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Subject: Percutaneous Electrical Nerve Stimulation(PENS)

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DESCRIPTION:

Percutaneous electrical nerve stimulation (PENS) is similar in concept to transcutaneous electrical nerve stimulation, but differs in that needles are inserted either around or immediately adjacent to the nerves serving the painful area, and then stimulated. PENS is generally reserved for those who fail to get pain relief from transcutaneous electrical nerve stimulation. PENS is also distinguished from acupuncture with electrical stimulation. In electrical acupuncture, needles are also inserted just below the skin, but the placement of needles is based on specific theories regarding energy flow throughout the human body. In PENS, the location of stimulation is determined by proximity to the pain.

Percutaneous neuromodulation therapy (PNT) is a variant of PENS in which fine filament electrode arrays are placed near the area causing pain. Some use the terms PENS and PNT interchangeably. It is proposed that PNT inhibits pain transmission by creating an electrical field that hyperpolarizes C fibers, thus preventing action potential propagation along the pain pathway.

Another type of neuromodulation, peripherally implanted nerve stimulators (also known as peripheral subcutaneous field stimulation, or peripheral nerve field stimulation) purport to treat chronic pain by targeting the peripheral nerve causing the chronic pain directly. An electrical current is transmitted via an electrode that has been implanted around the selected peripheral nerve. It is thought the electrical current blocks or disrupts the normal transmission of pain signals. The electrodes are connected by a wire to the peripherally implanted neurostimulator. An external generator (similar to a remote control device) controls the degree of stimulation the individual receives.

Percutaneous electrical nerve field stimulation (PENFS) (auricular neurostimulation) targets branches of cranial Nerves V, VII, IX and X, and the occipital nerves. It has been proposed as a treatment for functional abdominal pain associated with irritable bowel syndrome (IBS) in children and adolescents

(IB-Stim®); treatment of pain associated with opioid withdrawal (Bridge, Drug Relief V1, Morph Device); treatment of chronic intractable pain due to diabetic peripheral neuropathy (First Relief); post-cesarean section pain (Primary Relief); and treatment of pain after cardiac surgery (Primary Relief).

Remote electrical neuromodulation (REN) is purported to offer an alternative to pharmacologic interventions for acute migraine and/or prevention of migraines. The Nerivio® REN device is cleared for use by the Food and Drug Administration (FDA) and is worn on the upper arm. It stimulates the peripheral nerves to induce conditioned pain modulation (CPM). The conditioned pain in the arm induced by the Nerivio REN device is believed to reduce the perceived migraine pain intensity. Control of the REN device is accomplished through Bluetooth communication between the device and a smartphone or tablet. For acute treatment, at onset of migraine or aura and no later than within 1 hour of onset, the user initiates use of the device through their mobile application. When used for preventive treatment, the device should be used every other day, controlled by the individual through their smartphone or tablet application.

Restorative neurostimulation is described as a novel form of stimulation for refractory chronic mechanical low back pain (CLBP), targeting impaired neuromuscular control and degeneration of the multifidus muscle. The ReActiv8® Restorative Neurostimulation System targets underlying multifidus muscle dysfunction by delivering electrical pulses through proprietary self-anchoring lead technology placed adjacent to the medial branch of the dorsal ramus.

Summary and Analysis of Evidence: Beltran-Alacreu et al (2022) evaluated the effectiveness of PENS compared to transcutaneous electrical nerve stimulation (TENS) on the reduction of musculoskeletal pain. This systematic review and meta-analysis included a total of 9 RCTs in the qualitative analysis, with 7 in the quantitative analysis. Overall, there was low-quality evidence for increased pain intensity reduction with PENS over TENS, but the difference found was not deemed to be clinically significant. When only studies with low risk of bias were meta-analyzed, there was a moderate quality of evidence that there is no difference between TENS and PENS for pain intensity. Six out of the 9 studies presented high risk for the blinding of participants, and 7 out of 9 were high risk for blinding of personnel. Beyond these 2 items, the risk of bias in the included trials was either low or unclear. Protocols and parameters for the application of PENS and TENS were heterogenous across all trials.

In 2013, the National Institute for Health and Care Excellence (NICE) published guidance on PENS (Percutaneous electrical nerve stimulation for refractory neuropathic pain [IPG450]). It concluded that "current evidence on the safety of [PENS] for refractory neuropathic pain raises no major safety concerns and there is evidence of efficacy in the short term."

Yokoyama et al (2004) compared percutaneous electrical nerve stimulation PENS) with transcutaneous electrical nerve stimulation (TENS) for long-term pain relief in chronic low back pain. The authors concluded "(a) cumulative analgesic effect was observed in patients with chronic low back pain (LBP) after repeated percutaneous electrical nerve stimulation (PENS), but this effect gradually faded after the treatment was terminated. Results indicate that although PENS is effective for chronic LBP, treatments need to be continued to sustain analgesia."

Schwab et al (2025) reported outcomes of the RESTORE trial. Candidates were assessed for CLBP associated with multifidus dysfunction, with no indication for or history of lumbar spine surgery. The primary endpoint was a comparison of the mean change in the Oswestry Disability Index (ODI) between the treatment and control arms at 1 year, and secondary endpoints included pain (numeric rating scale

[NRS]) and health-related quality of life (EuroQol Five-Dimension [EQ-5D-5L]). A total of 203 patients, average age 47 years, and with an average 11-year history of low back pain, were included in the analysis. The primary endpoint was a statistically significant demonstration of a clinically relevant mean improvement in the Oswestry Disability Index (ODI) between restorative neurostimulation and OMM arms. Additionally, improvements in both the numeric rating scale and EuroQol Five-Dimension were statistically and clinically significant in the restorative neurostimulation arm compared to the OMM arm. The authors concluded that the RESTORE trial "demonstrates that restorative neurostimulation is a safe, reversible, clinically effective, and highly durable option for patients suffering with nonoperative CLBP associated with multifidus dysfunction". The authors further states the RESTORE trial has several limitations: "Participants in this trial were not blinded to their treatment, and as a result, those randomized to the control arm may have experienced a nocebo effect underestimating the clinical effect of OMM medical management. In addition, patients in the treatment arm may have experienced a placebo effect after being randomized to interventional treatment. Both of these effects were anticipated and contributed to the rationale for the timing of the 1-year primary endpoint. This timing allows for their impact to subside and for the full effects of OMM or restorative neurostimulation to accrue. The additional attention and monitoring afforded to patients in the treatment arm of this RCT were above standard management protocols for restorative neurostimulation. These additional clinical contact points may have resulted in consideration of additional interventions, artificially inflating healthcare utilization in the short term above what may typically be expected. The effect of longer follow-up on interventions will be reported in due course."

James, Ahern et al (2025) investigated whether targeted muscle activation via neurostimulation reverses or resolves muscle spindle fibrosis in a model of IVD injury. In eighteen sheep, lumbar L1–2 and L3-4 IVD degeneration was induced by partial thickness anulus fibrosis incision and a neurostimulator was implanted. After IVD-degeneration developed for 3 months, neurostimulation of the L2 nerve root activated multifidus in nine randomly selected animals. Multifidus muscle adjacent to the spinous process of L2 (non-stimulated) and L4 (stimulated) was harvested 3 months after activation. Muscle spindles were identified in Van Giessen's-stained sections. Connective tissue spindle capsule thickness, and cross-sectional area (CSA) of the spindle, its periaxial fluid and sensory elements were measured. Immunofluorescence assays evaluated Collagen-I and -III. Multifidus muscle spindle capsule thickness and Collagen-1 were significantly less in the neurostimulation animals than IVD-injury animals at L4 (stimulated muscle), but not L2 (non-stimulated muscle). Spindle capsule thickness was less in lateral than medial regions. CSA of the muscle spindle and sensory elements was less in neurostimulated animals at L4. The authors concluded "targeted multifidus activation reverses or prevents accumulation of connective tissue of the multifidus muscle spindle capsule caused by IVD injury. Reduced fibrosis should maintain sensory function of this important muscle mechanoreceptor and might provide an effective solution to resolve the commonly identified proprioceptive deficits in back pain and maintain healthy spine function." Several methodological considerations were noted, including infection at the site of the battery insertion in several animals; no animals without IVD injury were included in this study; no direct measure of the consequence of thickening on spindle mechanics and sensitivity; and no available data to make direct comparison between human and sheep multifidus muscles.

Gilligan, Volschenk (2024) conducted a prospective five-year longitudinal follow-up of the ReActiv8-B pivotal trial, participants (N = 204) had activity-limiting, moderate-to-severe, refractory, mechanical chronic low back pain, a positive prone instability test result indicating impaired multifidus muscle

control, and no indications for spine surgery. Low back pain intensity (10-cm visual analog scale [VAS]), disability (Oswestry Disability Index), and quality of life (EuroQol's "EQ-5D-5L" index) were compared with baseline and following the intent-to-treat principle, with a supporting mixed-effects model for repeated measures that accounted for missing data. At five years (n = 126), low back pain VAS had improved from 7.3 to 2.4 cm, and 71.8% of participants had a reduction of ≥50%. The Oswestry Disability Index improved from 39.1 to 16.5, and 61.1% of participants had reduction of ≥20 points. The EQ-5D-5L index improved from 0.585 to 0.807. Although the mixed-effects model attenuated completed-case results, conclusions and statistical significance were maintained. Of 52 subjects who were on opioids at baseline and had a five-year visit, 46% discontinued, and 23% decreased intake. The safety profile compared favorably with neurostimulator treatments for other types of back pain. No lead migrations were observed. The authors concluded that "over a five-year period, restorative neurostimulation provided clinically substantial and durable benefits with a favorable safety profile in patients with refractory chronic low back pain associated with multifidus muscle dysfunction." Potential study limitations included that owing to elective cross-over to therapeutic stimulation for ethical and trial-practical considerations, the sham-control group could not be maintained during the long-term follow-ups; device removals for various reasons, including 18 participants who underwent elective removals for resolution of symptoms (ie, success), contributed to participant withdrawals and subsequent missing data, and direct correlations with objective device usage and multifidus structure and function were not included in this follow-up.

Restorative neurostimulation therapy with the ReActiv8 system was evaluated in a multicenter, sham controlled RCT enrolling 204 individuals with chronic, refractory low back pain (ReActiv8-B, NCT02577354). Control group participants received treatment with the ReActiv8 system set to deliver low-level stimulation. The primary endpoint was the difference in proportions of responders in the treatment and control groups. Response was defined as the composite of 30% or greater reduction in VAS and no increase in pain medications, assessed at 120 days. At 120 days, there was no difference between groups on the primary endpoint of treatment response or the individual components of the primary endpoint. The controlled phase was only 120 days. In the longer-term, uncontrolled follow-up phase of the trial, there was continued improvement in VAS scores over time in those who were assessed, but the lack of a control group and high attrition limits drawing conclusions from these results. Data was available for 86.3% of participants at 1 year, 79% of participants at 2 years, and 63.7% of participants at 3 years. An uncontrolled follow-up phase of the RCT reported continued improvement in pain scores through 3 years but results are at high risk of bias due to lack of a control group and high attrition.

In September 2022, NICE published guidance on neurostimulation of lumbar muscles (Neurostimulation of lumbar muscles for refractory non-specific chronic low back pain [IPG739]) with the ReActiv8 system for refractory non-specific chronic low back pain. The guidance was based on a rapid review conducted in July 2021 and included the following statements "evidence on the efficacy and safety of neurostimulation of lumbar muscles for refractory non-specific chronic low back pain is limited in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or researh." It also stated that "(f)urther research should include suitably powered randomized controlled trials comparing the procedure with current best practice with appropriate duration. It should report details of patient selection and long-term outcomes."

Ardeshiri et al (2024) examined the effect of restorative neurostimulation in an older demographic using data from three clinical studies: ReActiv8-B (prospectively followed 204 patients); ReActiv8-C (prospectively followed 87 patients); and ReActiv8-PMCF (prospectively followed 42 patients). Two hundred and sixty-one patients were identified with complete 2-year follow-up and divided into cohorts of equal size based of age quartiles. The oldest quartile (n=65) had a median age of 60 (56-82) years compared with the entire population (n=261) who had a median age of 49 (22-82) years. The completer analysis on patients with 2 years of continuous data showed improvement of a 50% in pain was achieved by 62% and 65% and a 15-point ODI improvement in 48% and 60% in the oldest quartile and entire population, respectively. Author-noted limitations of this study include the small cohort of patients identified in the upper age group and the retrospective identification of the cohorts. Pain was collected differently between studies enabling a responder rate analysis only and no direct assessment of mean change from baseline. The inclusion and exclusion criteria for the various studies used in this analysis did vary slightly, however, the identification of these patients was achieved by applying the minimum requirements for inclusion for all patients.

Wong et al (2023) conducted an evidence review on the effectiveness of peripheral nerve field stimulation on chronic low back pain and persistent spinal pain syndrome. A total of 15 studies were included, including 4 randomized controlled trials (RCTs), 9 observational studies, and 2 case series. For patients receiving PNFS, a significant decrease in back pain intensity and analgesic consumption, together with a significant improvement in physical functioning, was observed upon implant of the permanent system. The authors stated "PNFS, when used alone or in combination with SCS, appears to be effective in managing back pain. However, high-quality evidence that supports the long-term analgesic efficacy and safety is still lacking. Hence, RCTs with a larger patient population and of a longer follow-up duration are warranted." In 2013, NICE issued guidance on peripheral subcutaneous field stimulation for chronic low back pain (Peripheral nerve-field stimulation for chronic low back pain [IPG451]), which stated "(c)urrent evidence on the efficacy of peripheral nerve-field stimulation for chronic low back pain is limited in both quantity and quality, and duration of follow-up is limited. Evidence on safety is also limited and there is a risk of complications from any implanted device.

Kalia et al (2025) conducted a retrospective observational study (9/1/19-1/31/23) of patients from the Nalu medical database to the OM1 Real-World Data Cloud (RWDC). Eligible patients received the micro-IPG implant for PNS, were identifiable in both databases, and had ≥ 12 months of RWDC pre/post-implantation claims data. Primary outcomes were all-cause HRCU and medical costs (12 months pre- and post-implantation); secondary outcomes were all-cause pharmacy costs, including opioids, over the same time. Patients (N = 122) had a higher mean number of outpatient visits pre-implantation than post-implantation. Post-implantation, the proportion of patients using opioids was 31.4% lower. The authors concluded that "PNS using the micro-IPG had reduced HCRU, costs, and opioid use." This study included several limitations, including a relatively small sample size with no formal statistical testing implemented due to the relatively recent introduction of the micro-IPG to the market (2019); missing data made it difficult to characterize this population in reference to the general population of patients with severe intractable chronic pain of peripheral nerve origin; patients with a cancer diagnosis were excluded, for example, because it is common for oncology patients to receive regular MRIs, and because patients with earlier PNS implants cannot receive MRIs, cancer centers do not currently treat patients with PNS. In addition, missing data included limits on available race and ethnicity (missing for approximately two-thirds of patients) and BMI and smoking status (unknown for ≥ 90%). It is also not

known whether or to what extent the COVID-19 pandemic influenced patient healthcare utilization and therefore the results of this study in 2020 and 2021.

Hatheway et al (2024) reported the results from the first large, postmarket, multicentre, randomised controlled trial (RCT) evaluating peripheral nerve stimulation (PNS) for the treatment of chronic peripheral pain with a micro-implantable pulse generator (micro-IPG). Subjects meeting eligibility were randomised (2:1) to either the active arm receiving PNS and conventional medical management (CMM) or the control arm receiving CMM alone. Treatments were limited to the following areas: lower back, shoulder, knee and foot/ankle. At 6 months, the active arm achieved an 88% responder rate with a 70% average reduction in pain. At the 3-month primary endpoint, the active arm achieved an 84% responder rate with an average pain reduction of 67% compared with the control arm, which achieved a 3% responder rate with an average pain reduction of 6%. Both responder rate and pain reduction in the active arm were significantly better than in the control arm. A majority of patient-reported outcomes also reached statistical significance. There were no reports of pocket pain and no serious adverse device effects. 81% of subjects found the external wearable component of the PNS system to be comfortable. The authors concluded that this study "successfully reached its primary endpoint-the active arm achieved a statistically significant superior responder rate as compared with the control arm at 3 months. These RCT results demonstrated that PNS, with this micro-IPG, is efficacious and safe. This ongoing study will follow subjects for 3 years, the results of which will be reported as they become available." Limitations of this study included that the control arm remained in CMM only for 3 months; a longer period was considered but was thought to be ethically problematic for those subjects with significant pain; in addition, the prevalence of females (70%) over males was unanticipated, but the randomization addressed potential bias, and this reflected the real-world population at the clinical sites.

McRoberts et al (2013) compared different methods of peripheral subcutaneous field stimulation. Among trial participants, 24 of 30 patients had at least a 50% reduction in pain with any type of peripheral subcutaneous field stimulation. However, because the RCT did not include a sham group or comparator with a different active intervention, this trial offers little evidence for efficacy beyond that of a prospective, uncontrolled study. Another RCT (Johnson et al, 2021) compared sham to external non-invasive peripheral electrical nerve stimulation, but found no significant differences in pain scores between groups after intervention. A third small, pilot RCT (Ilfeld et al, 2021) found significantly reduced opioid consumption and mean daily pain scores within the first 7 postoperative days in subjects receiving foot, ankle, knee, or shoulder surgery. However, differences in average pain, worst pain, and Defense and Veterans Pain Rating Scale scores were not significantly different between treatment and sham groups following completion of the treatment period on postoperative days 15 and 30. A fourth small, pilot feasibility RCT (Albright-Trainer et al, 2022) compared peripheral nerve stimulation with standard medical care to standard medical care alone in veterans undergoing lower extremity amputation. Greater reductions in average phantom limb pain, residual limb pain, and daily opioid consumption were reported through 3 months with the addition of peripheral nerve stimulation. Case series are insufficient to evaluate patient outcomes due to the variable nature of pain and the subjective nature of pain outcome measures. Larger, prospective controlled trials comparing peripheral subcutaneous field stimulation with placebo or alternative treatment modalities are needed to determine the efficacy of peripheral subcutaneous field stimulation for chronic pain.

There are few pharmacologic treatment options for children and adolescents with IBS. Non-pharmacologic options are commonly explored. Percutaneous electrical nerve field stimulation (PENFS)

(auricular neurostimulation) is a potential treatment option for these individuals.The evidence for PENFS with IB Stim® includes 2 randomized, double-blind, sham-controlled trials. PENFS has proven to be an effective and safe treatment for children and adolescents with functional abdominal pain disorders. PENFS with IB-Stim® showed an 81% improvement in overall symptoms, and approximately 59% of test subjects showed at least a 30% reduction in their worst pain (Kovacic et al, 2017; Krasaelap et al, 2020). The evidence for PENFS (auricular neurostimulation) for all other indications is insufficient.

Synowiec et al (2024) studied the long-term safety, utilization, and efficacy of REN during 12 consecutive usage months. Data from patients with migraine across the USA using REN to treat their migraine attacks were electronically collected from the Nerivio® device. All patients who used REN during 12 consecutive months were included, and data were compared across months. Safety was assessed by the number and type of adverse events. Utilization was measured by the number of monthly treatments. Efficacy was evaluated as consistent change in headache pain intensity, functional disability, and disappearance of associated symptoms from baseline to 2 hours post treatment. Data were analyzed from 409 people living with migraine who treated with REN for 12 consecutive months, performing a total of 39,531 treatments. The incidence of device-related adverse events (dAEs) was 1.96% (8/409), including two negligible (0.49%), five mild (1.22%), one moderate (0.24%), and no severe events. All patients continued treatment with REN despite dAEs. One-year average monthly utilization was 8.05 treatments. Month-to-month utilization did not change during 12 months of consecutive use [$F(4.895, 1997.204) = 2.014$, $p = 0.075$, repeated-measures ANOVA]. One-year average efficacy showed 74.1% of users reported consistent 2-h pain relief, and 26.0% reported consistent pain freedom. Month-to-month pain relief and pain freedom did not change during 12 months of consecutive use [$F(11, 1069) = 0.55$, $p = 0.873$ and $F(11, 1295) = 0.69$, $p = 0.750$ respectively; generalized linear mixed model analysis]. The authors concluded “REN is a safe and well-tolerated acute migraine treatment, with stable efficacy and utilization over 1 year, making it an advantageous non-drug option for the long-term management of this chronic disease. Several study limitations were acknowledged by the authors. First, the users included in this analysis constitute a subset of all REN device users and there is a concern for selection bias. Second, the current study did not incorporate additional outcomes such as standardized migraine questionnaires to measure the effects of REN on patients’ quality-of-life, which could show a wider effect than focusing mainly on measures of effectivity. Third, although 1-year consecutive use is considered a long period to track patients, studies looking at longer durations could benefit the medical and patient communities.

Monteith et al (2023) evaluated whether frequent use of REN for the acute treatment of migraine in adolescents resulted in a reduction in monthly migraine treatment days (MMTD), as previously demonstrated in adults through a dedicated prevention clinical trial (NCT04828707). The study included real-world prospective data from adolescent patients who used REN on at least 10 days every 28-day month, following the REN migraine prevention guideline of an every-other-day pattern. Additional requirements were at least three REN treatment days in each of the two subsequent months. The number of MMTD was used as a proxy measure for the number of monthly migraine days (MMD). The change in MMTD from the first month, taken as a "baseline," to each of the following months was used to evaluate the presence and size of potential migraine preventive benefits of REN in adolescents. A total of 83 adolescents were eligible for analysis. The users were 15.9 ± 1.3 years of age, and 89% of them were female. The results demonstrated a substantial month-to-month reduction in the mean number of REN treatment days from 12.6 MMTD in the first month to 9.0 MMTD in the second month,

and a further decrease to 7.4 MMTD in the third month. This indicates an accumulative reduction of 5.2 mean REN MMTD from the first month to the third month of consecutive REN treatment. The users also reported consistent 2-h acute pain responses in at least 50% of their treated attacks, with 61.9% of the users reported experiencing pain relief, 24.5% reported pain freedom, 67.4% indicated relief in functional disability, and 41.3% reported complete freedom from functional disability. The authors concluded that "frequent use of REN among adolescents as an acute treatment for migraine attacks resulted in a decrease in the mean number of monthly treatment days in the subsequent months, suggesting that REN may have potential preventive benefits for migraine in this subpopulation." The study had several limitations. First, the number of MMD was not measured directly but derived from the number of abortive MMTD, and preventive effects were extrapolated from using the device for acute treatment and not directly for migraine prevention. Second, as a post-marketing surveillance study, the cohort was selected from the users treated with the REN device, presumably reflecting that those who found it useful were likely to use it more. To directly assess preventive benefits from treating with the REN wearable device in adolescents, further research is needed with a pre-planned clinical trial including those who require migraine prevention treatment and will report their migraine attacks in a daily migraine diary (migraine days), which is available in the Nerivio® app. A dedicated study will further allow the collection of patient-centered outcomes, such as treatment satisfaction and quality of life. Third, frequency swings in the number of monthly migraine attacks are quite common, particularly in patients with chronic migraine (38), and thus using a single month for migraine baseline assessment may be short. However, 1 month is the most common baseline period used in migraine studies, including previous REN studies. Moreover, the reduction in number of MMTD between the first and third months was larger than the overall standard deviation of MMTD over all users during the three study months, indicating a larger effect of MMTD reduction over that of frequency swings, thus suggesting that the reduction of MMTD due to an efficacious REN treatment overcomes the natural fluctuations in migraine frequency. An extended study, tracking adolescents for more treatment months, will shed more light on the long-term efficacy of REN for migraine prevention in adolescents. Lastly, the patients in the study had a high attack frequency, which is a known risk factor for migraine chronification, and is associated with the sensitization of migraine-related structures. The wearable REN device activates an endogenous pain mechanism, the CPM, to abort attacks and preventive migraine days. However, there is a need for investigations designed to elucidate the underlying central mechanisms that drive the observed therapeutic clinical effects of migraine prevention with REN, and specifically the potential of brain reorganization and neuroplasticity.

For individuals with acute migraine due to episodic or chronic migraine who receive remote electrical neuromodulation (REN) , the evidence also includes 2 randomized controlled trials (RCTs) (Yarnitsky et al, 2019; Yarnitsky et al, 2017), and nonrandomized, uncontrolled studies. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Use of an active REN device resulted in more patients with improved pain and symptoms at 2-hour follow-up compared with a sham device based on 2 small (N=212) RCTs with numerous relevance limitations. Based on the existing evidence, it is unclear how Nerivio would fit into the current acute migraine management pathway. The specific intended use and associated empirically-documented recommended regimen(s) must be specified in order to adequately evaluate the net health benefit. Additionally, functional outcomes and quality of life must be evaluated in well-designed and conducted studies in defined populations using documented Nerivio regimens. Three single-arm, open-label clinical trials of the Nerivio device were used to inform US Food and Drug Administration (FDA) approval for use in patients

other than those with acute migraine due to episodic migraine. This includes 2 studies in patients with chronic migraine (Grosberg et al, 2021; Nierenburg et al, 2020) and 1 study in adolescents (Hershey et al, 2021). In the 2 studies of patients with chronic migraine, the mean age was 42 and 44 years, and mean age was 15 years in the study of adolescents. In all 3 studies most participants were female (60% to 83%) and of White race (86% to 100%). In the study conducted in adolescents, patients with episodic and chronic migraine were eligible for study inclusion. The studies reported on the effectiveness of the Nerivio device for acute migraine at 2 and 24 hours. The Nerivio device was associated with improvements in pain, symptoms, and function in all 3 studies. Adverse events related to the Nerivio device occurred in 1.0% to 2.0% of study participants across the 3 studies; no serious adverse events were reported in any of the studies. Results from these studies are limited due to their open label study design, lack of control groups, and small sample sizes with variable follow-up. For individuals with who may benefit from preventive migraine therapy, Tepper et al (2023) conducted a prospective, randomized, double-blind, placebo-controlled, multi-center trial, with 1:1 ratio to assess clinical efficacy of REN used every other day. The study consisted of a 4-week baseline observation phase, and an 8-week double-blind intervention phase in which participants used either REN or a placebo stimulation every other day. Throughout the study, participants reported their symptoms daily, via an electronic diary. Two hundred forty-eight participants were randomized (128 active, 120 placebo), of which 179 qualified for the modified intention-to-treat (mITT) analysis (95 active; 84 placebo). REN was superior to placebo in the primary endpoint, change in mean number of migraine days per month from baseline, with mean reduction of 4.0 ± SD of 4.0 days. The significance was maintained when analyzing the episodic and chronic migraine subgroups separately. REN was also superior to placebo in reduction of moderate/severe headache days, reduction of headache days of all severities, percentage of patients achieving 50% reduction in moderate/severe headache days, and reduction in days of acute medication intake. Similar results were obtained in the ITT analysis. No serious device-related adverse events were reported in any group. The authors concluded "(a)pplied every other day, REN is effective and safe for the prevention of migraine." These results are limited by the 8-week duration, shorter than the recommended 12-week duration by the International Headache Society guidelines for neuromodulation devices and lack of medical history reporting previous preventive medications used by participants. In 2021, the American Headache Society (AHS) issued guidance on the integration of new migraine treatments, including REN, into clinical practice. The AHS addressed the use of neuromodulatory devices as a group that included electrical trigeminal nerve stimulation, noninvasive vagus nerve stimulation, single-pulse transcranial magnetic stimulation, and REN; no guidance specific to REN use was issued. The AHS determined that initiation of a neuromodulatory device is appropriate when all of the following criteria are met:

Prescribed/recommended by a licensed clinician;
Patient is at least 18 years of age (the guidance noted that 3 devices, including REN, are approved for use in patients age 12 to 17 years);
Diagnosis of International Classification of Headache Disorders (ICHD)-3 migraine with aura, migraine without aura, or chronic migraine; and either of the following:
Contraindications to or inability to tolerate triptans; or
Inadequate response to 2 or more oral triptans.

UpToDate review "Acute treatment of migraine in adults" (Schwedt, Garza, 2025) states, "Data from several trials suggest that a <remote electrical neuromodulation> device applying nonpainful electrical skin stimulation can reduce acute migraine pain. In a sham-controlled crossover pilot trial of 71 patients,

the proportion of responders was higher with active stimulation compared with sham stimulation." Mild device-associated adverse events occurred in approximately 4 percent and included a warm sensation, arm or hand numbness, redness, itching, tingling, muscle spasm, arm pain, shoulder pain, and neck pain. There were no serious adverse events. UpToDate review "Preventive treatment of episodic migraine in adults" (Schwedt, Garza, 2025) states, "In a placebo-controlled trial of 248 patients with migraine, patients assigned to remote electrical neuromodulation had a greater reduction in the baseline number of monthly migraine days at 12 weeks than those assigned sham stimulation. Additional studies are needed to confirm these findings and clarify the potential role of this modality for migraine treatment." UpToDate review "Preventive treatment of migraine in children" (Mack, 2024) states, "(i)n an observational study of 83 adolescents who used the <REN> device at least 10 days a month, REN was associated with a reduction in monthly migraine treatment days from 12.6 days in the first treatment month to 7.4 days in the third month."

POSITION STATEMENT:

Percutaneous electrical nerve stimulation/percutaneous neuromodulation **meets the definition of medical necessity** when **ALL** of the following are met:

- Pain relief from TENS was not obtained due to presence of physical barriers to electrical conduction (e.g., obesity, scar tissue)
- Used for a trial period of 7 days to test the effectiveness of electrical stimulation (by PENS/PNS) to relieve pain*
- Used for one of the following:
    - Pain related to musculoskeletal conditions
    - Pain associated with active injury
    - Pain associated with post-trauma injury

***NOTE:** This diagnostic procedure involves stimulation of peripheral nerves by a needle electrode inserted through the skin. If pain is effectively controlled by percutaneous stimulation, implantation of electrodes is warranted.

Percutaneous peripheral implantable nerve stimulators, including but not limited to the Freedom Peripheral Nerve Stimulator (previously the StimQ PNS), Nalu Peripheral Neurostimulation System, Neuspera Nuity Neurostimulation System (NNS), the StimRouter Neuromodulation System, and the Sprint PNS System are considered **experimental or investigational**. Data in published medical literature are inadequate to permit scientific conclusions on long-term and net health outcomes.

Remote electrical neuromodulation (REN) (e.g., Nerivio®) is considered **experimental or investigational.** There is a lack of clinical scientific evidence published in peer-reviewed literature to permit conclusions on safety and net health outcomes.

Restorative neurostimulation (e.g., ReActiv8® Restorative Neurostimulation System) is considered **experimental or investigational**. There is a lack of clinical scientific evidence published in peer-reviewed literature to permit conclusions on safety and eficiacy.

Percutaneous electrical nerve field stimulation (PENFS) with IB-STIM® **meets the definition of medical necessity** in children and adolescents when **ALL** of the following are met:

- Age 8-18
- Diagnosed with a ROME IV criteria* defined-functional gastrointestinal disorder (functional abdominal pain, functional abdominal pain syndrome, irritable bowel syndrome, functional dyspepsia, or abdominal migraine) with symptoms present for at least 9 months
- Organic gastrointestinal disease (e.g., neoplasm, infection, etc.) has been ruled out
- Failed treatment with diet modification and probiotics
- Failed at least 3 months of treatment with acid suppressors**, antispasmodics***, and neuromodulators****
- Device will be used up to 120 hours per week, up to 3 consecutive weeks, not to exceed 4 weeks
- Will be applied to healthy, intact skin
- None of the following contraindications are present:
    - Cardiac pacemakers
    - Hemophilia
    - Psoriasis vulgaris

****Acid suppression** (includes H2-blockers and PPIs)

*****Antispasmodics** (includes hyoscyamine, dicyclomine erythromycin/linaclotide, prucalopride)

******Neuromodulators** (includes amitriptyline/nortriptyline/gabapentin)

Percutaneous electrical nerve field stimulation (PENFS) for all other indications is considered **experimental or investigational**. There is insufficient published clinical evidence to support safety and effectiveness.

***ROME Foundation**

ROME IV Diagnostic Criteria Disorders of Gut-Brain Interaction (DGBI)

H. CHILDHOOD FUNCTIONAL GI DISORDERS: CHILD/ADOLESCENT

H2. FUNCTIONAL ABDOMINAL PAIN DISORDER

H2a. Functional Dyspepsia

Diagnostic criteria:

Must include one or more of the following bothersome symptoms at least 4 times a month for at least 2 months prior to diagnosis:

1. Postprandial fullness
2. Early satiation
3. Epigastric pain or burning not associated with defecation

4. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

Functional dyspepsia subtypes:

H2a1. Postprandial distress syndrome includes bothersome postprandial fullness or early satiation which prevents finishing a regular meal. Supportive features include upper abdominal bloating, postprandial nausea, or excessive belching.

H2a2. Epigastric pain syndrome which includes all of the following: bothersome (severe enough to interfere with normal activities) pain or burning localized to the epigastrium. The pain is not generalized or localized to other abdominal or chest regions and is not relieved by defecation or passage of flatus. Supportive criteria can include (a) burning quality of the pain but without a retrosternal component, and (b) commonly induced or relieved by ingestion of a meal but may occur while fasting.

H2b. Irritable Bowel Syndrome

Diagnostic criteria:

Must include abdominal pain at least 4 days per month over at least 2 months associated with one or more of the following:

1. Related to defecation
2. A change in frequency of stool
3. A change in form (appearance) of stool
4. In children with abdominal pain and constipation, the pain does not resolve with resolution of the constipation (children in whom the pain resolves have functional constipation, not IBS)
5. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition
6. *Criteria fulfilled for at least 2 months prior to diagnosis

H2c. Abdominal Migraine

Diagnostic criteria:

Must include all of the following occurring at least twice:

1. Paroxysmal episodes of intense, acute periumbilical, midline or diffuse abdominal pain lasting 1 hour or more (should be the most severe and distressing symptom)
2. Episodes are separated by weeks to months
3. The pain is incapacitating and interferes with normal activities
4. Stereotypical pattern and symptoms in the individual patient

5. The pain is associated with two or more of the following:
    - Anorexia
    - Nausea
    - Vomiting
    - Headache
    - Photophobia
    - Pallor
6. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition
7. *Criteria fulfilled for at least 6 months prior to diagnosis

H2d. Functional Abdominal Pain – Not Otherwise Specified

Diagnostic criteria:

Must be fulfilled at least 4 times per month and include all of the following:

1. Episodic or continuous abdominal pain that does not occur solely during physiologic events (e.g., eating, menses)
2. Insufficient criteria for irritable bowel syndrome, functional dyspepsia, or abdominal migraine
3. After appropriate evaluation, the abdominal pain cannot be fully explained by another medical condition
4. *Criteria fulfilled for at least 2 months prior to diagnosis

BILLING/CODING INFORMATION:

CPT Coding

64555	Percutaneous implantation of neurostimulator electrode array; peripheral nerve (excludes sacral nerve)
64596	Insertion or replacement of percutaneous electrode array, peripheral nerve, with integrated neurostimulator, including imaging guidance, when performed; initial electrode array
64597	Insertion or replacement of percutaneous electrode array, peripheral nerve, with integrated neurostimulator, including imaging guidance, when performed; each additional electrode array (List separately in addition to code for primary procedure)
64598	Revision or removal of neurostimulator electrode array, peripheral nerve, with integrated neurostimulator
0720T	Percutaneous electrical nerve field stimulation, cranial nerves, without implantation

HCPCS Coding

A4540	Distal transcutaneous electrical nerve stimulator, stimulates peripheral nerves of the upper arm (**investigational**)
C9807	Nerve stimulator, percutaneous, peripheral (e.g., Sprint peripheral nerve stimulation system), including electrode and all disposable system components, non-opioid medical device (must be a qualifying medicare non-opioid medical device for post-surgical pain relief in accordance with section 4135 of the caa, 2023) **(investigational)**
L8678	Electrical stimulator supplies (external) for use with implantable neurostimulator, per month (**investigational**)

LOINC Codes:

The following information may be required documentation to support medical necessity: physician history and physical, physician progress notes, treatment plan, radiology report(s) and diagnostic studies.

Documentation Table	LOINC Codes	LOINC Time Frame Modifier Code	LOINC Time Frame Modifier Codes Narrative
Physician history and physical	28626-0	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim
Attending physician visit note	18733-6	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim.
Treatment plan	18776-5	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim.
Radiology report	18726-0	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim
Diagnostic studies (non-lab)	27899-4	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim.

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage products: The following National Coverage Determination (NCD) was reviewed on the last guideline reviewed date: Treatment of Motor Function Disorders with Electric Nerve Stimulation (160.2); Electrical Nerve Stimulators (160.7); and Assessing Patient's Suitability for Electrical Nerve Stimulation Therapy (160.7.1), located at cms.gov.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

None applicable.

RELATED GUIDELINES:

Transcutaneous Electric Nerve Stimulation (TENS), 02-61000-04

OTHER:

None applicable.

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11. Blue Cross Blue Shield Association Evidence Positioning System®. 7.0–.139 - Peripheral Subcutaneous Field Stimulation, 05/24.

12. Blue Cross Blue Shield Association Evidence Positioning System®. 7.0–.171 - Remote Electrical Neuromodulation for Migraines, 11/24.

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy and Coverage Committee on 04/25/24.

GUIDELINE UPDATE INFORMATION:

09/15/02	Medical Coverage Guideline Reformatted.
09/15/04	Scheduled review and revision to guideline; consisting of updated references and changed non-covered statement to investigational for electrical stimulation used for motor function disorders.
01/01/05	Annual HCPCS update; consisting of the revision of 64590.
01/01/07	HCPCS coding update consisting of the revision of 64590 and 64595.
07/15/07	Scheduled review, coverage and limitations maintained, Description, Billing/Coding Information, and Reimbursement Information section updated with CPT codes, guideline reformatted, and references updated.
09/15/09	Scheduled review; no change in position statement.
05/15/11	Revision; formatting changes.
09/15/11	Scheduled review; no change in position statement. Updated description section, billing/coding section and references, formatting changes.
05/11/14	Revision: Program Exceptions section updated.
01/01/18	Annual CPT/HCPCS coding update: deleted 64565 from Billing/Coding Information section. Revised Programs Exceptions section. Reformatted guideline.
10/15/19	Scheduled review. Revised description and index terms. Maintained position statement. Updated references.

11/15/19	Revision. Revised description, added coverage statement for peripherally implanted nerve stimulators. Updated references.
08/15/21	Scheduled review. Maintained position statement and updated references.
07/01/22	Quarterly CPT/HCPCS coding update. Added 0720T.
08/15/22	Unscheduled review. Updated references and added E/I coverage statement for percutaneous electrical nerve field stimulation (PENFS).
12/15/22	Revision. Updated references and maintained position statement.
04/01/23	Quarterly CPT/HCPCS coding update. Code L8678 added.
05/15/23	Scheduled review. Maintained position statement and updated references.
05/25/23	Update to Program Exceptions section.
09/15/23	Added code 64555.
01/01/24	Annual CPT/HCPCS coding update. Added 64596, 64597, 64598.
05/15/24	Scheduled review. Revised description and position statement (added coverage criteria for IB-Stim®). Updated references.
09/15/24	Revision. Revised description, maintained position statement and updated references.
11/15/24	Revision. Revised description, added coverage statement for remote electrical neuromodulation (REN) (eg, Nerivio®), added code A4540, and updated references.
12/15/24	Revision. Updated age criteria for PENFS with IB-STIM®. Updated references.
01/01/25	Annual CPT/HCPCS coding update. Added C9807.
04/15/25	Revision. Revised description. Updated references for remote electrical neuromodulation (REN) (eg, Nerivio®), peripheral nerve stimulation (PNS) with Nalu, and restorative neurostimulation with Reactiv8. Maintained position statement.