficiency is temporary.

Diaphragmatic/phrenic nerve stimulation and Diaphragm Pacing Systems are considered **not medically necessary** for all other indications including, but not limited to:

- Underlying cardiac, pulmonary or chest wall disease is present which is significant enough to prevent spontaneous breathing off a ventilator for more than 4 hours even with the use of the phrenic nerve or diaphragm pacemaker device; **or**
- In individuals with intact phrenic nerve and diaphragm function; **or**
- For treatment of any other condition where the phrenic nerve and diaphragm are intact (for example, chronic obstructive lung disease, restrictive lung disease, singultus [hiccups], central sleep apnea); **or**
- For adolescents, children and infants; **or**
- When the above criteria are not met.

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT

64575

Incision for implantation of neurostimulator electrodes; peripheral nerve (excludes sacral nerve) [when specified as phrenic nerve stimulator]

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Diaphragmatic/Phrenic Nerve Stimulation and Diaphragm Pacing Systems

64590	Insertion or replacement of peripheral or gastric neurostimulator pulse generator or receiver, direct or inductive coupling [when specified as phrenic nerve stimulator] <i>Note: the following CPT codes are considered not medically necessary</i>
0424T	Insertion or replacement of neurostimulator system for treatment of central sleep apnea; 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 sleep apnea; pulse generator only
0428T	Removal of neurostimulator system for treatment of central sleep apnea; pulse generator only
0429T	Removal of neurostimulator system for treatment of central sleep apnea; sensing lead only
0430T	Removal of neurostimulator system for treatment of central sleep apnea; stimulation lead only
0431T	Removal and replacement of neurostimulator system for treatment of central sleep apnea; pulse generator only
0432T	Repositioning of neurostimulator system for treatment of central sleep apnea; stimulation lead only
0433T	Repositioning of neurostimulator system for treatment of central sleep apnea; sensing lead only
0434T	Interrogation device evaluation implanted neurostimulator pulse generator system for central sleep apnea
0435T	Programming device evaluation of implanted neurostimulator pulse generator system for central sleep apnea; single session
0436T	Programming device evaluation of implanted neurostimulator pulse generator system for central sleep apnea; during sleep study

HCPCS

C1778	Lead, neurostimulator (implantable) [for phrenic nerve stimulator]
C1816	Receiver and/or transmitter, neurostimulator (implantable) [for phrenic nerve stimulator]
L8680	Implantable neurostimulator electrode, each [for phrenic nerve stimulator]
L8682	Implantable neurostimulator radiofrequency receiver [for phrenic nerve stimulator]
L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver [for phrenic nerve stimulator]

ICD-10 Procedure

0BHT0MZ-0BHT4MZ	Insertion of diaphragmatic pacemaker lead into diaphragm [by approach; includes codes 0BHT0MZ, 0BHT3MZ, 0BHT4MZ]
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ICD-10 Diagnosis

G12.20-G12.29	Motor neuron disease
G47.35	Congenital central alveolar hypoventilation syndrome
G82.50-G82.54	Quadriplegia
G83.89	Other specified paralytic syndromes [respiratory]
J96.10-J96.12	Chronic respiratory failure
J96.20-J96.22	Acute and chronic respiratory failure
R06.81	Apnea, not elsewhere classified [respiratory muscle paralysis]
Z99.11	Dependence on respirator [ventilator] status

Discussion/General Information

FDA clearance for distribution of the NeuRx DPS RA/4 Respiratory Stimulation System was granted under a Humanitarian Device Exemption (HDE) on June 17, 2008. The FDA-approved indications are:

For use in patients with stable, high spinal cord injuries with stimlatable diaphragms, but lack control of their diaphragms. The device is indicated to allow the patients to breathe without the assistance of a mechanical ventilator for at least 4 continuous hours a day and is for use only in patients 18 years of age or older.

This FDA approval is subject to the manufacturer developing “an acceptable method of tracking device implantation to individual patient recipients” (FDA, 2008).

The NeuRx DPS RA/4 Respiratory Stimulation System is implanted through minimally invasive laparoscopic surgery and provides electrical stimulation to muscles and nerves that run through the diaphragm. This eliminates any direct contact with the phrenic nerve, allows all circuitry and electronics to remain outside the body, and provides direct, selective activation to each hemidiaphragm. According to manufacturer information, when stimulated by the NeuRx DPS, the diaphragm contracts, mimicking natural breathing and allowing air to fill the upper and lower parts of the lungs, rather than forcing air in with a mechanical ventilator. The device uses four electrodes implanted in the muscle of the diaphragm to electronically stimulate contraction; this stimulation allows the user to inhale. The DPS is lightweight and battery powered, eliminating the need for an external power source.

FDA clearance of the NeuRx device was primarily based on a prospective, nonrandomized, multicenter clinical trial that included 50 subjects throughout the U.S. and Canada (Onders, 2009). In the clinical trial, 98% of subjects with spinal cord injury were able to breathe normally for at least 4 hours following implantation of the device, while 50% have been able to completely eliminate their need for mechanical ventilation. The study inclusion criteria were:

- Age 18 years or older;
- Cervical spinal cord injury with dependence on mechanical ventilation;
- Clinically stable following acute spinal cord injury;

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Diaphragmatic/Phrenic Nerve Stimulation and Diaphragm Pacing Systems

- Bilateral phrenic nerve function clinically acceptable as demonstrated with electromyography (EMG) recordings and nerve conduction times;
- Diaphragm movement with stimulation visible under fluoroscopy;
- Clinically acceptable oxygenation on room air (greater than 90% O₂ saturation);
- Hemodynamically stable;
- No medical co-morbidities that would interfere with the proper placement or function of the device;
- Committed primary caregiver;
- Negative pregnancy test in females of child-bearing potential;
- Informed consent from the device user or designated representative.

Exclusion criteria were:

- Co-morbid medical conditions that preclude surgery;
- Active lung disease (obstructive, restrictive or membrane diseases);
- Active cardiovascular disease;
- Active brain disease;
- Hemodynamic instability or low oxygen levels on room air;
- Hospitalization for or a treated active infection, within the last 3 months;
- Significant scoliosis or chest deformity;
- Marked obesity;
- Anticipated poor compliance with protocol by either the device user or primary caregiver;
- Currently breastfeeding.

The study's primary endpoint was to assess the ability of the NeuRx device to provide clinically acceptable tidal volume for at least 4 continuous hours of pacing. For a male subject, the tidal volume that is required to meet the basal metabolic requirement (VT-bmr) was defined as 7 ml/kg body weight. For a female subject, the VT-bmr was defined as 6 ml/kg body weight. The safety endpoint was to qualitatively assess the adverse event reports and compare these to a similar population. Secondary endpoints included reduction of dependence on mechanical ventilation and surgical implementation site independence. The study provided an average follow-up of 1.7 ± 1.4 years (median, 1.4; range 0.2-7.7). Overall, a total of 48 out of 50 subjects enrolled have been able to pace for longer than 4 consecutive hours while achieving tidal volumes greater than their basal metabolic requirements. At the end of the study period, 44 subjects were actively using the device. A total of 4 subjects died in the course of the study, and there were 11 incidents of aspiration and 3 incidents of upper airway obstruction that occurred in 3 subjects.

The length of the conditioning phase was variable. It ranged from 1 week for 18-20 year olds on mechanical ventilation for less than 1 year, to 14 weeks for 40-50 year olds on a ventilator for greater than 5 years. Use of the device for periods greater than 4 continuous hours a day occurred after a period of diaphragmatic conditioning that ranged from 1 week to several months. The study investigators concluded that this suggests that the use of the NeuRx DPS RA/4 Respiratory Stimulation System in individuals with high spinal cord injuries and stimlatable diaphragms may allow these subjects to be removed from the ventilator for at least 4 hours a day, provided that a mechanical ventilator is available at all times (as recommended in the labeling).

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The most frequent adverse event attributable to this device was capnothorax. The capnothorax occurred as a consequence of the surgical implantation procedure. A total of 42% of the subjects enrolled in the clinical study experienced this complication in association with implantation of the electrodes in the diaphragm. While no subjects experienced compromised pulmonary gas exchange or hemodynamic instability as a result of the capnothorax, affected subjects required treatment with a chest tube, for up to 2 days in 1 individual, and an extended hospital stay of 5 days in 1 person. Synapse Biomedical Inc. has addressed this risk in the labeling and training procedure provided with this device. There have been few additional clinical studies of these devices, most of which were case series of small numbers with short-term outcomes data only.

On September 28, 2011, the FDA issued an approval under an HDE application for use of the NeuRx DPS Diaphragm Pacing System in:

Amyotrophic lateral sclerosis (ALS) patients with a stimlatable diaphragm (both right and left portions) as demonstrated by voluntary contraction or phrenic nerve conduction studies, and who are experiencing chronic hypoventilation (CH), but not progressed to an FVC (forced vital capacity) less than 45% predicted. For use only in patients 21 years of age or older.

This approval was based on results of a multicenter, prospective study of the NeuRx Diaphragm Pacing Stimulation (DPS) System of motor-point stimulation for conditioning the diaphragm of subjects with ALS which showed the probable benefit to health from use of the device outweighed the risks of injury or illness from its use (FDA/HDE; SSPB, 2011).

Similar to the NeuRx DPS system, the Avery Breathing Pacemaker System (that is, the Mark IV™ Avery Biomedical Device, Inc., Commack, NY) is connected to the phrenic nerve by electrodes in the neck or chest area. The device consists of a surgically implanted receiver and electrodes which are connected to an external transmitter for transmitting the stimulating pulses across the skin to the implanted receiver. The pacemaker is classified as a Class III neurologic therapeutic device requiring premarket approval (PMA). The device is approved “for persons who require chronic ventilatory support because of upper motor neuron respiratory muscle paralysis (RMP) or because of central alveolar hypoventilation (CAH) and whose remaining phrenic nerve, lung, and diaphragm function is sufficient to accommodate electrical stimulation” (FDA, 2003).

In 2014, results of a retrospective review were published describing a multicenter, nonrandomized treatment protocol using a D/P system during the initial hospitalization phase following high (cervical) spinal cord injury. A total of 14 inpatient sites in the U.S. were included in this analysis, all of which used the same database for data collection, which included age, sex, mechanism and level of injury, date of injury, date of D/P system surgery, surgical findings, and outcomes. Twenty-nine subjects with an average age of 31.4 years (range, 17-65 years) were identified for this review; however, 7 subjects were subsequently disqualified due to pre-procedural findings from diaphragm motor point mapping that showed non-stimlatable diaphragms from either phrenic nerve damage or infarct. All subjects had experienced a traumatic high spinal cord injury with an elapsed time from injury to surgery of 40 days (range of 3-112 days). The post-procedure outcomes following laparoscopic D/P system implantation showed that 72.7% (16 of 22) were completely free of ventilator support in an average of 10.2 days (mean SE of 10.2 ± 13.1 days [range, 1-45 days]). The remaining 6 subjects who had undergone D/P system implantation

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experienced delayed weaning of 180 days (in 2 trial participants), and partial weaning was achieved in 3 subjects, reflecting a total success rate of 82%. It was possible to remove the D/P wires from 8 of the 22 implanted subjects due to complete respiratory recovery. The last subject needed transfer to a long-term acute care hospital and subsequently had life-prolonging measures withdrawn. The authors concluded that laparoscopic diaphragm motor point mapping early after traumatic cervical spinal cord injury can assist with diagnosing those with complete phrenic motor neuron loss or phrenic nerve injury for whom D/P system implantation is not indicated. Also, in those with intact phrenic nerve systems following injury, D/P system implantation can successfully wean them from ventilator support, although it is acknowledged that these individuals may have been successfully weaned from ventilator dependence over time during the course of their recovery without the use of DP (Posluszny, 2014).

Diaphragmatic/Phrenic Nerve Stimulators for Central Sleep Apnea

The Remedē System was approved by the FDA on October 6, 2017 for the treatment of moderate to severe central sleep apnea in adult individuals. The manufacturer describes the device 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.

Abraham and colleagues (2015) performed an industry-supported, prospective, multicenter, international, nonrandomized feasibility study to evaluate unilateral phrenic nerve stimulation to treat CSA. Eligible subjects (n=57) had apnea-hypopnea index (AHI) values of 20 or higher and at least 50% of their events were CSA as confirmed by polysomnography. The subjects were implanted with the Remedē System and evaluated after 1, 2, 3 and 6 months, with the primary endpoint of the study being AHI reduction by 50% after 3 months. The Remedē System was successfully implanted in 49 out of 57 subjects (86%); however, 10 subjects did not complete the study. A total of 26% of subjects had serious adverse events (AE) that were related to the procedure or the device and included lead repositioning problems, migraine, hematoma and atypical chest pain the first night of therapy. For the 47 subjects that completed 3 months of therapy, there was a mean reduction in AHI of 27.1 ± 17.7 episodes/h (55%, $p < 0.0001$) and a mean reduction in the central apnea index of 23.4 ± 15.3 episodes/h (84%, $p < 0.0001$). After 6 months, subjects reported improvement in sleepiness, and 56% reported a marked or moderate improvement in how they felt since starting the therapy. A total of 36 subjects with heart failure showed an average improvement of 10 points on the Minnesota Living with Heart Failure Questionnaire (95% confidence interval [CI], -16 to -4; $p = 0.0009$) at 6 months. Limitations of the study included a small sample size, lack of a control arm, short follow-up duration, and potential for referral bias. The authors concluded that unilateral phrenic nerve stimulation appears to be safe and effective for CSA, but large, prospective, randomized, controlled trials are needed.

In an industry-supported analysis, Jagielski and colleagues (2016) reported on the 12-month outcomes of the study by Abraham and colleagues (2015). The researchers analyzed 41 out of 47 of individuals that had been successfully implanted with the Remedē System. They found that the AHI was reduced from 49.9 ± 15.1 at baseline to 27.5 ± 18.3 ($p < 0.001$). The central apnea index was reduced from 28.2 ± 15.0 to 6.0 ± 9.2 ($p < 0.001$). They also noted improvements in the oxygen desaturation index, rapid eye movement, and sleep efficiency. On the

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quality of life assessment, 83% of subjects had a mild, moderate, or marked improvement at 12 months. A total of 3 subjects died before follow-up (2 from end-stage heart failure and 1 from sudden cardiac death); however, the deaths were adjudicated as unrelated to the procedure or the Remedē System. In addition to the adverse events already reported in the original study, 2 additional subjects had adverse events; 1 subject with impending pocket perforation and 1 subject with lead failure. Limitations of the study included loss to follow-up, the lack of a control group, open-label design, small sample size, and small number of female subjects. The researchers recommended large randomized controlled trials to confirm their results.

The FDA PMA of the Remedē System was based on an industry-supported, multicenter, prospective, randomized, controlled sham study that aimed to determine the safety and effectiveness for treating CSA (Costanzo, 2016). A total of 151 adult subjects were randomized to receive either medical management and the Remedē System (n=73), or medical management and an inactive sham Remedē System (n=78). The subjects in the study were an average of 65 years old and predominately Caucasian (95%) and male (89%). The primary endpoint was a 50% or greater reduction in AHI from baseline to 6 months, and the AHI was determined using polysomnography. 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 significantly 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 ($p<0.0001$). The success rate for the active Remedē System group was 51% compared to 11% in the sham group for a total difference of 41% (95% CI, 25% to 54%; $p<0.0001$). A total of 76% of subjects in the active Remedē System group reported improvement in quality of life. Safety results were based on ITT data for 12 months (n=151). There were 7 deaths but none were found to be related to the device or treatment. 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, lead component failure, lead displacement, and non-cardiac chest pain. The number of subjects who experienced non-serious AEs was 48%. Implants were unsuccessful in 5 subjects, and the rate of explants was 5.3% (8/151). The authors concluded that 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.

Costanzo and colleagues (2018) 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 $\geq 50\%$ 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 $\geq 50\%$ 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.

The evidence, to date, is 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.

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Definitions

Alveolar Hypoventilation Syndrome: Insufficient ventilation leading to an increase in PaCO₂ (that is, hypercapnia). Alveolar hypoventilation is caused by several disorders that are collectively referred to as hypoventilation syndromes. The term, central alveolar hypoventilation, is used to describe alveolar hypoventilation secondary to an underlying neurologic disease. Alveolar hypoventilation is a cause of hypoxemia. The presence of hypoxemia, along with hypercapnia, aggravates the clinical manifestations seen with hypoventilation syndromes.

Amyotrophic Lateral Sclerosis (ALS): A form of motor neuron disease that is caused by the progressive degeneration of upper and lower neurons in the spinal cord and brain that results in respiratory compromise and central alveolar hypoventilation syndrome due to muscle weakness and atrophy.

Capnothorax: A respiratory condition related to the implantation of device electrodes whereby air enters the pleural cavity. This condition is caused by the inflation of the abdomen with CO₂ during laparoscopic surgical procedures.

Central Sleep Apnea (CSA): A type of sleep apnea that occurs when the brain periodically fails to communicate with the muscles that are necessary for breathing.

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Diaphragmatic/Phrenic Nerve Stimulation and Diaphragm Pacing Systems

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Diaphragmatic/Phrenic Nerve Stimulation and Diaphragm Pacing Systems

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The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
New	11/08/2018	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development. Moved content of MED.00100 Diaphragmatic/Phrenic Nerve Stimulation and Diaphragm Pacing Systems to new clinical utilization management guideline document with the same title.

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